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REVIEW ARTICLE

Exercise: Putting Action into Our Epigenome

Joshua Denham · Francine Z. Marques · Brendan J. O'Brien · Fadi J. Charchar

Abstract Most human phenotypes are influenced by a combination of genomic and environmental factors. Engaging in regular physical exercise prevents many chronic diseases, decreases mortality risk and increases longevity. However, the mechanisms involved are poorly understood. The modulating effect of physical (aerobic and resistance) exercise on gene expression has been known for some time now and has provided us with an understanding of the biological responses to physical exercise. Emerging research data suggest that epigenetic modifications are extremely important for both development and disease in humans. In the current review, we summarise findings on the effect of exercise on epigenetic modifications and their effects on gene expression. Current research data suggest epigenetic modifications (DNA methylation and histone acetylation) and microRNAs (miRNAs) are responsive to acute aerobic and resistance exercise in brain, blood, skeletal and cardiac muscle, adipose tissue and even buccal cells. Six months of aerobic exercise alters whole-genome DNA methylation in skeletal muscle and adipose tissue and directly influences lipogenesis. Some miRNAs are related to maximal oxygen consumption (VO_{2max}) and VO_{2max} trainability, and are differentially expressed amongst individuals with high and low VO_{2max}. Remarkably, miRNA expression profiles discriminate between low and high responders to resistance exercise (miR-378, -26a, -29a and -451) and correlate to gains in lean body mass (miR-378). The emerging field of exercise epigenomics is expected to prosper and additional studies may elucidate the clinical relevance of miRNAs and epigenetic modifications, and delineate mechanisms by which exercise confers a healthier phenotype and improves performance.

1 Introduction

The human phenotype is influenced directly, or in combination with, our genes and the environment. There is a genetic predisposition to many diseases [1–4]. Interestingly, little is known as to how environmental stimuli impact our phenotype and what molecular mechanisms are involved.

Epigenetics is the study of changes to gene expression, independently of genotype, that, in certain instances, are trans-generationally heritable. The epigenome consists of a plethora of DNA and chromatin modifications that influence gene expression by performing conformational changes inside the nucleus of cells and governs tissue-specific gene expression [5, 6]. Aberrant epigenetic profiles are associated with numerous diseases [7–9]. Environmental stimuli may induce epigenetic modifications that, in turn, modulate gene expression. Furthermore, microRNAs (miRNAs) impact protein abundance through post-transcriptional regulation of messenger RNA (mRNA), and the expression of numerous miRNAs become dysfunctional with disease [10, 11].

Physical exercise is a financially viable and modifiable lifestyle choice under-utilised by many. The health and fitness benefits conferred by regular aerobic and resistance exercise training include alleviated risk of developing, and reduced severity of, some cardiovascular, metabolic and pulmonary diseases, obesity and certain types of cancer [12–14].

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J. Denham · F. Z. Marques · B. J. O'Brien · F. J. Charchar (✉)
School of Health Sciences, Federation University Australia, Room 228, Y Building, University Drive, Mt Helen, Ballarat, VIC 3350, Australia
e-mail: f.charchar@ballarat.edu.au

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In this review, we discuss data showing the influence that exercise has on DNA methylation, histone acetylation and miRNAs, and their impacts on gene expression and phenotype.

2 Biology of Epigenetic Modifications and MicroRNAs

The interaction of genetic and environmental factors significantly influences human phenotypes, including the susceptibility to many common diseases. Despite the original idea that the human genome is inert and imperturbable to structural changes, epigenetic studies have revealed quite the contrary [15]. The epigenome consists of a plethora of potent gene regulatory mechanisms (histone acetylation, DNA methylation, etc; see Table 1 for definitions of key terms) [16, 17]. Translated, 'epi' means above and 'genome' describes the heritable blueprints of an organism—the DNA. Therefore, these epigenetic modifications function by rearranging the conformation of DNA or the architecture of structures holding DNA (nucleosomes) inside the cell nucleus (Fig. 1). In doing so, they act to encourage or prevent transcription through an intricate interplay of molecular pathways that are, to date, not completely understood [5].

Although numerous epigenetic modifications are known [17], only DNA methylation and histone acetylation have been investigated in context with physical exercise. These include histone acetylation and DNA methylation, discussed below [18–21]. A detailed examination and outline of the intricate pathways involved in signalling epigenetic modifications is outside the scope of this review and have been outlined previously [5, 22]. Moreover, there is great diversity in genetic assays for quantifying miRNA and epigenetic modifications, and these have been described elsewhere [23–27].

2.1 Histone Acetylation

Nucleosomes consist of four, paired histone molecules (H2A, H2B, H3 and H4) and H1 (linker protein), of which approximately 150 base-pairs (bp) of DNA is wrapped around and stored. Epigenetic modifications at histone proteins alters chromatin structure and modulates gene expression, and these are dependent on the location and type of epigenetic modification (acetylation, phosphorylation, deamination, ubiquitylation, sumoylation, etc.), or degree of histone methylation (mono-, di- or tri-methylation) (Fig. 1) [17]. Not all chromatin modifications have been profiled in response to exercise and therefore this review will focus on those previously analysed with exercise, specifically, histone acetylation and DNA methylation. Histone proteins acquire an acetyl group (acetylation) through mechanisms reliant on the enzyme, histone acetyltransferases (HATs); conversely deacetylation is conducted predominantly by deacetylase enzymes (HDACs) (1–11) [28]. Acetylation of histone proteins shifts nucleosome position and, in doing so, either promotes or represses gene transcription by exposing sites necessary for the binding of the transcriptional machinery (Fig. 2) [5].

2.2 DNA Methylation

Another widely studied epigenetic modification is DNA methylation. DNA methylation involves the addition of a methyl group to the fifth carbon of a cytosine neighbouring a guanine nucleobase (CpG,p indicates the phosphate ion

Table 1 Definition of key terms

Chromatin	The elongated and condensed form of DNA housed inside the cell nucleus
DNA methylation	Epigenetic modification encompassing the addition of a methyl group to DNA CpG and non-CpG sites
DNA methyltransferase	Actively performs and catalyses DNA methylation. The methyltransferase enzymes include DNMT1, 3A, 3B and 3L
Epigenome	All epigenetic modifications including DNA methylation and numerous histone modifications described elsewhere [17]. These epigenetic modification all share common characteristics, specifically, they act on DNA or proteins associated with DNA packaging, to manipulate their structure. In doing so, these mechanisms either encourage or repress transcription, depending on the location of the modification
Histone acetylation	The chemical reaction involving the addition of an acetyl molecule to histone proteins
Histone acetyltransferase	Family of enzymes that catalyse histone acetylation
Histone deacetylase	Family of enzymes involved in the removal of acetyl groups from histone proteins
Histone proteins	Constitutes five histone proteins (histone H1, H2A, H2B, H3 and H4) involved in DNA packaging. Four paired histone proteins, H2A, H2B, H3 and H4, form an octamer and contribute to the formation of a nucleosome
Lysine	Protein sites vulnerable to acetylation and methylation changes along histone proteins
MicroRNA	Small non-coding RNA molecule, approximately 18–24 bases in length
Nucleosome	Repeated structural unit for DNA packaging consisting of eight histone proteins

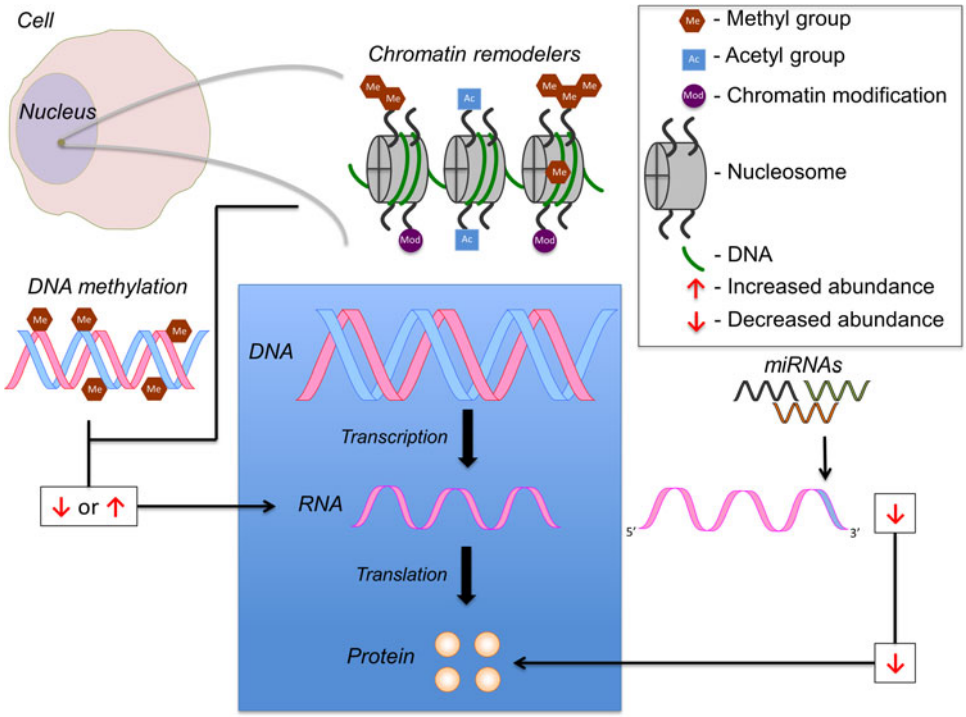

Fig. 1 Impact of epigenetic modifications and microRNAs (miRNAs). DNA is wrapped around an octomer complex, known as a nucleosome, made up of four pairs of histone proteins, plus histone H1 (linker protein). Histone protein sites (e.g. lysines and arginines) are vulnerable to epigenetic modifications, such as acetylation, methylation and several other chemical modifications, which change the formation of chromatin to an open, transcriptionally active or a closed, transcriptionally repressed state. However, DNA methylation directly changes the structure of DNA and, in doing so, allows active transcription or silencing of genes, depending on the location. Although not working above the genome, miRNAs function by mostly targeting specific 3′ untranslated regions (UTR) of messenger RNA (mRNAs) and negatively regulate protein abundance by post-transcriptional regulation of mRNA stability or through the degradation of mRNA molecules. The binding of 5′ UTRs is also possible, leading to either up- or down-regulation of mRNA levels (not shown in figure)

between the nucleobases) [29]. The human genome is predominantly methylated at CpG sites [30, 31], yet unmethylated CpG 'islands' are interspersed in repetitive groups throughout the genome and are most frequently found at the promoter region of genes [31]. Although not as common as CpG sites, non-CpG DNA methylation is possible and may have regulatory roles in cellular functions and tumour pathogenesis [32].

The effect that DNA methylation has on gene expression depends on its location within the genome. DNA methylation at the promoter and enhancer regions of genes is associated with transcriptional repression, whereas the unmethylated state is related to a transcriptionally permissive state [31]. Conversely, DNA methylation within the gene body is associated with active transcription (Fig. 3) [33]. DNA methylation changes the conformational layout of chromatin to a more condensed state, inaccessible to the transcriptional machinery. Moreover, methyl-binding proteins mediate histone modifications and direct DNA methylation cross-talk with histone modifications and also contribute to the DNA methylation-related transcriptional silencing [34, 35].

DNA methylation, in conjunction with other epigenetic modifications, is vital for genomic imprinting, as well as the transcriptional silencing of a single female X-chromosome [36–38]. Moreover, the increased DNA methylation at the promoter regions of tumour suppressor genes and loss of long interspersed repeat sequences (LINE-1) DNA methylation is associated with the pathogenesis of cancer [39–42]. Interestingly, discordant DNA methylation profiles are exhibited between monozygotic twins, who have phenotype discordances and who are otherwise genetically identical [15, 43, 44]. Importantly, epigenetic landscapes are cell-type specific and contribute to the unique gene expression profile [45].

DNA methylation is actively regulated by the enzyme family, DNA methyltransferases (DNMT), consisting of DNMT1, DNMT3A, DNMT3B and DNMT3L (Fig. 3) [46]. Whereas DNMT1 is primarily responsible for replicating DNA methylation in dividing cells [46] and also for chromosomal stability [47], DNMT3A and 3B are required for establishing early embryonic development and corresponding DNA methylation patterns [48]. However, DNMT3L lacks the catalytic activity to methylate CpG

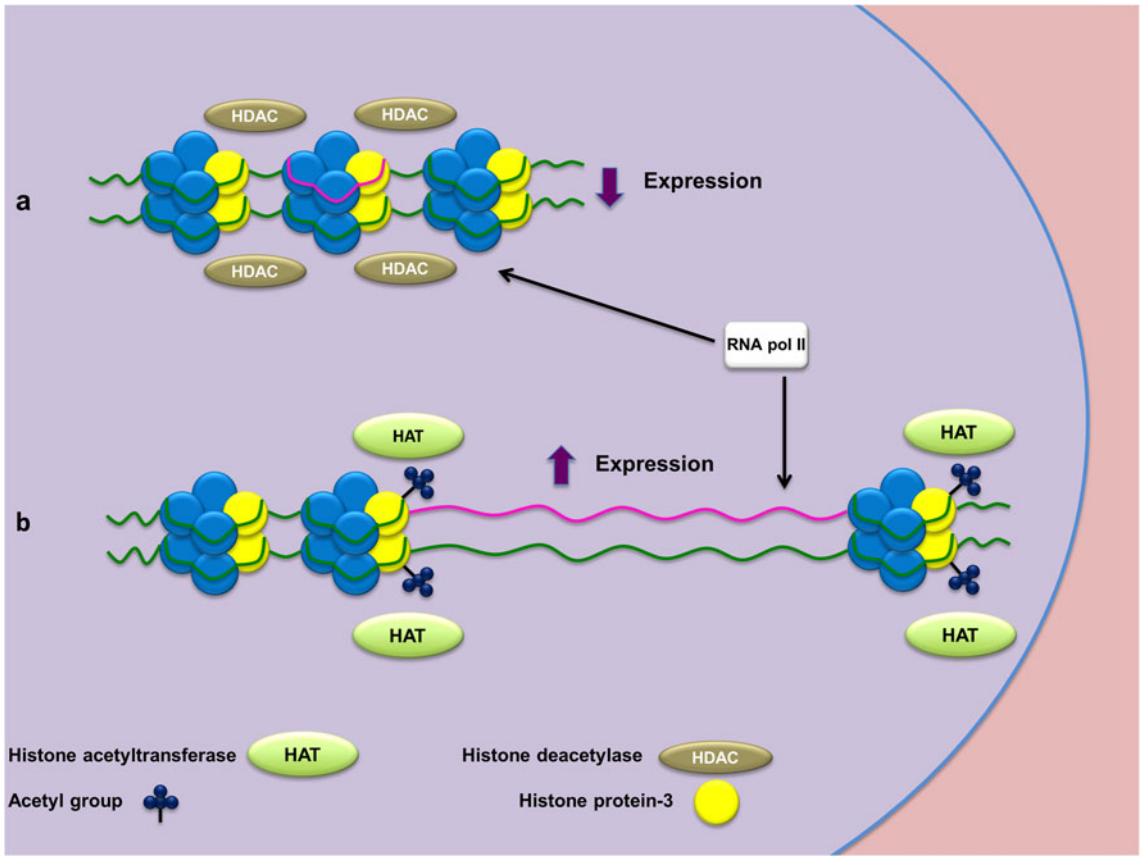

Fig. 2 Mechanisms of action of histone acetylation. **a** A gene (indicated by *pink lines*) is elegantly stored around three nucleosomes. The histone-3 proteins (*yellow circles*) are deacetylated at lysine-9 (H3K9) by histone deacetylase (HDAC) enzymes—an epigenetic mark of transcriptional repression. **b** Two nucleosomes housing a gene have been acetylated at histone-3 lysine-9 (H3K9ac)—an epigenetic mark of transcriptional activation, favouring gene transcription. This epigenetic modification is carried out by histone acetyltransferase (HAT) enzymes

sites but catalyses DNMT3A- and DNMT3B-induced DNA methylation [49]. DNA methylation is conducted by DNMT1 through the acquisition of a methyl group donated by the methyl-donor, *S*-adenosylmethionine [50]. How CpG sites are demethylated is not completely understood, but a number of possible mechanisms have been hypothesised. These include the conversion of carbon 5-methylcytosine to 5-hydroxmethylcytosine by the ten-eleven translocation (TET) proteins 1–3 [51], base excision repair (BER) of 5-methylcytosine, deamination of 5-methylcytosine followed by BER, oxidative DNA demethylation and activation-induced deaminase (AID); these have been discussed in recent reviews [52, 53].

2.3 MicroRNAs

miRNAs are non-coding RNAs approximately 18–24 bases long and they regulate mRNA and/or protein abundance by binding to either the 3′ untranslated region (UTR) of bases 2–7 (seed region) or 5′ UTR of mRNAs [24, 54]. The binding of miRNAs to a 3′ UTR leads to the decrease in the stability of the mRNA, resulting in its degradation, or to the repression of the translation of the mRNA into protein [11]. More recently, the binding of miRNAs to the 5′ UTR of mRNAs has been found to either up- or down-regulate translation [54, 55]. Although some recent investigations have shown that miRNAs are also able to up-regulate gene expression, there are no such examples in the literature related to exercise, and therefore, this will not be discussed in this review.

The miRNA biogenesis is illustrated in Fig. 4. Briefly, RNA polymerase II transcribes a miRNA-coding region, commonly found within genes [56], but also located across the genome [57, 58], thereby producing a primary miRNA (pri-miRNA). The enzyme, Drosha, along with the protein, Di George Syndrome critical region gene 8 (DGCR8), aid the formation of a preliminary miRNA (pre-miRNA) by cleaving the pri-miRNA [59, 60]. Once transported from the cell nucleus to the cytosol by Exportin-5 [61], the pre-miRNA is cleaved a second time by Dicer, consequently making the miRNA/passenger miRNA duplex [62, 63]. The mature, functional miRNA is finally added to the

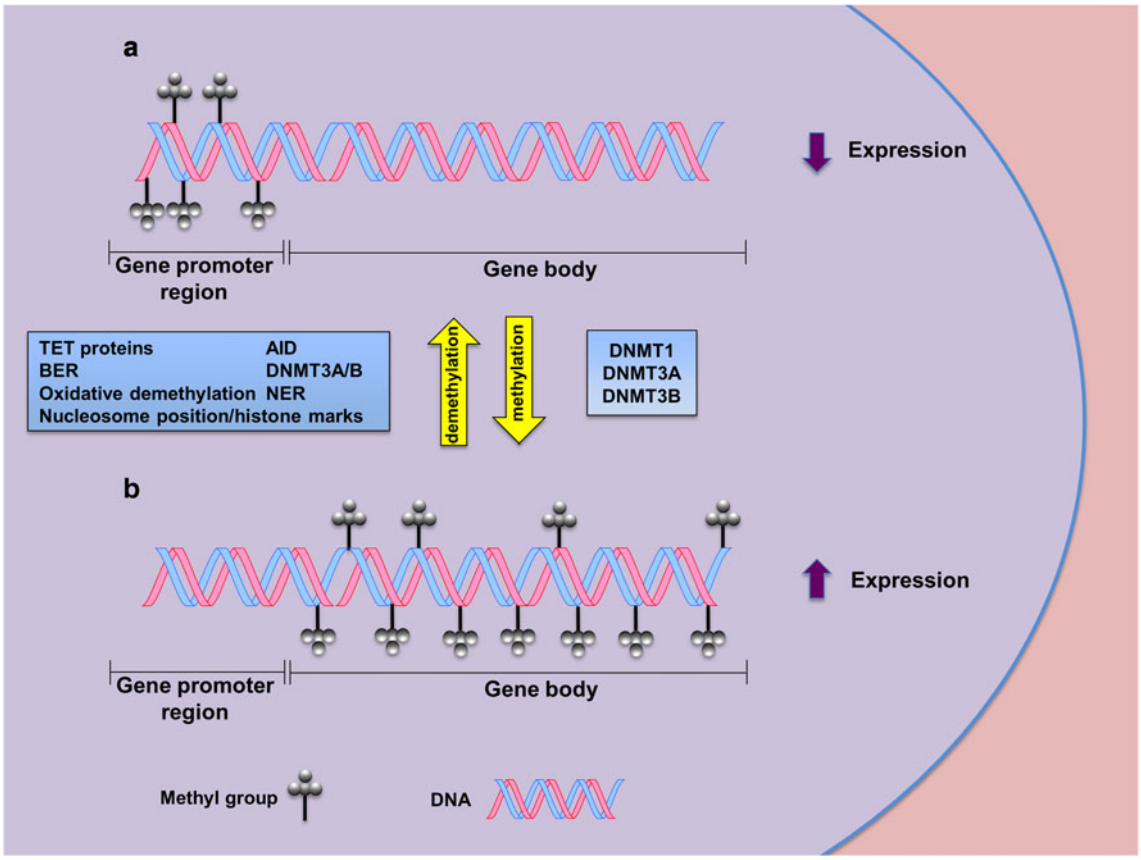

Fig. 3 The effect of DNA methylation on gene expression is dependent on its location within the genome. **a** DNA methylation within a gene's promoter region is associated with transcriptional repression. **b** Conversely, DNA methylation within the gene body is associated with transcriptional active DNA. DNA methylation is actively performed predominantly by DNA methyltransferase-1 (DNMT1), through the transfer of an accepted methyl group from a donating *S*-adenosylmethionine (SAM). However, DNMT3A and 3B are vital for embryonic DNA methylation and early development. Active and passive DNA demethylation is potentially conducted through many mechanisms (for detailed review, readers are referred elsewhere [52, 53]). *AID* activation-induced cytidine deaminase, *BER* base excision repair, *DNMT1* DNA methyltransferase-1, *DNMT3A* DNA methyltransferase-3A, *DNMT3B* DNA methyltransferase-3B, *NER* nucleotide excision repair, *TET* ten-eleven translocation protein (1–7)

RNA-induced silencing complex (RISC) together with an argonaute protein and is now able to regulate translation [64, 65].

Similarly to epigenetic modifications, miRNA expression is cell-type specific [66]. These miRNAs have enormous potential to regulate gene expression, as a single miRNA can have several mRNA targets. They are estimated to target more than 30 % of the genes in the human genome, and over 1,000 miRNAs are identified [67–69]. Dysfunctional miRNA expression is observed in patients with cardiovascular disease, cancer and type 2 diabetes mellitus—[70–72] these are diseases that are also partially prevented and attenuated by regular physical exercise [14].

Potential mRNA targets are predicted by matching their nucleotide sequence to that of a complementary miRNA sequence. Conveniently, databases are available to search for predicted mRNA targets for specific miRNAs using advanced algorithms, such as TargetScan, miRanda, PicTar and microRNA.org. Furthermore, other useful websites and software for miRNA assays and nomenclature include miRBase and MiRConverter, respectively. Notably, it is imperative to validate 'predicted' miRNA target gene transcripts, using luciferase assays or other in vitro experiments; this ensures justified conclusions are made regarding the biological function of the miRNA(s) under investigation. Furthermore, there are numerous technical considerations, such as RNA extraction, platform and house-keeping miRNA selection, when conducting miRNA studies; these have been extensively discussed by others [73–75].

Therefore, epigenetic modifications and miRNAs have the capacity to significantly influence transcription and translation, which may result in physiological and subsequent phenotypic changes. Epigenetic modifications work through an intricate molecular network to either encourage or repress gene expression by performing

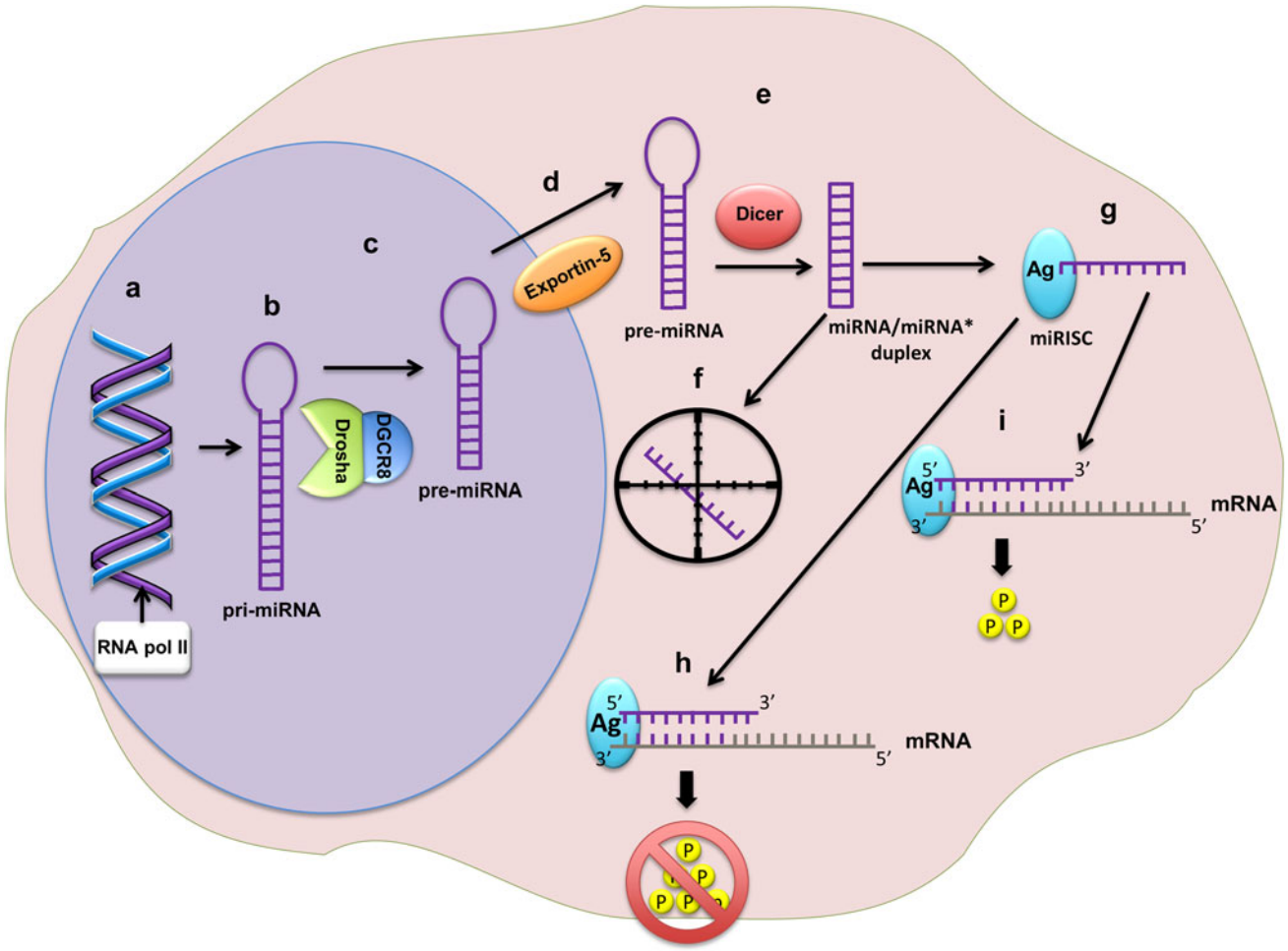

Fig. 4 MicroRNA (miRNA) biogenesis and down-regulation by binding to the 3′ untranslated region (UTR) of a messenger RNA (mRNA). **a** A gene coding a miRNA is transcribed by RNA polymerase II (RNA pol II), **b** producing a primary-miRNA (pri-miRNA). **c** The pri-miRNA is cleaved by the multi-protein complex, Drosha/Di George Syndrome critical region gene 8 (*DGCR8*), creating a preliminary-miRNA (pre-miRNA). **d** The pre-miRNA is transported from the cell nucleus to the cytosol by Exportin-5, **e** where it is further cleaved by Dicer, transforming it into the miRNA/passenger miRNA (miRNA/miRNA*) duplex. **f** The passenger miRNA (miRNA*) can be degraded, or recently it has been suggested to also have a role in mRNA regulation. **g** Any one of several argonaute proteins (Ag) attaches to the mature miRNA, thereby creating the miRNA-induced silencing complex (miRISC) assembly. **h** The miRISC is able to either regulate protein (P) abundance by negative repression of transcribed RNA when the seeding region of the miRNA is partially complementary to the 3′ UTR of the target mRNA (~7 bases in length), or **i** it can lead to mRNA repression and subsequent degradation when the seeding region is completely complementary to the 3′ UTR of the target mRNA

conformation changes to chromatin. Similarly, post-transcriptional gene regulation by miRNAs adds further complexities to the heavily governed expression of genes. Most intriguingly, both epigenetic modifications and miRNAs are associated with human health and disease, and are influenced by physical exercise.

3 The Influence of Exercise on Epigenetic Modifications

Modifiable lifestyle and environmental factors such as diet and exercise significantly influence gene expression, and this is in part orchestrated by epigenetic modifications (see Table 2 for summary of physical exercise-induced epigenetic responses). Here, we review the current literature on the influence that exercise has on histone acetylation and DNA methylation in different cell types.

3.1 Brain

Aerobic physical exercise produces numerous health benefits in the brain. Regular engagement in physical exercise enhances cognitive functioning, increases brain neurotrophic proteins, such as brain-derived neurotrophic factor (BDNF), and prevents cognitive diseases [76–78]. Recent

Table 2 Summary of relevant literature on DNA and histone modifications with physical exercise

Cell type	Participant or animal phenotypes[a,b,c,d,e]	Exercise[f,g,h,i,j]	Main finding	References
Human studies				
Leukocytes	647, 35–74, F	N/A	Highest physical activity level across three time-points associated with increased LINE-1 DNA methylation	White et al. [138]
Leukocytes	509, 70, M + F	N/A	Inverse relationship between physical activity levels and global DNA methylation	Luttropp et al. [139]
Adipocytes	15 (FH^+) vs. 16 (FH^-) of T2D, 37.3, M, SED, 33.1 ± 4.6	Chronic, aerobic (cycle and aerobics), 60, ~2, 6[l]	Changes to DNA methylation of 17,975 CpG sites in response to 6 months of exercise	Ronn et al. [114]
Myocytes	15 (FH^+) vs. 13 (FH^-) of T2D, 37.5 vs. 37.5, M, SED, 32.0 ± 3.5 vs. 33.0 ± 5.3	Chronic, aerobic (cycle and aerobics), 60, ~2, 6[l]	Discordant DNA methylation between men with and without a family history of type 2 diabetes mellitus and unique DNA methylation changes with intervention	Nitert et al. [113]
Leukocytes	24 obese individuals (12 high and 12 low responders), 13-16, M + F	10-week Multidisciplinary weight loss intervention	Differentially DNA methylation at 96 CpG sites between high and low responders after weight loss intervention	Moleres et al. [147]
Buccal cells	37 cases vs. 27 controls, 30.0 vs. 28.4, M + F, SED, 33.6 vs. 32.6[k]	Chronic, exercise promotion intervention [205], ~30, ~5, 12[l]	Average DNA methylation of over 27,000 CpG sites was significantly increased following intervention	Bryan et al. [146]
Buccal cells	237 cases vs. 263 controls, 64.6 vs. 62.6, F, RA (tai chi) vs. U[k]	N/A	Differential DNA methylation over six CpG (two subtelomeric) sites related to ageing in Tai Chi practitioners vs. healthy controls	Ren et al. [18]
Leukocytes	165, 18–78, M + F	N/A	No relationship between physical activity and LINE-1 or *IL-6* promoter DNA methylation	Zhang et al. [116]
Tumour cells	6 cases vs. 6 controls, U, F, SED[k]	Chronic, aerobic, 15–30, 3–5, 6[l]	Exercise intervention altered DNA methylation of 43 genes and of these; six were associated with patient survival	Zeng et al. [119]
Myocytes	14, 25, M + F, SED, 45.2 8, 24, M, SED, 40.2	Acute, aerobic (cycle VO_{2max} test) Acute, aerobic cycle (at either 40 or 80 % of VO_{2max})	Exercise intensity-dependent decrease in global and metabolic gene-specific promoter DNA methylation	Barres et al. [19]
Leukocytes	85, 45.4, M + F	N/A	DNA methylation at two *COMT* promoter regions associated with genotype and physical activity habits	Lott et al. [120]
Leukocytes	77 cases vs. 54 controls, 24.8 vs. 32.3, U, athletic (cases) SED (controls)	N/A	Unique polymorphism frequencies in genes coding enzymes responsible for DNA methylation in elite athletes	Terruzzi et al. [97]
Leukocytes	131, >40, M + F	N/A	26–30 min of moderate-intense physical activity per week associated with greater global DNA methylation (LINE-1) compared to more or less physical activity	Zhang et al. [115]
Leukocytes	23, 77.7, F	N/A	Physical capacity correlated with sub-telomeric DNA methylation and percentage of longer telomeres	Maeda et al. [117]
Leukocytes	Case (old exercising) vs. young control vs. old control, 230 vs. 153 vs. 34, M + F, U, 23.8 vs. 23.8 vs. 41.5	Chronic, aerobic (walking interval training), 52.2, ~4, 6[l]	Marked increase in *ASC* exon 1 CpG island DNA methylation in older adults after 6 month intervention	Nakajima et al. [118]
Myocytes	20, 25, U, 43.5	9 days of bed rest followed by aerobic retraining (chronic), cycling (70 % of VO_{2max}), 30, 6, 4	Four weeks of aerobic exercise training unable to completely alleviate the increased *PPARGC1A* promoter DNA methylation after 9 days of bed rest	Alibegovic et al. [112]
Myocytes	9, 23, M, U, 41	Acute, aerobic (cycling at ~75 % of VO_{2max}), 60	Increased global H3K36ac and removal of HDAC4 and 5 from the cell nucleus after exercise	McGee et al. [20]

Table 2 continued

Cell type	Participant or animal phenotypes[a,b,c,d,e]	Exercise[f,g,h,i,j]	Main finding	References
Breast epithelial cells	45, 43, F	N/A	No statistically significant correlation between physical activity and promoter DNA methylation of tumour suppressor genes—*APC* and *RASSF1A*	Coyle et al. [142]
Brain	Wistar rats, 3 (young) and 20 (old) months, M	Acute and chronic, aerobic (running at 60 % of VO_{2max}), 20 min, 7, 2	Differential effects of acute and chronic exercise-induced changes to H3K9meth and levels of DNMT1 and 3B in young and old rats	Elsner et al. [82]
Brain	C57BL/BJ mice, 46 days, M	Chronic, aerobic (wheel-running), U, 7,1	Increased H3ac and modulated gene expression of DNMTs and HDACs in cerebellum and hippocampus after exercise training	Abel et al. [81]
Brain	Sprague-Dawley rats, ~3 months, M	Chronic, aerobic (wheel-running), U, 7,1	Reduced DNA methylation and increased H3ac in the *Bdnf* promoter region in exercised rats	Gomez-Pinilla et al. [85]
Brain	Wistar rats, 2–3 months, M	Acute and chronic, aerobic (treadmill running), acute and chronic—20 (incremental treadmill exercise), 7 (chronic), 2 (chronic)	Decreased global HDAC activity and higher HAT activity at H4 but not H3 after acute but not chronic exercise	Elsner et al. [86]
Brain	Sprague-Dawley rats, U, M	Chronic, aerobic (wheel running)	Paralleled Increased H3-phospho-ac and c-Fos^+ neurons, coping in response to stress and improved learning strategies in exercised rats 2 h after novel environmental change and after forced swimming	Collins et al. [80]
Myocytes	Wistar rats, U, U	Acute, aerobic (resisted swimming), 5 sets of 17 min with 3 min rest between sets	Increased H3ac near *Mef2* bending site of *Glut4* promoter region	Smith et al. [79]
Brain	Wistar, U, M	Acute, aerobic (swimming)	Increase H3K14ac and c-Fos^+ neurons in exercised rats, peaking 2 h after exercise	Chandramohan et al. [21]

AMP-activated α-1 catalytic subunit, *AMPK* protein kinase, *APS* adenomatous polyposis coli, *ASC* apoptosis-associated spec-like protein containing a caspase recruitment domain, *c-Fos*$^+$ c-Fos-positive, *COMT* catechol-*O*-methyl transferase, *CpG* cytosine-guanine dinucleotide, *DNMT* DNA methyltransferase, *FH* without a family history of, *FH*$^+$ with a family history of, *Glut4* solute carrier family 2 (facilitated glucose transporter), member 4, *HAT* histone acetyltransferase, *HDAC* histone deacetylase, *H3K14ac* histone 3 lysine 14 acetylation, *H3K36ac* histone-3 lysine-36 acetylation, *H3K9meth* histone 3 lysine 9 methylation, *IL* interleukin, *LINE-1* long interspersed nuclear element-1, *Mef2* myocyte enhancer factor 2, *N/A* not applicable, *PPARGC1A* peroxisome proliferator-activated receptor gamma coactivator-α, *RASSF1A* as association (RalGDS/AF-6) domain family member 1,*T2D* type 2 diabetes mellitus, *U* unspecified/unknown data, ~ indicates approximately

[a] Number of subjects or breed of rodent

[b] Age of subjects (years)

[c] Sex of subjects—male (M)/female (F) or both genders (M + F)

[d] Physical activity level—sedentary (SED), recreationally active (RA), athletic, unspecified (U)

[e] Maximal aerobic fitness (VO_{2max}) measured in ml kg min^{-1}

[f] Type of exercise intervention—acute, chronic or acute and chronic exercise or not applicable (N/A)

[g] Mode of exercise—aerobic or resistance exercise

[h] Minutes of exercise training per session

[i] Day/s or sessions of exercise per week

[j] Weeks (or months[l]) of exercise training (if any)

[k] Indicates data from individuals from which the main findings originate

findings highlight a role for aerobic exercise in modulating chromatin remodelers [21, 79–82]. Histone-3 (H3) phosphorylation at serine-10 (Ser10) along with acetylation at lysine-14 (K14ac) was significantly increased in brain tissue (hippocampi) of rats, 15 min following the completion of 10 min of swimming exercise [21]. Histone H3 lysine 14 acetylation (H3K14ac) peaked 2 h after swimming exercise, returning to a non-significant amount 24 h after exercise had ceased. It was mediated by pathways involving the *N*-methyl-D-aspartate receptor, extracellular signal-regulated kinases 1/2, mitogen and stress-related kinase 1 and 2 [21]. These results were the first to demonstrate that acute and relatively short aerobic exercise modulates epigenetic modifications. The transient epigenetic modifications observed due to chronic running training have also been associated with improved learning and stress-coping strategies, epigenetic changes and increased c-Fos-positive neurons in dentate gyrus of rats [80].

BDNF is a protein involved in neurogenesis, brain development and learning [83], and exercise promotes BDNF production [84]. One week of voluntary running caused concurrent increased *Bdnf* mRNA (41 %) and protein (30 %) abundance with significant DNA de-methylation of the *Bdnf* exon 4 promoter region (CpG site, 148 bp downstream) in rat hippocampi [85]. Using chromatin immunoprecipitation (ChIP) assays, the authors revealed exercised rats exhibited marked H3 acetylation (H3ac) but not H4ac, possibly as a result of decreased *Hdac5* mRNA (25 %) and protein (91 %) abundance, and pathways involving cAMP-dependent, catalytic, α-protein kinase (cAMP), response element binding protein (Creb) and Ca^{2+}/calmodulin-dependent protein kinase (Camk) phosphorylation [85]. Histone acetyltransferase and deacetylase enzymes were up- and down-regulated, respectively, following acute but not chronic wheel running [86]. In contrast to previous findings [85], exercise-induced increase in HAT activity was found only on H4 [86]. Others have demonstrated that many of the histone deacetylase and methyltransferase genes are down-regulated by 1 week of voluntary wheel running in conjunction with increased cerebellum and hippocampus H3ac in juvenile mice [87]. Intriguingly, the exercise-induced modulation of epigenetic machinery may be blunted by ageing. At the protein level, Dnmt1 and Dnmt3b were decreased after 20 min of treadmill exercise in young rats only [82]. Unfortunately, the elevated stress experienced by rodents forced to swim or run may potentially confound results on epigenetic modifications found in the brain in response to exercise. Nonetheless, these studies demonstrate the existence of epigenetic changes after acute and chronic exercise and show they are associated with improved cognitive function and elevated markers of neurotrophic factors and neuronal activity (BDNF and c-Fos). These exercise-induced changes seem to be mediated by DNA methylation and histone H3 and H4 modifications through DNMTs (DNMT1 and 3A/B), HATs and HDACs (e.g. HDAC5–8). However, further animal model studies are required to elucidate whether epigenetic modifications and underpinning modifying enzymes are required for the exercised-induced benefits in the brain.

3.2 Skeletal Muscle

An acute bout of interval-training-like exercise (five sets of 17 min swimming efforts with a load equivalent to 3 % of body weight) caused a paralleled elevation in CAMK-2 phosphorylation, H3ac at the myocyte enhancer factor 2 (*Mef2*) on the glucose transporter-4 (*Glut4*) gene, *Mef2a*, *Glut4* mRNA and protein abundance in rat triceps muscle [79]. The authors suggested the molecular alterations observed might be a result of the exercise-induced CAMK-2 activation and, subsequently, higher *Glut4* expression, through accessible binding of *Mef2a* promoting transcription [79]. Notably, others have demonstrated elevated phosphorylated CAMK-2 and epigenetic modifications enhancing transcription after voluntary aerobic exercise in mice and humans [20, 85, 88], supporting a role for CAMK-2-mediated chromatin remodelling. Additionally, epigenetic modifications may regulate muscle gene expression through motor unit recruitment, as neuronal activity modulates Mef2, HDACs and histone modifications in mice [89, 90]. An alternative potential mechanism may be that the transcriptional changes and epigenetic modifications induced by exercise involve the modulated cytosol calcium content, which has been shown to cause paralleled epigenetic and transcriptional changes in C_2C_{12} muscle cells treated with caffeine [91].

Genetic predisposition to athletic performance has been the topic of intense investigation, as many single nucleotide polymorphisms (SNPs) and other molecular biomarkers are associated with muscle growth, endurance performance and trainability [92–96]. DNA methylation was related to muscle growth and endurance performance, with a greater number of genetic polymorphisms associated with enzymes involved in DNA methylation (5,10-methylenetetrahydrofolate reductase, methionine synthase and methionine synthase reductase) found in elite endurance athletes compared with apparently healthy controls [97]. Thus, there may be a heritable predisposition to a less-methylated genetic environment [97]. In vitro analysis using murine C_2C_{12} cells with chemically induced DNA-hypomethylation, confirmed that hypomethylation enhances intermediate and late myocyte differentiation, with myocytes and myotubes exhibiting greater myogenic gene expression and cross-sectional area, respectively [97].

Although human myoblasts were not used for in vitro analyses, these results add compelling evidence suggesting that hypomethylation in differentiating myoblasts may promote muscle growth and maintenance. For further discussion on the role of epigenetic modifications in the adaptation to exercise and performance, readers are referred to other publications [88, 98, 99].

Histone HDACs and HATs regulate the extent of histone acetylation and inevitably gene expression [17]. Moderate- and high-intensity aerobic exercise promotes chromatin remodelling and enzymes responsible for acetylation. Cycling for 60 min at approximately 75 % of peak pulmonary oxygen uptake (VO_{2peak}) increased H3K36ac without H3K9ac and H3K14ac in skeletal muscle of young men [20]. These histone modifications were observed in conjunction with decreased nuclear HDAC4 and 5, along with increased AMP-activated protein kinase (AMPK) and CAMK phosphorylation immediately after exercise [20]. Increased phosphorylation of HDAC4, 5 and 7 was observed immediately after high-intensity exercise (80 % of VO_{2peak}), and was accompanied by phosphorylated AMPK, CAMK, activating transcription factor and acetyl-CoA carboxylase [100], supporting previous results noting AMPK and CAMK involvement in myocyte chromatin remodelling [20]. Moreover, ameliorated HDAC4 protein abundance was reported in young and older humans 6 h following acute resistance exercise in conjunction with altered miRNA dynamics [101], highlighting the interplay between epigenetic modifications and miRNAs in regulating gene expression. Additionally, in men, the miRNA processing enzymes (Drosha, Dicer and Exportin) and HDAC4 protein abundance was increased with modulated myomiRs, including decreased miR-31, in skeletal muscle of young men after acute aerobic exercise [102]. Interestingly, miR-31 expression was further reduced after 10 days of exercise training [102]. Through luciferase assays, miR-31 was demonstrated to bind to and reduce *HDAC4* and *NRF1* mRNA expression—two genes responsible for transcriptional regulation [102]. Indeed, other small non-coding RNAs are involved in DNA methylation by targeting of CpG sites and directing DNA methylation [103, 104].

The physical exercise-induced decrease in specific cancer risk and increased longevity is intensity- and dose-dependent [14, 105–108]. Similarly, physiological adaption to physical exercise is proportional to exercise intensity and volume [14, 109, 110]. An exercise intensity- and dose-dependent relationship was demonstrated at specific promoter regions of genes involved in skeletal muscle metabolism [19]. Acute aerobic-exercise decreased global DNA methylation [19], an indicator that temporarily modulated transcriptional changes caused by exercise may be required for exercised-induced adaptations. Furthermore, the quantification of DNA methylation at CpG sites related to genes involved in metabolism—peroxisome proliferator-activated receptor-γ, coactivator 1-α (*PPARGC1A*), peroxisome proliferator-activated receptor-δ (*PPARD*) and mitochondrial transcription factor-α (*TFAM*) revealed decreased DNA methylation with paralleled increased gene expression after acute exercise [19]. The reduction in DNA methylation described was dependent on exercise intensity, with more intense exercise causing greater post-exercise DNA demethylation [19].

While regular moderate amounts of physical activity confers health benefits, potentially through epigenetic modifications, physical inactivity is detrimental and also may regulate the epigenome [111, 112]. As little as 9 days of physical inactivity (bed rest) is enough to increase insulin resistance and methylation of *PPARGC1A* CpG promoter region [112]. Remarkably, after short-term physical inactivity, physical aerobic re-training did not fully alleviate the bed-rest-induced DNA methylation [112]. Therefore, both acute exercise [19] and 9 days of physical inactivity [112] regulates *PPARGC1A* DNA methylation and gene expression in muscle. These results also advocate the need for maintaining physical activity and highlight the potentially deleterious short-term epigenetic modifications caused by physical inactivity.

The consequences of physical inactivity to health and disease risk are well known (e.g. elevated risk of heart disease, cancer and type 2 diabetes). Interestingly, there are differences in the resting skeletal muscle DNA methylation profile of individuals with and without a family history of type 2 diabetes mellitus [113]. Furthermore, 6 months of aerobic exercise altered DNA methylation in genes involved in unique pathways amongst men with and without a family history of type 2 diabetes mellitus [113]. Of the 21 candidate genes for type 2 diabetes mellitus, two (*THADA* and *RBMS1*) were significantly down-regulated by aerobic exercise [113]. Aerobic exercise training for 6 months also changed whole-genome DNA methylation in adipocytes [114]. Specifically, the aerobic exercise training induced changes in DNA methylation in 24 and 45 CpG sites, corresponding to 18 candidate genes for obesity and 21 for type 2 diabetes mellitus, respectively [114]. Importantly, the authors performed luciferase assays and small interfering RNA (siRNA) in vitro experiments to demonstrate that the exercise-induced increased DNA methylation in the CpG sites relating to the promoter regions of *RALBP1*, *NCOR2* and *HDAC4* down-regulated gene expression and consequently increased lipogenesis [114]. This novel study has provided compelling evidence that suggests adaptations conferred by exercise involves (to a certain extent) epigenetic modifications.

Collectively, the acute and chronic (6 months of aerobic exercise) aerobic exercise training-induced changes to skeletal muscle DNA methylation have been studied.

While the effect of acute aerobic exercise on specific CpG sites in some genes are known, there is scope for the profiling of acute exercise-induced changes to whole-genome DNA methylation. Moreover, acute aerobic exercise influences H3ac [20, 79], but whether these histone modifications and other epigenetic changes directly influence, or are a response to, the exercise-induced changes to phenotype requires explanation. Finally, the analysis of epigenetic changes in skeletal muscle caused by resistance exercise training is also warranted.

3.3 Peripheral Blood

Physical activity and aerobic training alters DNA methylation status of leukocytes [18, 115–120]. Immune system dysfunction can result in chronic low-grade inflammation, which is a hallmark characteristic shared by numerous diseases, including cardiovascular disease, cancer, autoimmune disorders and ageing [121–124]. Regular engagement in aerobic exercise training is associated with the lowering of basal levels of inflammation [125–127], and the mechanisms of this therapeutic effect may be mediated by DNA and chromatin remodelers.

The majority of the human genome is methylated [30, 31], and loss of leukocyte DNA methylation is observed with ageing [15, 128]. Furthermore, loss of DNA methylation and other aberrant DNA methylation signatures are involved in numerous disease pathophysiology and development [129, 130]. Methylation of promoter pro-inflammatory and apoptotic gene, apoptosis-associated spec-like protein containing a caspase recruitment domain—*PYCARD* (*ASC*) —declines with age [118]. However, 6 months of moderate-intense aerobic training attenuated the age-related loss of DNA methylation at CpG islands (exon 1) within the *ASC* gene in older adult circulating leukocytes [118].

Sub-telomeric DNA methylation is important for maintaining telomere dynamics and chromosomal stability. Telomeres are the genetically conserved repeated DNA sequences capping the ends of our chromosomes [131] and are implicated in ageing, chronic disease and mortality risk [132, 133]. Lifestyle factors, such as regular participation in aerobic endurance exercise, are associated with the attenuated telomere length attrition associated with ageing [134]. Physical capacity and improvement in physical capacity is positively correlated with sub-telomeric DNA methylation and with longer telomeres in previously deconditioned older-adult patients with cerebrovascular disease [117]. Tai Chi practitioners exhibit ameliorated epigenetic age-related DNA methylation changes at six specific CpG sites (two located at subtelomeric regions) compared with apparently healthy individuals [18]. For additional comprehensive discussions on exercise-induced epigenetics modifications in relation to ageing and disease, the reader is directed elsewhere [135–137]. While there seems to be a relationship between DNA methylation changes with ageing, whether these are blunted or prevented by exercise requires further clarification.

Notably, those who exercised moderately, defined as 26–30 min per day (measured with accelerometers), demonstrated greater global leukocyte DNA methylation (LINE-1) than those who engaged in less and more physical activity [115]. Self-reported physical activity levels during childhood, adolescence and in the 12 months before sample collection was positively associated with leukocyte LINE-1 DNA methylation in women [138]. Conversely, physical activity (assessed by questionnaires) was not correlated to LINE-1 and interleukin (*IL)-6* promoter-specific leukocyte DNA methylation [116]. Also, average global DNA methylation was inversely related to physical activity levels in older adults (>70 years) [139]. Therefore, additional studies will help validate whether exercise may prevent the risk of cancer by mechanisms involving increased LINE-1 DNA methylation, as loss of LINE-1 DNA methylation is associated with cancer and carcinogenesis [140, 141]. Physical activity seems to be constructive at ameliorating the risk of certain cancers, and it is positively associated with mitigating dysfunction DNA methylation related to cancer [142–145]. A stand-alone, randomized clinical trial demonstrated that 43 genes were differentially expressed as a result of DNA methylation alterations induced by a 6-month, moderate-intense aerobic training intervention [119]. A link was observed between reduced *L3MBTL1* DNA methylation, increased *L3MBTL1* gene expression in blood and tumour samples and patient survival [119]. They suggested that peripheral blood DNA methylation may be a clinically relevant biomarker and reflective of epigenetic changes in other tissues [119].

DNA methylation changes may be a useful tool for monitoring exercise training interventions. Participant VO_{2max} and physical activity levels were correlated to buccal cell DNA methylation at a number of CpG sites located in candidate genes for breast cancer [146]. Moreover, average buccal cell DNA methylation, quantified at over 27,000 CpG sites, significantly increased after a 12-month exercise promotion intervention [146]. Furthermore, an epigenetic score calculated from leukocyte DNA methylation of 97 CpG sites after a 10-week multi-disciplinary health intervention (encompassing physical training, as well as diet and psychological support), related to decreases in body mass index [147].

Together, these studies identified the effects of physical activity levels and long-term (>12 months) exercise training has on leukocyte DNA methylation. Leukocyte DNA methylation changes caused by ageing may be somewhat attenuated by aerobic exercise training, but require further study. Notably, the acute effects of exercise on leukocyte

DNA methylation are yet to be reported. Investigations into histone modifications in leukocytes after exercise are also yet to be studied. Notably, epigenetic changes caused by exercise in differentiated leukocytes are warranted to elucidate the specific biological impacts of these on cell-specific functions. Finally, identifying the sensitivity and the DNA methylation signatures altered by exercise training will further highlight its usefulness in monitoring exercise training.

In summary, short and long-term exercise training results in dynamic changes to DNA methylation and histone modifications in a variety of tissues. To our knowledge, the effects of resistance exercise training on epigenetic modifications have not yet been reported. Delineating the cause or effect relationship between exercise-induced adaptation to phenotype and epigenetic changes will be a challenge for future studies.

4 Are Exercise-Induced Epigenetic Modifications Trans-Generationally Inherited?

Certain epigenetic modifications are passed on to subsequent generations and affect gene expression [148–150]. Not only does the maternal and paternal environment impact on epigenetic modifications and gene expression, but it also influences that of the offspring. Environmental stimuli, such as endocrine disruptors [151, 152] and various diets [150, 153, 154], cause distinct inheritance of epigenetic modifications, which have also been shown to be trans-generationally heritable [148, 152, 154]. For example, a maternal protein-restricted diet throughout pregnancy produced lower hepatic *Ppara* promoter DNA methylation across the next two generations of rats [154]. Similarly, paternal low-protein diet from weaning until sexual maturity caused increased *Ppara* enhancer-region DNA methylation and markedly altered gene expression in mouse offspring compared with normal diet controls [148]. Late-gestational calorie restriction in mice caused decreased placental DNA methylation and transcript expression in genes enriched for metabolic and cardiovascular system developmental pathways when compared with mice fed a normal chow diet [155]. In humans, paternal obesity was inversely correlated with DNA methylation at three CpG sites upstream of exon 3 of the imprinted insulin-like growth factor *(IGF)-2* gene from the umbilical cord blood of newborns [156]. Notably, physical exercise modulates gene expression and DNA methylation of many metabolic genes affected by diet, including some of the peroxisome-proliferator activated receptor-associated genes [19, 113]. Physical exercise may be another environmental stimulus shaping epigenetic modifications and gene expression of not only the individual performing the physical exercise, but also that of their progenies.

5 The Influence of Exercise in miRNA Expression

Contrasting epigenetic mediators, miRNAs also regulate gene expression and protein abundance via post-transcriptional modifications [24]. Of the hundreds (>1,000) of miRNA currently known, a relatively small subset are responsive to acute [157, 158] and chronic [159, 160] physical exercise (refer to Electronic Supplementary Material Table S1 for a comprehensive outline of miRNAs responsive to physical exercise).

5.1 Central Nervous System

The brain and spinal cord are highly plastic tissues. Damage to either organ can result in potential catastrophic and physically debilitating conditions. Aerobic exercise positively regulates neurotrophic factors and has been implicated in the rehabilitation of the central nervous system [161, 162]. Due to the highly invasive nature of collecting neuronal samples or brain tissue, human studies are not feasible. Therefore, rodents have been used. Interestingly, miRNAs have recently been implicated in spinal cord rehabilitation. Spinal cord injury-associated inflammation and apoptosis was attenuated via reduced spinal cord miR-15b and elevated miR-21 after 5, but not 20 days of aerobic exercise in rats [163]. Therefore, initial exercise may be pivotal to preventing spinal cord injury-associated apoptosis and this may, in turn, be regulated by phosphatase and tensin homolog (Pten)/mammalian target of rapamycin (mTor) signalling [163]. Although these results are intriguing, tissue samples were taken 1 h after the last training session, suggesting that the authors were measuring the adaptation to acute response to exercise, which may not be as essential to rehabilitation as the overall training adaptation of miRNAs measured at rest. Nonetheless, attenuated spinal cord miRNA dynamics by exercise is possible and warrants further investigation. The aerobic exercise training-induced changes to miRNA profile in the brain seem to be intensity-dependent [164]. These few studies provide a basis for further exploration into potential miRNAs involved in brain and neuronal development and recovery via aerobic exercise.

5.2 Cardiovascular System

Engaging in regular aerobic exercise causes a concomitant increase in non-pathological left ventricular hypertrophy that can be concentric or eccentric, depending on the mode of exercise and the miRNAs involved (for detailed reviews see papers by Fernandes et al. [165] and Gielen et al. [166]). In contrast with pathological cardiac hypertrophy, non-pathological cardiac hypertrophy induced by physical exercise involves increased sarcolemma adjacent and in

series in the heart muscle, without clinical molecular biomarkers (atrial natriuretic factor or perturbed skeletal muscle α-myosin heavy chain to β-myosin heavy chain ratio) [165]. This contributes to greater heart contractile capacity and subsequently cardiac output, cardiopulmonary efficiency and exercise performance. A 10-week aerobic training intervention caused a dose-dependent reduction in miR-1, -133a and -133b and increased miR-29a and -29c paralleled with cardiac hypertrophy in rats [167], results that were reproducible in different rats [168]. Whether these miRNAs directly affect expression of genes related to the renin–angiotensin system, such as the angiotensin-converting enzyme (*Ace*) and *Ace2*, thereby causing cardiac hypertrophy, is unknown [168]. Moreover, others have shown a role for miRNAs—miR-21, -124, -144 and -145—in phosphoinositide-3-kinase catalytic-α polypeptide (Pik3a)/Akt/mTor signalling pathway-associated non-pathological cardiac hypertrophy after chronic swimming exercise in female rats [169].

Dysfunctional angiogenesis is observed in patients with arteriosclerotic disease [170]. However, aerobic endurance training promotes angiogenesis, which may be, in part, regulated by miRNAs. Treadmill running re-establishes normal expression of miR-16, -21 and -126 in the spontaneously hypertensive rat (SHR), increases biomarkers of vascularisation and decreases blood pressure [171]. miR-126 is paramount for maintaining endothelial integrity, as deletion causes severe endothelial cell dysfunction [172, 173]. Furthermore, angiogenesis is enhanced by aerobic exercise-induced elevation in miR-126 expression, leading to decreased Spred-1 protein and *Pi3kr2* mRNA abundance by regulating mitogen-activated protein kinase (MAPK)-1 and PI3KR2 signalling pathways [174]. These novel findings suggest miR-16, -21 and -126 as targets for blood pressure control and vascular functioning in cardiovascular disease. Notably, miR-21 expression increased after chronic exercise training and was related to non-pathological cardiac hypertrophy [169], as well as blunting of endothelial cell dysfunction and hypertension [171]. Therefore, regulation of miR-21 may be one mechanism by which exercise provides favourable benefits to cardiovascular health and performance. Whether miRNAs are manipulated by exercise to augment lower resting blood pressure in hypertensive humans remains to be determined.

5.3 Skeletal Muscle

5.3.1 Resistance Exercise

Acute resistance exercise causes anabolic gene expression, increasing myocyte transcription factors and protein synthesis [175–177]. By identifying the pathways and molecular mechanisms regulating these muscle growth factors, we may be able to not only ameliorate muscular pathologies (e.g. muscular dystrophies and sarcopenia), but also enhance rehabilitation efficiency and sporting performance. Studies have implicated miRNAs in muscle anabolic mechanisms [101, 178–180], such as miR-1, -26a, -29a, -133a, -378 and -451. However, additional studies are required to validate and further establish the functional biological relevance of these miRNAs.

It is well known that miRNA expression is cell type-specific, and this is consistent with a novel study that indicated differential basal miRNA and pri-miRNA expression between mouse soleus and plantaris muscles [180]. In mice, muscle under mechanically induced functional overload increased expression of pri-miR-1-2, 133a-2 and -206 after 7 days, with concomitant increases in the activity of miRNA-processing enzymes Drosha and Exportin-5, but not Dicer [180]. Along with the observed changes to miRNAs and processing enzymes, there was a 45 % increase in plantaris muscle wet-weight [180]. These early results emphasise that miRNAs are muscle specific, and their involvement in skeletal muscle hypertrophy. Furthermore, these data provide insights into miRNA biogenesis enzyme activity during hypertrophic stimuli.

Sarcopenia is an age-related disease involving the muscle atrophy and the laying down of connective tissue. Indeed, the ability to maintain lean muscle mass is hindered with ageing. Similarly, miRNA dynamics are also disturbed with ageing [181, 182]. In humans, young and older adults' pri-, pre-miRNA expression and miRNA biogenesis enzyme mRNA (Exportin-5 and Drosha) expression differs in response to acute resistance exercise with complementary leucine-enriched essential amino acid ingestion [101]. Interestingly, myocyte miR-1 expression was reduced in young adults and was unchanged in older adults resulting from leg extension resistance exercise (eight sets of ten repetitions, with 70 % of one repetition maximum [1 RM]) with essential amino acid ingestion [101]. miR-1 is a muscle-specific miRNA and a well defined facilitator of muscle cell growth and regeneration [183–185]. Perplexingly, there are no clear patterns of miR-1 expression in response to resistance and aerobic exercise training. Resistance training for 12 weeks attenuated basal miR-1 expression in older adult human volunteers [179]. However, in young men, basal miR-1 expression was unchanged following a similar 12-week resistance training intervention [178]. Acute aerobic endurance exercise up-regulates miR-1 expression [102, 160, 186], and is subsequently down-regulated at basal levels in healthy males after 12 weeks of aerobic exercise training [160]. Others have found increased basal miR-1 and miR-29b expression after 10 days of aerobic exercise training [102]. Conversely, miR-1 expression is attenuated after 7 days of bed-rest and unchanged following acute

one-legged knee extension exercise in men [111]. The function of miR-1 in the adaptation to exercise is therefore unclear, but may be delineated with additional functional, animal and in vitro studies.

Through the analysis of SNPs and gene expression profiles, researchers have differentiated between high and low responders to aerobic exercise, suggesting that genes are correlated to physical performance [92–94, 187, 188]. In an attempt to distinguish genetic predisposition and anabolic response to resistance exercise using miRNAs, young adults were divided into low and high responders according to gains in lean muscle mass and muscle cross-sectional area [178]. Of the 21 miRNAs investigated, miR-378 and -29a were lower and miR-451 was higher in low responders than in high responders [178]. Additionally, miR-378 was significantly correlated with gains in lean body mass [178]. Sedentary behaviour also induced expression changes in subsets of miRNAs (lower miR-1 and -133a [111], miR-107, -221 and -499 [189]). Importantly, miR-499 was validated by luciferase transfection assays to target the transcription factor, *Sox6* [189]. These results provide evidence supporting the involvement of miRNAs in regulating skeletal muscle phenotype through physical inactivity and exercise training. Identifying other miRNAs differentially expressed in high and low responders to exercise, and discovering how these miRNAs function and influence phenotype, are likely to be the next step.

5.3.2 Aerobic Exercise

Data from miRNA arrays has suggested moderate-intense aerobic exercise induces the differential expression of numerous miRNAs, involving pathways such as regulation of transcription, metabolism, cell and muscle development and other cellular processes [94]. The regulation of metabolic genes involved in disease and endurance performance are also mediated by miRNAs. For example, expression of miR-23, predicted to target *Ppargc1a*—the transcriptional co-activator and positive regulator of genes involved in mitochondria activity, glucose and lipid metabolism—is decreased, in conjunction with higher *Ppargc1a* mRNA and protein abundance, in response to prolonged aerobic exercise in mice [186]. Similarly, *Ppargc1a* miRNA-regulating candidate, miR-696, was lower in mouse skeletal muscle after 4 weeks of progressive aerobic exercise training and higher after unilateral hind-limb immobilisation [190]. Cultured myocyte experiments subsequently validated miR-696 as a negative regulator of Ppargc1a protein abundance in C_2C_{12} myoblasts [190]. Whether the stress associated with hind-limb suspension mediated the change to miR-696 is unknown, as stress can modulate miRNA dynamics [191]. *Ppargc1a* is a transcriptional co-activator controlling exercise induced angiogenesis [192], muscle fibre type [193] and mitochondrial biogenesis [194, 195] and, for this reason, is a gene doping candidate for enhancing sporting performance [196]. Downstream molecules of *Ppargc1a* signalling cascade (PDK4 and COXII) are targeted by miR-696, which decreases after aerobic exercise training in mice, thereby contributing to increased fatty acid oxidation and mitochondrial biogenesis [190]. Moreover, through luciferase and in vitro knockdown experiments, miR-494 was validated to target *Tfam* and forkhead box j3 (*Foxj3*) [190]. Acute aerobic endurance exercise increased Tfam and Foxj3 protein abundance, along with increased *Ppargc1a* expression and mitochondrial biogenesis, through lowering miR-494 expression in mice [197].

miRNA biogenesis is regulated by a subset of enzymes with specific roles involved in producing a functional miRNA (Fig. 1). Drosha, DGCR8 and Dicer are unaltered 3 h after an acute prolonged bout of aerobic exercise [186]. However, in mice, Drosha and Exportin-5 are increased in response to mechanically induced functional overload, without changes to Dicer content [180]. Therefore, further studies may elucidate how the miRNA-processing enzymes govern miRNA dynamics with exercise training.

The acute exercise-induced effect of aerobic and resistance exercise is indicative of an immediate damage response, which in turn produces numerous molecular cascades to inevitably cause super-compensation and adaption to the exercise stimulus. This may consequently alter resting miRNA/gene expression profiles and blunt the physiological response to the initial physical exercise stimuli. A 12-week aerobic endurance training intervention caused an ameliorated response to acute exercise-induced miR-1 and -133a expression [160]. Moreover, basal miR-1, -133a/b and -206 expression were also reduced as a result of the aerobic training intervention [160]. However, the reduced basal miRNA expression returned to the pre-exercise profile following 2 weeks without structured physical exercise training [160]. The attenuated miRNA expression may have been a result of increased $\dot{V}O_{2max}$ and more favourable body composition observed in participants [160]. Furthermore, there may be a direct relationship between histone deacetylase activity and miRNAs. In the skeletal muscle of young men, miRNA-processing enzymes (Drosha, Dicer and Exportin) and HDAC4 protein abundance was increased in conjunction with modulated myomiRs, including decreased miR-31, after acute aerobic exercise [102]. Interestingly, basal miR-31 decreased after 10 days of exercise training and it was demonstrated to target and subsequently reduce *HDAC4* and *NRF1* expression—two genes responsible for transcriptional regulation—in vitro [102]. Skeletal muscle biopsies are invasive, and sample collection across multiple timepoints

is sometimes not feasible. However, trends exist between aerobic exercise performance and expression of specific miRNAs from circulating blood.

5.4 Aerobic Exercise Influences miRNAs in Blood

The miRNAs from plasma and serum are indicative of not only immune system function, but they have also been proposed as biomarkers of physical fitness and performance because they originate from numerous tissues and are mobilised into peripheral circulation. Plasma miR-146a and miR-20a predict VO_{2max} and the trainability of VO_{2max}, respectively [159]. Similarly, serum miR-21 and miR-210 are inversely related to VO_{2max} and are more highly expressed in individuals with categorically low VO_{2max} than in those with a high VO_{2max} [198]. It was also found that miR-210 expression alone or combined with miR-21 accounted for 12 and 15 %, respectively, of the variation in VO_{2max} values of 100 individuals [198]. Serum miR-486 was down-regulated after acute and 4 weeks of thrice-weekly cycling; the change in expression was negatively correlated to VO_{2max} [199]. Therefore, miRNAs from blood may be useful biomarkers for exercise capacity and trainability. Plasma miRNAs have been implicated as biomarkers of health and disease risk [200]. Notably, to date, no one has investigated whether physical exercise can attenuate dysfunctional miRNA biomarkers of human disease. Using the miRNAs miR-126 and miR-133 as surrogate biomarkers for endothelial cell and muscle cell damage, respectively, the effects of different exercise modes were investigated [201]. Interestingly, while miR-126 expression was increased after both a maximal cycle ergometer VO_{2max} test (by 2.1-fold) and a 4 h cycle at 70 % of VO_{2max} (4-fold), miR-133 expression increased after resistance exercise training (2.1-fold) [201]. However, after a marathon, both miR-126 and miR-133 expression increased dramatically (3.4-fold and 8.9-fold, respectively) [201]. Although the authors could not account for the potential effects of gender and fitness levels (or physical activity levels) of participants in each of the exercise groups, these results suggest a role for miRNAs in monitoring adverse effects caused by acute exercise. Additionally, positive relationships have been identified between specific miRNAs and cardiovascular risk factors—C-reactive protein (miR-21), aspartate aminotransferase (miR-210), Finish Type 2 Diabetes Risk Score (miR-21) and age (let-7d and miR-103) [198]. Additionally, replication studies are required to reproduce miRNA responses to exercise, to further establish their relevance as biomarkers.

The miRNA profile of differentiated white blood cells represent genes involved in immune processes, cell adhesion and cytokine production, and are more reflective of vascular health and immunity. It was reported that individuals who completed 30 min of intermittent (2 min) bouts of cycling at approximately 76 % of VO_{2max} exhibited altered expression of 38 miRNAs, potentially targeting 4,724 genes in neutrophils [202]. Additionally, 34 miRNAs were altered by the same exercise protocol, including six similarly expressed between neutrophils and leukocytes [157, 202]. Although the authors validated four and seven miRNAs in the consecutive studies, respectively, further studies are required to validate their miRNA mRNA targets. Finally, results from the same laboratory revealed 23 modulated miRNAs and gene expression patterns in natural killer cells as a result of acute aerobic exercise [158]. Specifically, gene pathways altered included those involved in type 1 diabetes mellitus, prostate cancer, chemokine signalling, leukocyte trans-endothelial migration and p53 signalling pathway [158]. Interestingly, after acute aerobic running exercise at 80 % of VO_{2max}, expression of miRNAs—miR-21-5p, -24-2-5p, -27a-5p and -181a-5p—were increased in National-level ski athletes' leukocytes [203]. In silico prediction was employed and showed enrichment for genes involved in metabolic pathways, immune response, transcriptional regulation and apoptosis [203]. Finally, acute resistance exercise increased serum miR-149* and decreased miR-146a and miR-221 expression 3 days after exercise, which, along with other miRNAs were correlated to growth hormone, IGF-1 and testosterone concentration [204]. Interestingly, the resistance exercise-induced change to miR-146a and -221 trended in the opposite direction to that observed after acute aerobic exercise in plasma [159].

Thus, a number of blood miRNAs have been correlated to VO_{2max} and VO_{2max} trainability. Similarly, expression of specific miRNAs is associated with cardiovascular disease risk factors and adverse effects of acute exercise. Their validity and reliability for biomarkers of VO_{2max} and adverse risk factors will require further testing. Furthermore, whether unique miRNA dynamics are perturbed with over-training or over-reaching is unknown. Modulated miRNAs in blood and other tissues will need to be validated and subsequently functionally tested in order to reveal their biological function and make clear interpretations of how they regulate a phenotype through exercise training.

6 Conclusions and Future Directions

Epigenetic modifications and miRNA dynamics become dysfunctional with disease and ageing. While the current evidence supports physical exercise as a modulator of histone acetylation, DNA methylation and expression of various miRNAs, the effects on other epigenetic modifications (eg. histone methylation, sumoylation, deimination and ubiquitylation) are left for investigation. These gene expression

regulators seem to be intensity- and volume-specific. Apart from a single study analysing miRNAs in serum and those analysing skeletal muscle, the effects of resistance exercise on miRNAs in human blood cells and other types of tissues are unknown. Similarly, the effect of resistance exercise on epigenetic modifications in human tissues requires further study. Few studies have validated 'predicted' gene targets and demonstrated a biological function of miRNAs influenced by physical exercise in humans. Data on the effect of exercise on miRNA or epigenetic modifications in clinical or athletic human populations is sparse. Further studies may provide us with molecular (epigenetic, miRNA and gene expression) signatures specific to health benefits conferred by exercise, as well as attenuation of disease. More data on the time-course of epigenetic and miRNA changes caused by exercise are required. Additionally, identification of novel molecular biomarkers in the form of miRNAs and epigenetic modifications may be suitable for monitoring training interventions. The comprehensive study of DNA methylation and other epigenetic modifications in various tissues in response to different modes and volumes (intensity, frequency and duration) of exercise will aid our understanding of the ability of exercise to influence our epigenome. Finally, animal model experiments will help determine the cause or effect relationship between epigenetic modifications and miRNAs with exercise-induced adaptations. The emerging field of exercise epigenomics is expected to prosper, and further studies may elucidate the clinical relevance of miRNA and epigenetic modifications, and demonstrate how exercise benefits health and physical performance.

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