Journal of Applied Biomedicine 15 (2017) 63–70

Contents lists available at ScienceDirect

Journal of Applied Biomedicine

journal homepage: www.elsevier.com/locate/jab

Review Article

Exercise-induced epigenetic regulations in inflammatory related cells

Małgorzata Zawadzka, MSc*, Paweł Piotr Jagodziński

Department of Biochemistry and Molecular Biology, Poznań University of Medical Sciences, Poland

ARTICLE INFO

Article history:
Received 23 May 2016
Accepted 22 September 2016
Available online 10 October 2016

Keywords:
Epigenetic
Physical activity
Exercise
PBMCs
Inflammation
Immunity

ABSTRACT

Physical activity has been correlated with transient immune impairment. However, such activities lead to improvement in immunity rather than dysfunction. The major benefit of regular exercise is the reduction of low-grade inflammation which consequently prevents or attenuates metabolic diseases, such as atherosclerosis and type 2 diabetes, neurodegenerative disorders, cancer or even depression. As a major factor responsible for general improvements in the immune system, scientists have examined epigenetics. Epigenetic mechanisms include cytosine methylation, micro-RNA expression and post-transcriptional modifications of histones, which regulate tissue-specific gene expression in response to environmental stimulation. This review will summarize the recent data regarding the impact of exercise and the role of epigenetic mechanisms on gene expression changes in Peripheral Blood Mononuclear Cells (PBMCs).

Contents

Introduction

During the last decade, the social awareness regarding physical activity and its influence on health and the general understanding of well-being has increased. This awareness has focused on many forms of physical activity, which is typically the easiest and cheapest strategy to maintain physical and mental health throughout one's lifespan. Despite the current fashion for "being fit", scientists have been trying to recognize and clarify the phenomenon of physical effort and its significant impact on the human body for many years. In 1989, attention was turned to the immune system as a result of a study by Nieman et al.. The researchers assumed that chronic, moderate exercise enhanced immunity and reduced the risk of illness compared with sedentary individuals, yet intense prolonged exercise showed the opposite effects, potentially leading to an increased risk of upper respiratory tract infections (URTI) (Nieman et al., 1989). These relationships were further illustrated on a J-curve as a result of cross-section analysis of marathon runners and sedentary men and women [Fig. 1] (Nieman, 1994). Furthermore, the "Open-Window" theory has been proposed to explain the phenomenon responsible for immune impairment and the increased risk of illness among athletes subjected to exhaustive physical efforts [Fig. 2] (Pedersen and Ullum, 1994). Further research in the field of exercise immunology showed that even a single bout of exercise could

* Corresponding author at: Department of Biochemistry and Molecular Biology, Poznań University of Medical Sciences, Święcickiego 6 St., 60-781 Poznań, Poland.
E-mail address: malgorzata.zawadzka@ump.edu.pl (M. Zawadzka).

http://dx.doi.org/10.1016/j.jab.2016.09.002
1214-021X/

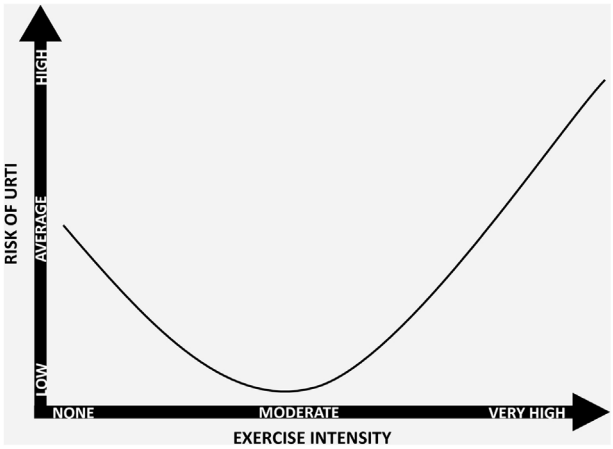

Fig. 1. J-curve model illustrated relationship between intensity of undertaken physical activity and the risk of URTI infection. According to Nieman et al. chronic, moderate exercise decreases the susceptibility for URTI, while very intense, prolonged exercise increases it (Nielsen, 2013). ©2013 Hamlin M, Draper N, Kathiravel Y. Published in (Nielsen, 2013) under CC BY 3.0 license. Available from: http://dx.doi.org/10.5772/54681.

disrupt the homeostasis of the number, distribution and function of various types of immune cells as well as systemic cytokine levels (Stewart et al., 2007). The patterns of pro-inflammatory cytokines released during and after strenuous exercise have been reported as having "similarities to the acute phase response to sepsis and trauma" (Pedersen et al., 1998). Despite the transient increased risk of URTI induced by strenuous prolonged exercise, physical activity has been strongly correlated with the reduction of low-grade inflammation and overall immune improvement (McFarlin et al., 2006; Walsh et al., 2011). These results suggest that the initial burst of pro-inflammatory mediators is modulated by a subsequent influx of anti-inflammatory cytokines (Pedersen, 2000). The balance between pro- and anti-inflammatory mediators, followed by the systemic reduction of the inflammatory milieu, has been indicated as the primary factor contributing to the prevention or attenuation of diseases such as atherosclerosis, type 2 diabetes, neurodegenerative disorders, cancer and depression (Golbidi and Lather, 2012; Çolak et al., 2016; Kampert et al., 1996; Wang et al., 2016). The beneficial role of physical activity remains undeniable.

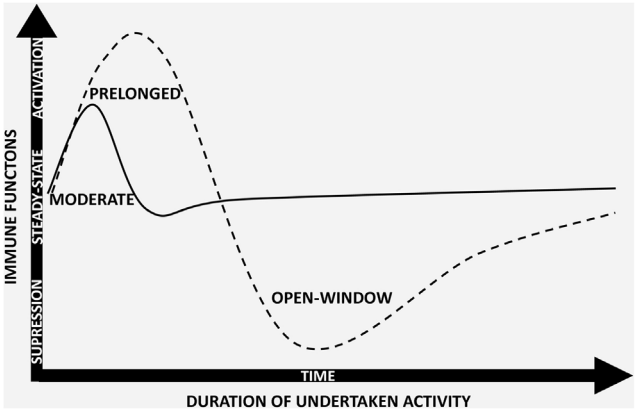

Fig. 2. Open-Window theory proposed by Pendersen and Ullum explains the phenomenon of higher susceptibility of URTI infection among elite athletes. Exercise initially activates immune functions, which during recovery back to steady-state regarding moderate exercise but strenuous prolonged exercise leave the "open-window" which correlates to temporary suppression of immune functions (Nielsen, 2013). ©2013 Hamlin M, Draper N, Kathiravel Y. Published in (Nielsen, 2013) under CC BY 3.0 license. Available from: http://dx.doi.org/10.5772/54681.

However, despite extensive research in this field, questions regarding the precise mechanisms that regulate the immune systems of exercising individuals remain unanswered.

Epigenetics

Inarguably, physical activity strongly influences the transcription of various genes, including those involved in immunological processes, which could provide some insight into epigenetic modifications as important modulators of dynamic physiological responses to exercise (Gjevestad et al., 2015; Bouchard, 2015). Waddington (1942) first introduced the term "epigenetics" as "a branch of biology which studies the casual interaction between genes and their products which bring phenotype into being". Currently, epigenetics is primarily correlated with changes in DNA or chromatin structure (Li, 2002) which can be induced by environmental factors such as diet, stress, chemical exposure or physical activity (Feil and Fraga, 2012). However, the changes involved in the modulation of gene expression occur without altering the underlying sequences (Fraga et al., 2005). The major mechanisms that respond to environmental factors by the regulation of the expression of specific genes are cytosine methylation, histone modification and microRNA (mi-RNA) expression (Suzuki and Bird, 2008; Bannister and Kouzarides, 2011; Chuang and Jones, 2007).

Post-transcriptional modifications of histone proteins

The double-stranded helix of DNA in the nucleus of a single cell is approximately 2 m long and has to be highly organized to fulfill its proper functions. The strands of DNA are rolled into a complex of 8 histone proteins called an octamer, forming nucleosomes that are further condensed into chromatin fibers (Khorasanizadeh, 2004). Chromatin generally occurs in two forms, heterochromatin and euchromatin. Heterochromatin is tightly packed and transcriptionally inactive, whereas euchromatin is loosely packed and accessible to proteins involved in gene transcription (Wolffe, 1998). Various post-transcriptional modifications of histone N-terminal tails are major contributors to chromatin remodeling and thereby promote or suppress gene expression (Fischle et al., 2003). Among these, the best-characterized modification is the acetylation of lysine (K) residues catalyzed by Histone Acetyltransferases (HATs) (Grunstein, 1997). When bound to lysine, the acetyl group decreases the affinity of histones for DNA by the neutralization of positive charges, thereby promoting chromatin relaxation and gene activation. Acetylation is highly dynamic, and acetyl groups can be removed from histone tails by Histone Deacetylases (HDACs), leading to chromatin condensation and gene silencing (Turner, 2000). Another important modification of histone proteins is methylation. In contrast to acetylation, methylation does not perturb the charge of the histone (Rice and Allis, 2001). The direct effect of methylation depends on the location of the methyl groups added by Histone Methyltransferase (HMT), thereby either repressing or promoting transcription. For example, the trimethylation of histone H3 at lysine 4 or the methylation of arginine (R) on histones H3 or H4 is correlated with transcriptional activation, while the trimethylation of lysine 9 or 27 on histone H3 is correlated with repression (Zhang and Reinberg, 2001). Other post-transcriptional histone modifications include phosphorylation, deimination, ubiquitylation, sumoylation or ADP ribosylation (Peterson and Laniel, 2004; Strahl and Allis, 2000; Berger, 2002).

DNA methylation

The most extensively studied mechanism of epigenetic modification is DNA methylation, which primarily occurs at

cytosine nucleotides, localized mainly but not exclusively at CpG dinucleotide sites (He and Ecker, 2014). DNA methylation is performed by DNA methyltranferases (DNMTs), which covalently incorporate methyl groups (CH_3) from methyl donor – *S*-adenosyl methionine (SAM), to the fifth carbon in the pyrimidine ring of cytosine, thereby generating 5-methylcytosine (5-mC) (Niculescu and Zeisel, 2002). DNMT1 is necessary for the maintenance of proper methylation patterns but requires a second previously methylated DNA strand as a template (Hirasawa et al., 2008). Conversely, DNMT3a and DNMT3b, acting with DNMT3L, establish new methylation marks at CpG sites which were previously not methylated (Hermann et al., 2004; Bestor, 2000). DNA methylation within a gene promoter region silences gene expression through the attraction of methylated DNA-binding proteins (MDBPs). MDBPs further recruit various factors involved in chromatin remodeling, including HDACs, thereby making these genes transcriptionally inactive (Bogdanović and Veenstra, 2009). Interestingly, recent studies have revealed that in contrast to the promoter, gene body methylation is positively associated with gene expression (Jones, 2012). Although such a paradox is not clearly explained, some studies have suggested that methylation within the gene body represses transcription from the intragenic promoter, thereby promoting transcriptional elongation (Jjingo et al., 2012). Until the discovery of Ten-eleven translocation enzymes (TETs), cytosine methylation was proposed as a stable modification that was only passively lost as a consequence of DNMT inhibition during cell division (Wu and Zhang, 2010). Currently, it is proven that demethylation occurs also actively through the oxidative capacities of TET enzymes, which convert 5-mC to 5-hydroxymethylcytosine (5-hmC) and subsequently to 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC) (Delatte et al., 2014). Oxidized cytosine derivatives are further processed to unmodified cytosine by several different pathways, including the activities of Thymine-DNA glycosylase (TDG) and the Base Excision Repair (BER) system (Gehring et al., 2009). Thus, DNA methylation has recently been implicated to play a part in dynamic epigenetic regulation in response to external stimuli.

Micro-RNAs

In addition to chromatin remodeling and DNA methylation, short non-coding RNA regulates gene expression at the post-transcriptional level (He and Hannon, 2004). Micro-RNA (miRNA) coding regions are located across the genome, also in introns and intergenic regions from which they are transcribed by RNA polymerase II (Lagos-Quintana et al., 2001). To become fully functional, primary miRNA transcript must be processed through the enzyme Drosha and subsequently translocated to the cytoplasm by exportin-5, where it is converted to its mature form via final processing by the enzyme Dicer (Bartel, 2004). Functional miRNAs are single-stranded and approximately 21 nucleotides (nt) in length, acting together with the RNA-induced silencing complex (RISC) as a suppressor of protein translation (Gregory et al., 2005). Interactions between miRNAs and their targeted mRNAs occur on the basis of their sequence complementarity. Typically, miRNAs bind to 3′ untranslated region (UTR) of mRNA transcripts; however, functional interactions in the 5′UTR of transcripts have been also demonstrated (Lytle et al., 2000). Full complementarity between both sequences results in transcript cleavage and degradation. Nonetheless, partial complementarity is also sufficient to silence gene expression through translation suppression of targeted mRNA (Eulalio et al., 2008), albeit perfect matching between the transcript and conserved sequences of 6–8nt at 5′UTR of miRNA called seed region is required (Lewis et al., 2005). Moreover, despite the suggestion that miRNAs primarily play only an inhibitory roles, some studies have suggested that these molecules can also promote and activate translation (Lee and Vasudevan, 2013; Vasudevan et al., 2007).

Exercise and PBMCs

Many studies have described the epigenetic regulation that is induced through exercise in the context of muscle and adipose tissue metabolism or mitochondria biogenesis as an adaptation to physical effort (Barres et al., 2012; Lochmann et al., 2015). Indeed, muscle contraction is a sufficient stimulus for chromatin remodeling by the activation of calmodulin-dependent kinases (CaMKs) and AMP kinase (AMPK) (Ferraro et al., 2014). Together, they lead to the phosphorylation of HDACs and their subsequent translocation to the cytoplasm. Consequently, the absence of HDACs in the nucleus promotes chromatin relaxation (Flück et al., 2000; McKinsey et al., 2000). Regarding the process of inflammation, muscle tissues produce large amounts of the immunomodulatory myokine IL-6 (up to 100-fold increase) in response to muscle micro-damage after exercise (Keller et al., 2001). However, in the present review we will focus on the epigenetic alteration and regulation of Peripheral Blood Mononuclear Cells (PBMCs), including lymphocytes B, lymphocytes T, Natural Killer (NK) cells and monocytes, which are major contributors in directing immune responses (Bauer et al., 1999). Moreover, PBMCs can be easily obtained from peripheral blood, making these cells more convenient to work with and sample compared with invasive biopsies of muscle or adipose tissue.

Physical activity strongly disrupts the distribution and number of circulating immune cells, including cytotoxic Natural Killer (NK) cells, which recognize and destroy infected cells or tumor cells (Mitchell et al., 2002). Zimmer et al. (2015) showed that a single session of intense exercise affects NK-cell activity through chromatin remodeling. These authors examined the expression of the NK-cell receptor NKG2D and the H4K5 acetylation levels in 14 cancer patients and 14 healthy controls after a half-marathon race. The expression of NKG2D and H4K5 acetylation was significantly increased in both groups with no considerable changes to DNA methylation, and such effect was maintained for a minimum of 24 h after the race. The results indicated that the physical effort involved in long-distance running was sufficient to affect histone acetylation in NK-cells and likely correlated with elevated NKG2D expression. Therefore, NK-cells are seems to be activated by exercise-induced epigenetic alterations. Additionally, Zimmer et al. (2014) previously showed that exercise-induced changes in cytokine levels affect histone acetylation in NK-cell and $CD8^+$ T-lymphocytes in Non-Hodgkin-Lymphoma (NHL) patients. NHL patients reveal higher serum levels of Macrophage migration inhibiting factor (MIF) and Interleukin- (IL-) 6 and lower NK-cell H3K9 acetylation compared with the healthy control group. Furthermore, a significant negative correlation between increased MIF levels and lower NK-cell H4K5 acetylation was also observed, indicating that MIF may inhibits NK-cell activity. In the context of $CD8^+$ cells, a single 30 min bout of moderate ergometer bicycle exercise increased H4K5 acetylation levels in the exercising NHL group, confirming the positive influence of exercise on tumor-competitive lymphocytes.

Several studies have reported dramatic elevations of pleiotropic IL-6 in plasma after strenuous exercise (Pedersen and Fischer, 2007). Robson-Ansley et al. (2013) examined the influence of IL-6 on methylation status in PBMCs. The study involved 8 healthy, trained males that underwent a treadmill test (120 min at 60% vVO_{2max}, followed by a 5 km time trial under fasted conditions). Blood samples were collected prior to and immediately after the test, as well as after 24 h of rest. As expected, the levels of IL-6 significantly increased immediately after exercise and declined to initial levels after 24 h. Although there were no significant changes

in global methylation, 114 CpG sites showed changes in methylation that correlated with IL-6 elevations in plasma. After adjusting for multiple testing, eleven of these CpG sites remained significant. Interestingly, the genes with altered methylation are involved in inflammatory response pathways. Among these genes is interleukin 1 receptor associated kinase 3 (IRAK3), which plays a role in the attenuation of inflammatory processes and whose demethylation is associated with IL-6 levels. IRAK3 also regulates plasmatic IL-6, suggesting that site-specific methylation is one of the mechanisms modulating exercise-associated immune responses. In addition, elevated levels of IL-6 in circulation after exercise have been reported to attenuate nuclear concentrations of DNMT3B in PBMCs, which can partially explain the hypo-methylation of various genes induced by exercise (Horsburgh et al., 2015).

Other important genes associated with inflammation are apoptosis-associated speck-like proteins containing a caspase recruitment domain (ASC) and nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (NFkB2) (Mariathasan et al., 2004; Hoesel and Schmid, 2013). ASC has many functions, including participating in inflammasomes, activating procaspase 1 and being involved in the processing of proIL-1β and proIL-18 to their mature forms and is also required for the secretion of other pro-inflammatory cytokines, such as IL-6, IL-8 and tumor necrosis factor alpha (TNFα) (Martinon and Tschopp, 2004). It has been demonstrated that ASC expression increases in an age-dependent manner, leading to an elevated risk of inflammatory-related diseases in the elderly. Studies were performed on 436 healthy elders divided into exercising and non-exercising groups, and on 37 students as a young control. The first group underwent 6 months of a high-intensive interval walking (IWT) regimen. The study validated the increased expression of ASC in the older non-exercising group, reflecting decreased ASC methylation compared with the young control group. Furthermore, the influence of chronic moderate exercise on ASC methylation was examined. The elders in the exercise group showed significantly higher ASC gene methylation (mean $6.29 \pm 0.26\%$) compared with the older control group (mean $5.33 \pm 0.14\%$). Therefore, the exercise group showed a decreased expression of the pro-inflammatory ASC gene. Moreover, the elders from the exercising group had a mean ASC methylation value similar to that of the young control group (Nakajima et al., 2010). NFkB2 is a subunit of nuclear factor kappa-B (NFkB), a major transcription factor of various inflammatory genes, including cytokines. Thus, NFkB plays a central role in the induction of inflammation (Tak and Firestein, 2001). NFkB2, similar to ASC, is age-dependently up-regulated, thereby contributing to inflammation-related diseases such as atherosclerosis. Zhang et al. (2015) examined genome-wide methylation in a group of 7 IWT exercising elders and 6 non-exercising elderly controls and revealed over 40 genes that were either hypo- or hyper-methylated after exercise. After correlating the methylation status with total energy consumption, 4 hypo-methylated and 3 hyper-methylated (including NFkB2) genes were determined as significant. The promoter-driven hyper-methylation of NFkB2, as a consequence of interval walking training, was further confirmed by quantitative pyrosequencing to also be significant in different IWT participants. Additionally, early growth response 2 (EGR2), which is likely involved in the suppression of chronic inflammation, was found to be demethylated after the training regimen. These results provide an explanation for the mechanism of long-term benefits induced by chronic moderate exercise. The mechanism involves the reduction of the inflammatory milieu by the hyper-methylation of pro-inflammatory genes and hypo-methylation of genes associated with the suppression of inflammatory responses. Since these effects were obtained after a long-term training program (6 months), Denham and colleagues (2014) examined the influence of intense, short-term (4 weeks) exercise training on the leukocyte methylome. Using Infinium HumanMethylation450 BeadChip (Illumina), researchers identified 205,987 CpG sites with aberrant methylation. Among genes with the largest methylation changes were epidermal growth factor (EGF) and uracil DNA glycosylase (UNG), whose promoters were significantly demethylated. Interestingly, the increased activity of EGF has been demonstrated in cancers with an overexpression of epidermal growth factor receptor (EGFR) (Normanno et al., 2006). Despite the demethylation of EGF induced by exercise, the expression of this gene was significantly decreased, suggesting that other epigenetic mechanisms may counteract its expression. Moreover, the demethylation of UNG, responsible for the prevention of mutagenesis by participation in the initiation of base-excision repair (BER) pathways (Krokan et al., 2000), was followed by increased expression. Indeed, in addition to the anti-inflammatory properties of exercise, this research provided evidence for its potential role in the attenuation or prevention of carcinogenesis (Denham et al., 2014). In the context of cancer, the increased demethylation of repetitive sequences has been observed in various cancer types (Ross et al., 2010). Long interspersed repeat elements (LINE-1) have been identified across the human genome, and the majority of these sequences are highly methylated (Chalitchagorn et al., 2004). Aging is generally associated with the reduction of global methylation marks, including LINE-1, resulting in the instability of the genome and an elevated occurrence of mutations and carcinogenesis (Miousse and Koturbash, 2015). Zhang et al. (2011) analyzed the global methylation of LINE-1 in a total of 131 subjects of middle and elderly age whose daily physical activity was recorded using an accelerometer. Individuals who participated in physical activity approximately 26–30 min per day had higher levels of global leukocyte methylation as measured by LINE-1. However, after adjusting for age, gender and ethnicity, these results were no longer statistically significant. In the other hand, White et al. (2013) demonstrated significant global DNA methylation, measured by LINE-1, in women declared as physically active during childhood, teenage years and in the past 12 months. Because these results are based on evidence from aerobic exercises, little is known about the influence of resistance training on the human methylome. Denham et al. (2016) analyzed the influence of 8-week resistance exercise training (RET) on the leukocyte methylome of 8 healthy human subjects. The study reveals the altered methylation of 57,384 CpG sites, 28,397 sites with increased methylation and 28,987 sites with decreased methylation. Among the demethylated genes was interleukin 1 receptor associated kinase 4 (IRAK4), which plays a meaningful role in the toll-like receptor (TLR) signaling cascade (Kawagoe et al., 2007), and its deficiency has been correlated with an increased susceptibility to bacterial infection (Wang et al., 2009). Other genes with altered methylation have been associated with various signaling pathways, including cancers, diabetes, cell adhesion molecules or anabolic signaling (Denham et al., 2016).

Significant changes in the methylome of physically active people have occurred over longer periods of time (Zhang et al., 2011; White et al., 2013). The expression of miRNAs is a dynamic process that leads to the rapid down-regulation of target transcripts. To understand the mechanism underlying how exercise influences miRNA expression in immune cells, Radom-Azik and colleagues performed a series of elegant studies that subjected groups of healthy young men to brief sessions of heavy ergometer exercise and assessed the expression of miRNA prior to and after testing. In PBMCs, 34 miRNAs showed altered expression, among which 15 miRNAs were up-regulated. Compared with previously reported changes in gene expression affected by the same exercise regimen, these results revealed 12 common biological pathways. Among these, the transforming growth factor beta (TGFβ) and calcium signaling pathways were both associated

with the regulation of inflammatory responses. Among individual miRNAs worthy of attention is the up-regulation of the miR-181 family (miR-181a, b and c) (Radom-Aizik et al., 2012). The down-regulation of these transcripts contributes to the development of glioblastoma and aggressive leukemia (Ciafre et al., 2005; Pekarsky et al., 2006), confirming the beneficial role of physical activity in cancer prevention. miR-181a also enhances T cell sensitivity toward antigens and therefore may increases resistance to infection (Li et al., 2007). With respect to NK-cells, 986 genes and 23 miRNAs (11 up-regulated) showed altered expression. Seven common pathways in cancer and p53 signaling have been reported (Radom-Aizik et al., 2013). Among the up-regulated miRNAs, miR-29a, miR-29b and miR-29c has been found to revert aberrant methylation in lung cancer by targeting DNMT 3A and 3B, whose expression is associated with poor prognosis (Fabbri et al., 2007). Expression changes have been exclusively examined in monocytes, revealing significant alterations in 19 miRNAs and 1236 genes (Radom-Aizik et al., 2014). Among common pathways in which altered miRNAs were engaged, the most interesting is the Jak-STAT signaling pathway, which plays a meaningful role in

Table 1
Summary of the relevant literature regarding epigenetic changes induced by physical activity in PBMCs.

Article	Participants	Exercise	Cell Type/ Tissue	Main Results
Histone Modification:				
Zimmer et al. (2015)	14 cancer patients and 14 healthy controls	Half-marathon	NK-cells	Increased expression of NKG2D receptor and H4K5 acetylation levels after competition
Zimmer et al. (2014)	26 NHL patients and 10 healthy controls	Bicycle ergometer, 30min at moderate intensity	NK-cells, $CD8^+$ T-lymphocytes	Increased H4K5 acetylation level in $CD8^+$ cells in the exercising NHL group
DNA methylation:				
Robson-Ansley et al. (2013)	8 healthy trained males	Treadmill run (120 min, 60% vVO_{2max}) followed by 5km time trial	PBMCs	Elevated level of plasma IL-6 after acute bout of exercise influences methylation of CpG sites in 11 genes associated with inflammation
Nakajimaet al. (2010)	34 young control group, 153 older control group and 230 older exercise group	6 months of high-intensity interval walking regimen	Leukocytes	Increased methylation of pro-inflammatory ASC gene in elderly to level comparably with young control.
Zhang et al. (2015)	7 exercising and 6 control elders	6 months of high-intensity interval walking regimen	Leukocytes	Increased promoter methylation of NFkB2 gene
Denham et al. (2014)	26 healthy young males	4 weeks of aerobic exercise regimen	Leukocytes	Short-term intense exercise decreased methylation of EGF and UNG genes.
Zhang et al. (2011)	161 participants aged 45-75 years	N/A	Leukocytes	26-30 min of physical activity per day is associated with higher global DNA methylation measured by LINE-1
Denham et al. (2016)	647 non-Hispanic white women	N/A	Leukocytes	LINE-1 methylation is significantly higher in woman which was physical active during their life-span
White et al. (2013)	8 young males	8 weeks of resistance exercise training	Leukocytes	57,384 CpG sites with altered methylation
miRNA expression:				
Radom-Aizik et al. (2012)	12 healthy young males	Brief cycle ergometer interval session	PBMCs	Brief bouts of heavy exercise altered expression of 34 miRNAs associated with 12 common pathways e.g. TGFβ and Calcium signalling pathways
Radom-Aizik et al. (2013)	13 healthy young males	Brief cycle ergometer interval session	NK-cells	Brief bouts of exercise altered 23 miRNA associated with 7 common pathways founded in cancer and p53 signalling
Radom-Aizik et al. (2014)	12 health young males	Brief cycle ergometer interval session	Monocytes	Brief bouts of exercise are associated with changes of 19 miRNAs founded to share common pathways e.g. in JAK-STAT signalling
Radom-Aizik et al. (2010)	11 healthy males	Brief cycle ergometer interval session	Neutrophils	38 altered miRNAs by exercise are associated with three common pathways: Ubiquitin mediated proteolysis, JAK-STAT signalling pathway and Hedgehog signalling pathways
Circulating miRNA:				
Mooren et al. (2014)	14 healthy males	Marathon	Plasma	No significant changes in circulating levels of miR-21 after the race
Nielsen et al. (2014)	13 healthy males in group of acute exercise and 7 healthy males in endurance training group.	Acute – 60 min of cycle ergometer session Endurance – 12 weeks of cycling 5 times/week	Plasma	c-miR-21 and c-miR-146a significantly down-regulated in both group after exercise
Baggish et al. (2011)	10 healthy male athletes	Acute, exhaustive cycling	Plasma	c-miR-21 and c-miR-146a significantly up-regulated immediately after acute bout of exercise
Baggish et al. (2014)	10 healthy male athletes	Marathon	Plasma	miR-146a up-regulated after the race
Xu et al.(2016)	28 chronic heart failure patients	Acute, exhaustive treadmill session	Plasma	Up-regulated miR-21 after exercise
Sawada et al. (2013)	12 healthy males	Acute, resistance exercise	Plasma	Decreased level of miR-146a at 3 days after exercise bout
de Gonzalo-Calvo et al. (2015)	9 healthy males	10-km race, half-marathon and marathon race each separated by 1 month	Plasma	c-miR-150-5p significantly up-regulated after 10km-race (low inflammation responses) and let-7d-3p, let-7f-2-3p, c-miR-125b-5p, c-miR-132-3p, c-miR-143-3p, c-miR-148a-3p, -miR-223-3p, c-miR233-5p, c-miR-29a-3p, c-miR34a-5p, c-miR-424-3p and c-miR-425-5p significantly up-regulated after marathon race (high inflammatory responses)

immune development and when mutated leads to inflammatory diseases, such as atherosclerosis (Sikorski et al., 2011). Moreover, exercise significantly enhanced the expression of miR-30e, which is down-regulated in atherosclerotic lesions (Ding et al., 2014). Further, significant down-regulation of cluster of differentiation 36 (CD36), TNF and TLR4 gene expression were also observed after sessions of exercise, while the up-regulation of these genes has been reported in patients with vascular diseases (Radom-Aizik et al., 2014). Despite the PBMCs, Radom-Aizik et al. (2010) also showed that significantly altered genes and miRNAs in neutrophils were involved in ubiquitin-mediated proteolysis, Jak-STAT signaling pathways and Hedgehog signaling pathways. All three pathways play a significant role in the inflammatory process.

In addition to the tissue- or cell-specific expression of miRNAs have also been founded in the circulation, where they are secreted within exosomes or associated with lipoproteins or ribonucleoprotein complexes for protection from RNases (Ma et al., 2012). Circulating miRNAs (c-miRNAs), similar to cytokines and hormones, play a role in autocrine, paracrine and endocrine communication between different cells and can potentially be used as biomarkers of health conditions (Heneghan et al., 2010). In the context of physical activity, several independent studies displayed aberrations in serum levels of miR-21 and miR-146a, which are known to be involved in inflammation (Rusca and Monticelli, 2011). Although, Mooren et al. (2014) did not observe significant changes in circulating levels of miR-21 either immediately or at 24 h after marathon distance running, Nielsen et al. (2014) revealed the significant down-regulation of miR-21 and miR-146a after an acute session of exercise and after 12 weeks of chronic exercise regimens, respectively. However, these results are inconsistent with the previously reported up-regulation of both miR-146a and miR-21 immediately after acute exercise (Baggish et al., 2011) and miR-146a up-regulation after a marathon race (Baggish et al., 2014). Furthermore, in serum collected from chronic heart failure patients immediately after acute exhaustive exercise, miR-21 but not miR-146a was up-regulated (Xu et al., 2016). Surprisingly, in contrast to aerobic exercise, an acute session of resistance training has been shown to decrease the level of miR-146a at three days after exercise (Sawada et al., 2013). Moreover, de Gonzalo-Calvo et al. (2015) examined dose-dependent changes in c-miRNAs associated with inflammation (c-inflamma-miRs), observing the significant elevation of miR-150-5p immediately after a 10-km run (low inflammatory responses) and 12 c-inflamma-miRs including let-7d-3p, let-7f-2-3p, miR-125b-5p, miR-132-3p, miR-143-3p, miR-148a-3p, miR-223-3p, miR233-5p, miR-29a-3p, miR34a-5p, miR-424-3p and miR-425-5p immediately after a marathon race (high inflammatory responses). Increased levels of c-inflamma-miRs were positively correlated with standard inflammatory parameters (white blood cell counts and acute phase protein levels), confirming the hypothesis that prolonged exhaustive exercise can lead to a transiently noxious inflammatory response (Cooper et al., 2007) (Table 1).

Summary

Physical activity is undeniably correlated with the perturbation of immune system homeostasis. However, these aberrations primarily ameliorated overall health by anti-inflammatory properties of cytokines released during exercise, and when regularly repeated reduces the low-grade inflammation milieu as frequently observed in obese and inactive individuals. However, a recent study revealed the importance of epigenetic modifications induced by exercise for the maintenance and improvement of health, therefore making the shift from a physiological to molecular level of understanding how exercise influences the human body. This review highlights the epigenetic alterations in Peripheral Blood Mononuclear Cells, including B and T lymphocytes, NK-cells and monocytes, which play a meaningful role in recognizing and eliminating pathogens, mediating immune responses by cytokine production and destroying tumor cells. Physical activity has a positive influence on the development or activation of at least a portion of PBMCs. The over-expression of miR-181 has been associated with the increased maturation of hematopoietic progenitor cells (HPCs) to NK-cells, while histone acetylation is associated with the activation of these cells. Indeed, ergometric exercise up-regulates miR-181 expression in PBMCs and running promoted histone acetylation, which was significantly correlated with the expression of the NKG2D receptor – important for NK-cells activating. Moreover, despite initially increased levels of pro-inflammatory mediators, such as IL-6, physical activity simultaneously leads to changes in gene expression favoring anti-inflammatory processes mediated by PBMCs. The effects of physical activity on the human genome depend on the dose and duration of undertaken activity. Chronic, long-term exercise regimens potentially contribute to maintaining genome stability, reflected in the exercise-related methylation of repetitive sequences. Moreover, genome methylation patterns are lost during senescence, contributing to various age-related diseases. Chronic exercise may play a role in restoring the appropriate methylation patterns of inflammatory genes in PBMCs, influencing the well-being of the elderly. Nevertheless, even brief sessions of acute exercise positively influence health by rapid miRNA expression, which attenuates excessive inflammatory responses in PBMCs. However, the majority of previous studies have primarily focused on aerobic and endurance training. With the exception of a few studies, how resistance training affects the epigenome of PBMCs has not yet been elucidated and requires further research. Circulating miRNAs have recently been suggested as an attractive source of potential biomarkers for health conditions and trainability and in the future could serve as an enormously useful tool for the optimization of personal training regimens. However, the highly variable results of different studies likely reflects the various methods of miRNA isolation and processing between labs, thus it is necessary to unify a standard protocol. There was also no available information concerning how specific sport disciplines influence the epigenome and health. Such information, combined with clinical studies, may be helpful in establishing optimal training regimens and supporting conventional therapies, with differences regarding health disorders. Finally, most of the research describes the influence of physical activity on the epigenome from chronic-moderate or acute exercise but not chronic exercise. To our knowledge, the effect of a long-term high training load on the epigenome of professional athletes and whether such influence has positive or quite negative outcomes remains unknown and indeed should be further elucidated.

Acknowledgements

The authors would like to thank Patrycja Pawlik for providing language help and Adrian Chachuła for critical reading and discussion of the manuscript.

References

Baggish, A.L., Hale, A., Weiner, R.B., Lewis, G.D., Systrom, D., Wang, F., Wang, T.J., Chan, S.Y., 2011. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. J. Physiol. 589 (16), 3983–3994.

Baggish, A.L., Park, J., Min, P.K., Isaacs, S., Parker, B.A., Thompson, P.D., Troyanos, C., D'Hemecourt, P., Dyer, S., Thiel, M., Hale, A., Chan, S.C., 2014. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. J. Appl. Physiol. 116 (5), 522–531.

Bannister, A.J., Kouzarides, T., 2011. Regulation of chromatin by histone modifications. Cell Res. 21 (3), 381–395.

Barres, R., Yan, J., Egan, B., Treebak, J.T., Rasmussen, M., Fritz, T., Caidahl, K., Krook, A., O'Gorman, D.J., Zierath, J.R., 2012. Acute exercise remodels promoter methylation in human skeletal muscle. Cell Metab. 15 (3), 405–411.
Bartel, D.P., 2004. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116 (2), 281–297.
Bauer, M., Heeg, K., Wagner, H., Lipford, G.B., 1999. DNA activates human immune cells through a CpG sequence-dependent manner. Immunology 97 (4), 699–705.
Berger, S.L., 2002. Histone modifications in transcriptional regulation. Curr. Opin. Genet Dev. 12 (2), 142–148.
Bestor, T.H., 2000. The DNA methyltransferases of mammals. Hum. Mol. Genet. 9 (16), 2395–2402.
Bogdanović, O., Veenstra, G.J.C., 2009. DNA methylation and methyl-CpG binding proteins: developmental requirements and function. Chromosoma 118 (5), 549–565.
Bouchard, C., 2015. Exercise genomics – a paradigm shift is needed: a commentary. Br. J. Sports Med. 49, 1492–1496.
Chalitchagorn, K., Shuangshoti, S., Hourpai, N., Kongruttanachok, N., Tangkijvanich, P., Thong-ngam, D., Voravud, N., Sriuranpong, V., Mutirangura, A., 2004. Distinctive pattern of LINE-1 methylation level in normal tissues and the association with carcinogenesis. Oncogene 23 (54), 8841–8846.
Chuang, J.C., Jones, P.A., 2007. Epigenetics and microRNAs. Pediatr. Res. 61, 24R–29R.
Ciafre, S.A., Galardi, S., Mangiola, A., Ferracin, M., Liu, C.G., Sabatino, G., Negrini, M., Maira, C.M., Croce, M.G., Farace, M.G., 2005. Extensive modulation of a set of microRNAs in primary glioblastoma. Biochem. Biophys. Res. Commun. 334 (4), 1351–1358.
Çolak, T.K., Acar, G., Dereli, E.E., Özgül, B., Demirbüken, İ., Alkaç, Ç., Polat, M.G., 2016. Association between the physical activity level and the quality of life of patients with type 2 diabetes mellitus. J. Phys. Ther. Sci. 28 (1), 142–147.
Cooper, D.M., Radom-Aizik, S., Schwindt, C., Zaldivar Jr., F., 2007. Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity. J. Appl. Physiol. 103 (2), 700–709.
de Gonzalo-Calvo, D., Dávalos, A., Montero, A., García-González, Á., Tyshkovska, I., Medina, A.G., Díaz-Martínez, Á.E., 2015. Circulating inflammatory miRNA signature in response to different doses of aerobic exercise. J. Appl. Physiol. 199, 124–134.
Delatte, B., Deplus, R., Fuks, F., 2014. Playing TETris with DNA modifications. EMBO J. 33 (11), 1198–1211.
Denham, J., O'Brien, B.J., Marques, F.Z., Charchar, F.J., 2014. Changes in the leukocyte methylome and its effect on cardiovascular related genes after exercise. J. Appl. Physiol. 118, 475–488.
Denham, J., Marques, F.Z., Bruns, E.L., O'Brien, B.J., Charchar, F.J., 2016. Epigenetic changes in leukocytes after 8 weeks of resistance exercise training. Eur. J. Appl. Physiol. 116 (6), 1245–1253.
Ding, W., Li, J., Singh, J., Alif, R., Vazquez-Padron, R.I., Gomes, S.A., Hare, J.M., Shehadeh, L.A., 2014. MiR-30e targets IGF2-regulated osteogenesis in bone marrow derived mesenchymal stem cells, aortic smooth muscle cells, and APOE-/-mice. Circulation 130, A18084.
Eulalio, A., Huntzinger, E., Izaurralde, E., 2008. Getting to the root of miRNA-mediated gene silencing. Cell 132 (1), 9–14.
Fabbri, M., Garzon, R., Cimmino, A., Liu, Z., Zanesi, N., Callegari, E., Liu, S., Alder, H., Costinean, S., Fernandez-Cymering, C., Volinia, S., Guler, G., Morrison, C.D., Chan, K.K., Marcucci, G., Calin, G.A., Huebner, K., Croce, C.M., 2007. MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. Proc. Natl. Acad. Sci. U. S.A. 104 (40), 15805–15810.
Feil, R., Fraga, M.F., 2012. Epigenetics and the environment: emerging patterns and implications. Nat. Rev. Genet. 13 (2), 97–109.
Ferraro, E., Giammarioli, A.M., Chiandotto, S., Spoletini, I., Rosano, G., 2014. Exercise-induced skeletal muscle remodeling and metabolic adaptation: redox signaling and role of autophagy. Antioxid. Redox Signal. 21 (1), 154–176.
Fischle, W., Wang, Y., Allis, C.D., 2003. Histone and chromatin cross-talk. Curr. Opin. Cell Biol. 15 (2), 172–183.
Flück, M., Waxham, M.N., Hamilton, M.T., Booth, F.W., 2000. Skeletal muscle Ca2 +-independent kinase activity increases during either hypertrophy or running. J. Appl. Physiol. 88 (1), 352–358.
Fraga, M.F., Ballestar, E., Paz, M.F., Ropero, S., Setien, F., Ballestar, M.L., Heine-Suñer, D., Cigudosa, J.C., Urioste, M., Benitez, J., Boix-Chornet, M., Sanchez-Aqualera, A., Ling, C., Carlsson, E., Poulsen, P., Vaag, A., Stephan, Z., Spector, T.D., Wu, Y.Z., Plass, C., Esteller, M., 2005. Epigenetic differences arise during the lifetime of monozygotc twins. Proc. Natl. Acad. Sci. U. S. A. 102 (30), 10604–10609.
Gehring, M., Reik, W., Henikoff, S., 2009. DNA demethylation by DNA repair. Trends Genet. 25 (2), 82–90.
Gjevestad, G.O., Holven, K.B., Ulven, S.M., 2015. Effects of exercise on gene expression of inflammatory markers in human peripheral blood cells: a systematic review. Curr. Cardiovasc. Risk Rep. 9 (7), 1–17.
Golbidi, S., Lather, L., 2012. Exercise and the cardiovascular system. Cardiol. Res. Pract. 2012, 210852.
Gregory, R.I., Chendrimada, T.P., Cooch, N., Shiekhattar, R., 2005. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. Cell 123 (4), 631–640.
Grunstein, M., 1997. Histone acetylation in chromatin structure and transcription. Nature 389 (6649), 349–352.
He, Y., Ecker, J.R., 2014. Non-CG methylation in the human genome. Annu. Rev. Genomics Hum. Genet. 16, 55–77.
He, L., Hannon, G.J., 2004. MicroRNAs: small RNAs with a big role in gene regulation. Nat. Rev. Genet. 5 (7), 522–531.
Heneghan, H.M., Miller, N., Lowery, A.J., Sweeney, K.J., Newell, J., Kerin, M.J., 2010. Circulating microRNAs as novel minimally invasive biomarkers for breast cancer. Ann. Surg. 251 (3), 499–505.
Hermann, A., Gowher, H., Jeltsh, A., 2004. Biochemistry and biology of mammalian DNA methylotransferases. Cell. Mol. Life Sci. 61 (19–20), 2571–2587.
Hirasawa, R., Chiba, H., Kaneda, M., Tajima, S., Li, E., Jaenisch, R., Sasaki, H., 2008. Maternal and zygotic Dnmt1 are necessary and sufficient for the maintenance of DNA methylation imprints during preimplantation development. Genes Dev. 22 (12), 1607–1616.
Hoesel, B., Schmid, J.A., 2013. The complexity of NF-κB signaling in inflammation and cancer. Mol. Cancer 12 (1), 1.
Horsburgh, S., Todryk, S., Toms, C., Moran, C.N., Ansley, L., 2015. Exercise-conditioned plasma attenuates nuclear concentrations of DNA methyltransferase 3 B in human peripheral blood mononuclear cells. Physiol. Rep. 3 (12), e12621.
Jjingo, D., Conley, A.B., Soojin, V.Y., Lunyak, V.V., Jordan, I.K., 2012. On the presence and role of human gene-body DNA methylation. Oncotarget 3 (4), 462–474.
Jones, P.A., 2012. Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat. Rev. Genet. 13 (7), 484–492.
Kampert, J.B., Blair, S.N., Berlow, C.E., Kohl, H.W., 1996. Physical activity, physical fitness, and all-cause and cancer mortality: a prospective study of men and women. Ann. epidemiol. 6 (5), 452–457.
Kawagoe, T., Sato, S., Jung, A., Yamamoto, M., Matsui, K., Kato, H., Uematsu, S., Takeuchi, O., Akira, S., 2007. Essential role of IRAK-4 protein and its kinase activity in Toll-like receptor–mediated immune responses but not in TCR signaling. J. Exp. Med. 204 (5), 1.
Keller, C., Steensberg, A., Pilegaard, H., Osada, T., Saltin, B., Pedersen, B.K., Neufer, P. D., 2001. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. FASEB J. 15 (14), 2748–2750.
Khorasanizadeh, S., 2004. The nucleosome: from genomic organization to genomic regulation. Cell 116 (2), 259–272.
Krokan, H.E., Nilsen, H., Skorpen, F., Otterlei, M., Slupphaug, G., 2000. Base excision repair of DNA in mammalian cells. FEBS 476 (1–2), 73–77.
Lagos-Quintana, M., Rauhut, R., Lendeckel, W., Tuschl, T., 2001. Identification of novel genes coding for small expressed RNAs. Science 294 (5543), 853–858.
Lee, S., Vasudevan, S., 2013. Post-transcriptional stimulation of gene expression by microRNAs. Adv. Exp. Med. Biol. 768, 97–126.
Lewis, B.P., Burge, C.B., Bartel, D.P., 2005. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 120 (1), 15–20.
Li, Q.J., Chau, J., Ebert, P.J., Sylvester, G., Min, H., Liu, G., Braich, R., Monoharan, M., Soutschek, J., Skare, P., Klein, L.O., Davis, M.M., Chen, C.Z., 2007. miR-181a is an intrinsic modulator of T cell sensitivity and selection. Cell 129 (1), 147–161.
Li, E., 2002. Chromatin modification and epigenetic reprogramming in mammalian development. Nat. Rev. Genet. 3 (9), 662–673.
Lochmann, T.L., Thomas, R.R., Bennett Jr, J.P., Taylor, S.M., 2015. Epigenetic modifications of the PGC-1α promoter during exercise induced expression in mice. PLoS One 10 (6), e0129647.
Lytle, J.R., Yario, T.A., Steitz, J.A., 2000. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5′ UTR as in the 3′ UTR. PNAS 104 (23), 9667–9672.
Ma, R., Jiang, T., Kang, X., 2012. Circulating microRNAs in cancer: origin, function and application. J. Exp. Clin. Cancer Res. 31 (1), 1.
Mariathasan, S., Newton, K., Monack, D.M., Vucic, D., French, D.M., Lee, W.P., Roose-Girma, M., Erickson, S., Dixit, V.M., 2004. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. Nature 430 (6996), 213–218.
Martinon, F., Tschopp, J., 2004. Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. Cell 117 (5), 561–574.
McFarlin, B.K., Flynn, M.G., Campbell, W.W., Craig, B.A., Robinson, J.P., Stewart, L.K., Timmerman, K.L., Coen, P.M., 2006. Physical activity status, but not age, influences inflammatory biomarkers and toll-like receptor 4. J. Gerontol. A Biol. Sci. Med. Sci. 61 (4), 388–393.
McKinsey, T.A., Zhang, C.L., Lu, J., Olson, E.N., 2000. Signal-dependent nuclear export of a histone deacetylase regulates muscle differentiation. Nature 408 (6808), 106–111.
Miousse, I.R., Koturbash, I., 2015. The fine LINE: methylation drawing the cancer landscape. Biomed. Res. Int. 2015, 131547.
Mitchell, J.B., Dugas, J.P., McFarlin, B.K., Nelson, M.J., 2002. Effect of exercise, heat stress, and hydration on immune cell number and function. Med. Sci. Sports Exerc. 34 (12), 1941–1950.
Mooren, F.C., Viereck, J., Krüger, K., Thum, T., 2014. Circulating microRNAs as potential biomarkers of aerobic exercise capacity. Am. J. Physiol. Heart Circ. Physiol. 306 (4), H557–H563.
Nakajima, K., Takeoka, M., Mori, M., Hashimoto, S., Sakurai, A., Nose, H., Taniguchi, S., 2010. Exercise effects on methylation of ASC gene. Int. J. Sports Med. 31, 671–675.
Niculescu, M.D., Zeisel, S.H., 2002. Diet, methyl donors and DNA methylation: interactions between dietary folate, methionine and choline. J. Nutr. 132 (8), 2333S–2335S.
Nielsen, H.G., 2013. Exercise and Immunity. Current Issues in Sports and Exercise Medicine 121–140.

Nielsen, S., Åkerström, T., Rinnov, A., Yfanti, C., Scheele, C., Pedersen, B.K., Laye, M.J., 2014. The miRNA plasma signature in response to acute aerobic exercise and endurance training. PLoS One 9 (2), e87308.
Nieman, D.C., Johanssen, L.M., Lee, J.W., 1989. Infectious episodes in runners before and after a roadrace. J. Sports Med. Phys. Fitness 29 (3), 289–296.
Nieman, D.C., 1994. Exercise, infection, and immunity. Int. J. Sports Med. 15, 131–141.
Normanno, N., De Luca, A., Bianco, C., Strizzi, L., Mancino, M., Maiello, M.R., Carotenuto, A., De Feo, G., Caponigro, F., Salomon, D.S., 2006. Epidermal growth factor receptor (EGFR) signaling in cancer. Gene 366 (1), 2–16.
Pedersen, B.K., Fischer, C.P., 2007. Beneficial health effects of exercise – the role of IL-6 as a myokine. Trends Pharmacol. Sci. 28 (4), 152–156.
Pedersen, B.K., Ullum, H., 1994. NK cell response to physical activity: possible mechanism of action. Med. Sci. Sports Exerc. 26 (2), 140–146.
Pedersen, B.K., Ostrowski, K., Rohde, T., Bruunsgaard, H., 1998. The cytokine response to strenuous exercise. Can. J. Physiol. Pharmacol. 76 (5), 501–511.
Pedersen, B.K., 2000. Exercise and cytokines. Immunol. Cell Biol. 78, 532–535.
Pekarsky, Y., Santanam, U., Cimmino, A., Palamarchuk, A., Efanov, A., Maximov, V., Volinia, S., Alder, H., Liu, C.G., Rassenti, L., Calin, G.A., Hagan, J.P., Kipps, T., Croce, C.M., 2006. Tcl1 expression in chronic lymphocytic leukemia is regulated by miR-29 and miR-181. Cancer Res. 66 (24), 11590–11593.
Peterson, C.L., Laniel, M.A., 2004. Histones and histone modifications. Curr. Biol. 14 (14), R546–R551.
Radom-Aizik, S., Zaldivar, F., Oliver, S., Galassetti, P., Cooper, D.M., 2010. Evidence for microRNA involvement in exercise-associated neutrophil gene expression changes. J. Appl. Physiol. 109 (1), 252–261.
Radom-Aizik, S., Zaldivar, F., Leu, S.Y., Adams, G.R., Oliver, S., Cooper, D.M., 2012. Effects of exercise on microRNA expression in young males peripheral blood mononuclear cells. Clin. Transl. Sci. 5 (1), 32–38.
Radom-Aizik, S., Zaldivar, F., Haddad, F., Cooper, D.M., 2013. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. J. Appl. Physiol. 114 (5), 628–636.
Radom-Aizik, S., Zaldivar, F.P., Haddad, F., Cooper, D.M., 2014. Impact of brief exercise on circulating monocyte gene and microRNA expression: implications for atherosclerotic vascular disease. Brain Behav. Immun. 39, 121–129.
Rice, J.C., Allis, C.D., 2001. Histone methylation versus histone acetylation: new insights into epigenetic regulation. Curr. Opin. Cell Biol. 13 (3), 263–273.
Robson-Ansley, P.J., Saini, A., Toms, C., Ansley, L., Walshe, I.H., Nimmo, M.A., Curtin, J. A., 2013. Dynamic changes in dna methylation status in peripheral blood Mononuclear cells following an acute bout of exercise: potential impact of exercise-induced elevations in interleukin-6 concentration. J. Biol. Regul. Homeost. Agents 28 (3), 407–417.
Ross, J.P., Rand, K.N., Molloy, P.L., 2010. Hypomethylation of repeated DNA sequences in cancer. Epigenomics 2 (2), 245–269.
Rusca, N., Monticelli, S., 2011. MiR-146a in immunity and disease. Mol. Biol. Int. 2011, 437301.
Sawada, S., Kon, M., Wada, S., Ushida, T., Suzuki, K., Akimoto, T., 2013. Profiling of circulating microRNAs after a bout of acute resistance exercise in humans. PLoS One 8 (7), e70823.
Sikorski, K., Chmielewski, S., Przybył, Ł., Heemann, U., Baumann, M., Wesoły, J.Z., Bluyssen, H.A., 2011. STAT1-mediated signal integration between IFNł and LPS leads to increased EC and SMC activation and monocot adhesion. Am. J. Physiol. Cell Physiol. 300, 1137–1344.
Stewart, L.K., Flynn, M.G., Campbell, W.W., Craig, B.A., Robinson, J.P., Timmerman, K. L., McFarlin, B.K., Coen, P.M., Talbert, E., 2007. The influence of exercise training on inflammatory cytokines and C-reactive protein. Med. Sci. Sports Exerc. 39 (10), 1714–1719.
Strahl, B.D., Allis, C.D., 2000. The language of covalent histone modifications. Nature 403 (6765), 41–45.
Suzuki, M.M., Bird, A., 2008. DNA methylation landscapes: provocative insights from epigenomics. Nat. Rev. Genet. 9 (6), 465–476.
Tak, P.P., Firestein, G.S., 2001. NF-κB: a key role in inflammatory diseases. J. Clin. Invest. 107 (1), 7–11.
Turner, B.M., 2000. Histone acetylation and an epigenetic code. Bioessays 22 (9), 836–845.
Vasudevan, S., Tong, Y., Steitz, J.A., 2007. Switching from repression to activation: microRNAs can up-regulate translation. Science 318 (5858), 1931–1934.
Waddington, C.H., 1942. The epigenotype. Endeavour 1, 18–20.
Walsh, N.P., Gleeson, M., Shepard, R.J., Gleeson, M., Woods, J.A., Bishop, N.C., Fleshner, M., Green, C., Pedersen, B.K., Hoffman-Goetz, L., Rogers, C.J., Northoff, H., Abbasi, A., Simon, P., 2011. Position statement. Part one: immune function and exercise. Exerc. Immunol. Rev. 11, 6–63.
Wang, Z., Wesche, H., Stevens, T., Walker, N., Yeh, W.C., 2009. IRAK-4 inhibitors for inflammation. Curr. Top. Med. Chem. 9 (8), 724–737.
Wang, Y., Xu, Y., Sheng, H., Ni, X., Lu, J., 2016. Exercise amelioration of depression-like behaviour in OVX mice is associated with suppression of NLRP3 inflammasome activation in hippocampus. Behav. Bran Res. 307, 18–24.
White, A.J., Sandler, D.P., Bolick, S.C., Xu, Z., Taylor, J.A., DeRoo, L.A., 2013. Recreational and household physical activity at different time points and DNA global methylation. Eur. J. Cancer 49 (9), 2199–2206.
Wolffe, A., 1998. Chro Matin: Structure and Function. Academic press, Cambridge.
Wu, S.C., Zhang, Y., 2010. Active DNA demethylation: many roads lead to Rome. Nat. Rev. Mol. Cell Biol. 11 (9), 607–620.
Xu, T., Zhou, Q., Che, L., Das, S., Wang, L., Jiang, J., Li, G., Xu, J., Yao, J., Wang, H., Dai, Y., Xiao, J., 2016. Circulating miR-21, miR-378, and miR-940 increase in response to an acute exhaustive exercise in chronic heart failure patients. Oncotarget 7 (11), 12414–12425.
Zhang, Y., Reinberg, D., 2001. Transcription regulation by histone methylation: interplay between different covalent modifications of the core histone tails. Genes Dev. 15 (18), 2343–2360.
Zhang, F.F., Cardarelli, R., Carroll, J., Zhang, S., Fulda, K.G., Gonzalez, K., Vishwanatha, J.K., Morabia, A., Santella, R.M., 2011. Physical activity and global genomic DNA methylation in a cancer-free population. Epigenetics 6 (3), 293–299.
Zhang, Y., Hashimoto, S., Fujii, C., Hida, S., Ito, K., Matsumura, T., Sakaizawa, T., Morikawa, M., Masuki, S., Nose, H., Higuchi, K., Nakijama, K., Taniguchi, S., 2015. NFκB2 gene as a novel candidate that epigenetically responds to interval walking training. Int. J. Sports Med. 36 (9), 769–775.
Zimmer, P., Baumann, F.T., Bloch, W., Schenk, A., Koliamitra, C., Jensen, P., Mierau, A., Hülsdünker, T., Reinart, A., Hallek, M., Elter, T., 2014. Impact of exercise on pro inflammatory cytokine levels and epigenetic modulations of tumor-competitive lymphocytes in Non-Hodgkin-Lymphoma patients-randomized controlled trial. Eur. J. Haematol. 93 (6), 527–532.
Zimmer, P., Bloch, W., Schenk, A., Zopf, E.M., Hildebrandt, U., Streckmann, F., Beulertz, J., Koliamitra, C., Schollmayer, F., Baumann, F., 2015. Exercise-induced natural killer cell activation is driven by epigenetic modifications. Int. J. Sporst Med. 36 (6), 510–515.