Epigenetics & Chromatin

REVIEW

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Physical exercise and epigenetic modifications in skeletal muscle, brain, and heart

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Abstract

The origins of many diseases can be traced to the dynamic interplay of genetic predispositions and environmental exposures post-birth. Epigenetic modifications have recently gained prominence as a significant mediator between genetic information and environmental factors, influencing the occurrence and progression of disease. There is a burgeoning body of evidence supports that physical exercise, acting as an external environmental stimulus, exerts a discernible impact on major epigenetic modifications, including histone modifications, DNA methylation, RNA methylation, and non-coding RNA. This effect assumes a pivotal role in the pathogenesis of various human diseases. Exploring the epigenetic molecular mechanisms through which physical exercise enhances human health holds the promise of deepening our understanding of how it improves physiological functions, mitigates disease risks, and establishes a theoretical foundation for employing physical exercise as a non-pharmacological intervention in disease prevention and treatment.

Keywords Physical exercise, DNA methylation, Histone modifications, RNA methylation, Non-coding RNA, Skeletal muscle, Brain, Heart

Background

Physical exercise is widely recognized for its profound benefits on both physical and psychological health. It regulates glucose and lipid metabolism, alleviates anxiety and depression, and mitigates cognitive decline, particularly in neurodegenerative diseases like Alzheimer's disease [1, 2]. Exercise also serves a cost-effective and non-pharmacological strategy for preventing cardiovascular diseases and promoting a healthier lifestyle [3]. Despite these established benefits, the precise biological mechanisms underlying the health-promoting effects of physical exercise remain incompletely understood.

Recent research has increasingly highlighted the role of physical exercise as an environmental modulator capable of driving epigenetic changes, which are crucial in fine-tuning gene expression and regulating diverse physiological processes [4–6]. Epigenetic modifications, encompassing DNA methylation, histone modifications, RNA methylation, and non-coding RNAs, mediate heritable changes in gene expression without altering the underlying DNA sequence. These modifications respond dynamically to environmental factors such as diet, chemical exposures, and physical activity and are implicated in the development of various diseases, including cardiovascular disorders, metabolic syndrome, and psychiatric

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conditions [7–9]. The epigenetic changes induced by physical exercise are believed to be a key molecular mechanism underlying the enhancement of physiological functions and the mitigation of disease risks.

Several reviews have provided valuable insights into the interplay between physical exercise and epigenetics, often focusing on specific epigenetic mechanisms or individual tissue types, such as skeletal muscle or the brain [6, 10–15]. Additionally, some reviews have highlighted the therapeutic potential of exercise-induced epigenetic changes in addressing specific diseases, such as cardiovascular or metabolic disorders [16–18]. While these efforts have significantly advanced the field, there remains an opportunity to synthesize findings across tissues and to explore both shared and unique mechanisms in greater detail. In this review, we aim to build on these prior efforts by offering a broader perspective on exercise-induced epigenetic modifications across skeletal muscle, brain, and cardiac tissues. By summarizing current findings and identifying areas that warrant further investigation, we hope to contribute to a more comprehensive understanding of how exercise influences gene expression and its potential to promote health and mitigate disease risks.

Overview of epigenetic changes

DNA methylation

DNA methylation involves DNA methyltransferases (DNMTs) transferring a methyl group from S-adenosyl methionine (SAM) to cytosine bases, primarily at cytosine-phosphate-guanine (CpG) sites. The human genome encodes five main DNMTs: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L. DNMT1 is primarily responsible for maintaining DNA methylation patterns during DNA replication, ensuring the inheritance of methylation marks [19, 20]. DNMT3A and DNMT3B mediate de novo methylation, establishing new methylation patterns during development and in response to environmental stimuli [21–23]. DNMT2 functions as a tRNA transferase, while DNMT3L regulates DNMT3A and DNMT3B activity [24–29]. DNA methylation generates products like 5-methylcytosine (m5C), N4-methylcytosine (m4C), and N6-methyladenine (m6A), with m5C being the most common and stable in eukaryotes. This modification constitutes a reversible process, with enzymes like the demethylase Ten-eleven translocation (TET) orchestrating the iterative oxidation of m5C, gradually generating 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), 5-carboxylcytosine (5caC), and ultimately yielding unmethylated cytosine (C). The effect of DNA methylation on gene expression varies by locus and context, either suppressing or activating transcription depending on the specific situation. Typically, methylation represses gene expression by blocking the transcription machinery, especially in CpG dinucleotides. However, CpG islands in promoters remain unmethylated to allow transcription to start. Methylation in intronic regions can also recruit factors that increase transcription [30–32].

DNA methylation is integral to a multitude of biological processes, encompassing the regulation of gene expression, genomic imprinting, embryonic development, and the preservation of genomic stability [33]. Dysregulation of DNA methylation patterns has been implicated in a spectrum of diseases, spanning neurological disorders, cardiovascular diseases, diabetes, autoimmune diseases, inflammatory disorders, and cancer [34, 35]. Physical exercise has been correlated with modifications in the overall methylation status of DNA in humans, potentially contributing to the preservation of genomic stability [36–38]. Additionally, physical exercise is capable of triggering gene-specific methylation changes in aged human skeletal muscle, predominantly in genes that govern metabolic pathways, inflammatory responses, and oxidative stress [39]. The effects of exercise-induced DNA methylation alterations can vary depending on the tissue involved, highlighting the tissue-specific nature of these impacts.

Histone modification

Histone modifications involve a suite of chemical alterations to histone proteins, which are essential for the dynamic regulation of gene expression. These modifications adjust the three-dimensional architecture of chromosomes, thereby influencing the accessibility of DNA and the overall structure of chromatin. The most prevalent types of histone modifications include acetylation, phosphorylation, methylation, and ubiquitination. These modifications are regulated by various enzymes: histone acetyltransferases (HATs) add acetyl groups to increase chromatin flexibility, histone methyltransferases (HMTs) add methyl groups to activate or repress gene expression, histone deacetylases (HDACs) remove acetyl groups to condense chromatin, and histone demethylases (HDMs) remove methyl groups to activate gene expression.

Histone modifications are collectively referred to as the "histone code," a sophisticated and dynamic regulatory language that cells utilize to modulate gene expression. The specific patterning of these modifications is subject to modulation by a variety of cellular signals and environmental cues, and they are instrumental in fundamental biological processes such as developmental programming, cellular differentiation, and adaptation to external stimuli [40, 41]. Perturbations in the regulation of histone modifications have been associated with a range of diseases, including but not limited to cardiovascular disease, neurological disorders and cancer [42–44]. The relationship between exercise and histone modifications

is complex, but research suggests that exercise may modulate these epigenetic marks. For instance, Elsner et al. observed that exercise elevates the activity of HATs in the hippocampus of rats, while concurrently reducing the activity of HDACs, a shift that favors histone acetylation [45]. The accumulation of certain metabolic byproducts that result from increased exercise intensity, such as lactate, has been shown to inhibit HDAC activity and promote gene expression [46]. These findings suggest that physical exercise may serve as a non-invasive strategy to influence the histone code, with potential implications for disease prevention and health promotion.

RNA methylation

RNA methylation is a key post-transcriptional modification that entails the addition of methyl groups to specific RNA nucleotides, exerting significant influence over RNA stability, splicing, translation efficiency, and the ability of RNA molecules to interact with other cellular components. It regulates RNA at all stages, from synthesis to degradation, and plays a key role in gene expression and cellular processes. Key RNA methylation types include m5C, m6A, m1A (N1-methyladenosine), and m7G (7-methylguanosine), each with distinct effects on RNA function and cellular outcomes. These methylation events are catalyzed by a specific set of enzymes, including methyltransferases that add the methyl groups and demethylases that remove them, creating a dynamic and reversible system. While DNA serves as the carrier of genetic information, RNA modifications add another layer of complexity to the regulation of gene expression. They enable cells to fine-tune their response to internal and external signals, allowing for the adaptation to changing environments and the execution of specialized functions. RNA methylation is thus an essential component of the cellular machinery that ensures the accurate and efficient operation of gene expression programs, contributing to the overall homeostasis and adaptability of the cell.

m6A, a prevalent RNA methylation, plays a significant role in a multitude of physiological processes. This modification involves the methylation of the nitrogen-6 position of adenosine residues within RNA molecules, which is crucial for the regulation of gene expression and cellular function. Disruptions in the precise regulation of m6A are linked to psychiatric disorders, metabolic diseases, and cancer [47]. Physical exercise has been shown to alterations in m6A modification patterns within mRNA transcripts, which in turn can influence key aspects of mRNA metabolism [48]. Exercise-induced changes in m6A contribute to adaptive cellular responses, enhancing metabolism and overall performance. For instance, research has indicated that exercise induces specific changes in m6A modification in genes that are pertinent to metabolic regulation and muscle function [10].

Non-coding RNAs

Non-coding RNAs (ncRNAs) constitute a diverse class of RNA molecules that, despite not encoding proteins, serve critical regulatory functions in the modulation of gene expression. This category encompasses several distinct types, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), each with unique mechanisms of action and biological roles.

MiRNAs are small RNA molecules that typically function as post-transcriptional regulators by binding to the 3' untranslated region (UTR), 5'UTR, or coding sequences of target messenger RNAs (mRNAs). This binding leads to either mRNA degradation or translational repression, depending on the degree of complementarity between the miRNA and its target [49, 50]. Physical exercise has been shown to influence the expression profiles of miRNAs, thereby affecting muscle adaptation, metabolic regulation, and the inflammatory response [51, 52]. This suggests that miRNAs may mediate the adaptive responses to exercise and could be potential targets for therapeutic interventions aimed at enhancing exercise benefits.

LncRNAs are longer RNA molecules that engage in the regulation of gene expression through chromatin remodeling, transcriptional regulation and interaction with other molecules. Physical exercise has been correlated with changes in the expression of specific lncRNAs that are involved in muscle development, metabolic homeostasis, and cardiovascular function [53–55]. These findings highlight the potential of lncRNAs as key mediators of the exercise-induced adaptations that are essential for maintaining health and preventing disease.

CircRNAs represent a novel class of non-coding RNAs with a circular structure that act as miRNA sponges, preventing miRNAs from interacting with target mRNAs. Physical exercise has been observed to induce changes of circRNAs expression in skeletal muscle, brain, and heart in both human and animal studies [56], potentially contributing to its beneficial effects by modulating miRNAs activity and their downstream targets.

Effects of physical exercise on epigenetic changes in specific tissues

Physical inactivity is a pervasive and modifiable risk factor that significantly contributes to the development and exacerbation of various diseases, posing a substantial threat to global public health [57]. Engaging in regular physical activity has profound effects on the human body, extending beyond the immediate physiological responses to exertion. Emerging evidence indicates that physical exercise can modulate the epigenetic mechanisms

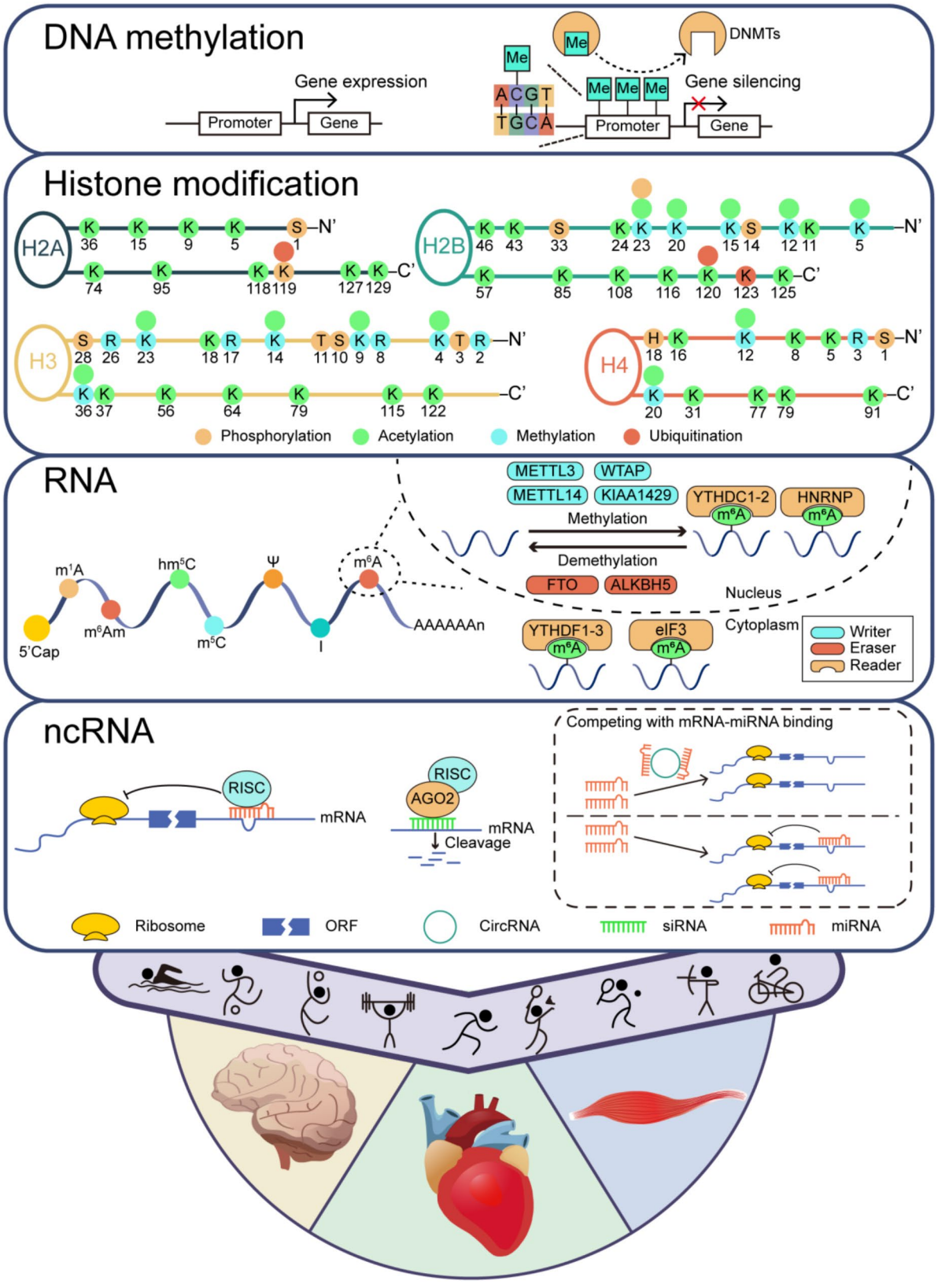

Fig. 1 (See legend on next page.)

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Fig. 1 Exercise induces epigenetic modifications in skeletal muscle, brain and heart. DNA methylation, catalyzed by DNMTs, modulates gene expression through the addition and removal of methyl groups. Histone modifications, including phosphorylation, acetylation, methylation, and ubiquitination on histone tails adjust chromatin compaction, thereby regulating gene accessibility. RNA modifications, particularly m6A methylation, mediated by 'writer' enzymes like METTL3, reversed by 'eraser' enzymes such as FTO, and recognized by 'reader' proteins like YTHDC1-2, critically modulates mRNA stability, translation, and decay. Non-coding RNAs, such as circRNA, miRNA, and siRNA, interact with the RISC complex involving AGO2, to modulate mRNA stability and gene silencing. The nuclear and cytoplasmic distribution of these processes suggests a spatial regulation in response to exercise, collectively contributing to the enhancement of muscle performance, cognitive function, and cardiac health by precisely tuning gene expression. ME = methyl group; DNMTs = DNA Methyltransferases; RISC = RNA-induced silencing complex; AGO2 = Argonaute 2; ORF = Open reading frame

associated with a variety of human diseases [58]. The tissue-specific responses to exercise-induced epigenetic changes underscore the nuanced and targeted impact of physical activity on diverse physiological systems. This review explores the epigenetic regulatory mechanisms of exercise in muscle, brain, and cardiac tissues, elucidating the targeted effects of physical activity on their specific functions (Fig. 1).

In skeletal muscle

Physical exercise has a profound impact on the human body, particularly on the skeletal muscle, by inducing epigenetic changes that influence gene expression and, consequently, metabolism and muscle function. A key exercise-induced modification in skeletal muscle is DNA hypomethylation (Fig. 2A). Barrés et al. first reported that acute exercise induces hypomethylation of key metabolic gene promoters in human skeletal muscle, including peroxisome proliferator-activated receptor-γ coactivator 1α (*PGC1α*), peroxisome proliferator-activated receptor-δ (*PPAR-δ*), and pyruvate dehydrogenase kinase 4 (*PDK4*) [59]. Moreover, they identified that exercise induces hypomethylation at the CpG sites in the promoter region of *PGC1α*, located 337–139 bp upstream from the transcription start site (TSS). Of note, *PGC1α*, a transcriptional coactivator involved in mitochondrial biogenesis and metabolic regulation, is rapidly upregulated in response to physical activity, with its expression modulated by nucleosome positioning and DNA methylation changes [60, 61]. Additionally, exercise-induced demethylation of *PGC1α* has been observed in individuals with spinal cord injuries following long-term electrically induced muscle exercise, suggesting that even populations with limited mobility may experience epigenetic changes in response to exercise [62]. Studies also show that acute aerobic exercise, particularly at higher intensities, promotes the hypomethylation of genes like *NR4A3* (cg11666140 and cg20661548) and *VEGFA* (cg01116220, cg04629501 and cg21099624) [63]. Furthermore, resistance and high-intensity interval exercise (HIIT) similarly induce DNA demethylation of myogenic regulatory factors (e.g., MYOD1, MYF5, and MYF6), with the timing and nature of these changes being dependent on the exercise modality and duration [64]. These findings illustrate how exercise, across different modalities and intensities, induces dynamic and context-specific changes in the skeletal muscle epigenome. Notably, a comparative analysis of acute and chronic resistance exercise, detraining, and retraining by Turner et al. revealed that both hypomethylated and hypermethylated genes are associated with essential functions such as matrix/actin structure remodeling, mechanotransduction, and protein synthesis [65]. Moreover, in a study of healthy aging men, Sailani et al. identified 714 promoter regions with hypomethylation of genes linked to metabolism, myogenesis, contractile properties, and oxidative stress in individuals who had engaged in lifelong exercise, suggesting that sustained physical activity may preserve skeletal muscle function through epigenetic "memory" [39]. These studies underscore the complexity and adaptability of skeletal muscle epigenetic responses to exercise, providing valuable insights into how regular physical activity can modulate gene expression and maintain muscle health throughout life.

Physical exercise modulates glucose homeostasis in skeletal muscle, in part through histone modifications that regulate the expression of key genes involved in glucose uptake (Fig. 2B). One of the primary targets of exercise-induced epigenetic changes is the glucose transporter 4 (GLUT4), which facilitates glucose uptake into muscle cells. Physical exercise upregulates *GLUT4* expression, primarily by promoting histone H3 hyperacetylation at the MEF2 binding domain on the *GLUT4* promoter [66]. This process is further driven by the activation of key signaling molecules, including AMP-activated protein kinase (AMPK) and calcium-calmodulin-dependent protein kinase II (CaMKII), both of which play critical roles in the regulation of metabolic responses to exercise. AMPK activation is enhanced by an increased AMP/ATP ratio and phosphorylation by LKB1 and CaMKK, whereas muscle contraction during exercise increases intracellular calcium levels, which in turn activate CaMKII through the formation of a calcium/calmodulin complex [66–69]. The activation of both AMPK and CaMKII leads to the phosphorylation of class IIa HDACs, specifically HDAC4 and HDAC5, promoting their nuclear export [70, 71]. Gong et al. demonstrated that exercise training results in increased nuclear content of MEF2A and its binding to the *GLUT4* promoter, a process that is dependent on AMPK activity [72]. This observation suggests that the exercise-induced increase in histone H3 acetylation at the MEF2 binding site on

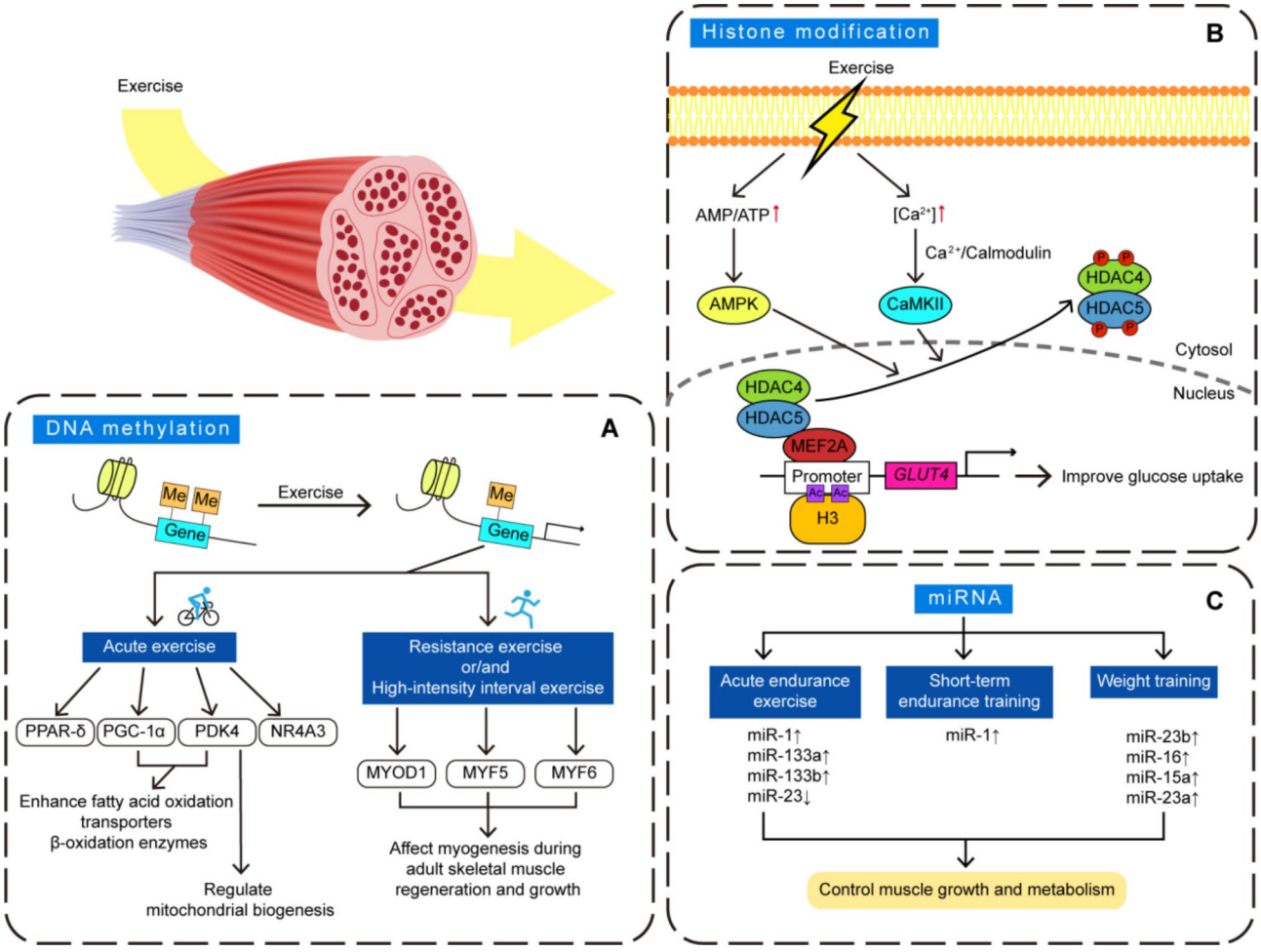

Fig. 2 Exercise-induced epigenetic changes in skeletal muscle. (**A**) DNA Methylation: Exercise induces changes in DNA methylation patterns that regulate gene expression. (**B**) Histone Modification: Exercise increases AMPK activation through AMP/ATP ratio changes and calcium signaling via CaMKII. These pathways lead to the phosphorylation of HDAC4 and HDAC5, which promote MEF2A-dependent activation of the GLUT4 promoter, improving glucose uptake and enhancing metabolic adaptations. (**C**) miRNA Regulation: Different types of exercise, such as acute endurance exercise, short-term endurance training, and weight training, influence the expression of specific miRNAs, which play crucial roles in regulating muscle growth and metabolism

the *GLUT4* promoter is facilitated by the nuclear export of HDAC5, which is mediated by AMPK and CaMKII. Upon activation, AMPK phosphorylates HDAC5, leading to its dissociation from MEF2 and its export from the nucleus [73, 74]. Given that HDAC5 is a potent repressor of MEF2 transcriptional activity when bound to it, its export from the nucleus effectively enhances the acetylation of histones at the *GLUT4* promoter, thereby promoting *GLUT4* expression and improving glucose uptake [75]. Together, these findings highlight the intricate interplay between signaling pathways and histone modifications in regulating *GLUT4* expression during physical exercise. The coordinated actions of AMPK and CaMKII in modifying histone acetylation patterns not only enhance *GLUT4* transcription but also underscore the importance of chromatin remodeling in exercise-induced metabolic adaptations.

In the context of skeletal muscle, miRNAs have been identified that are specifically expressed and functional, collectively termed myomiRs. The myomiRs currently classified include miR-1, miR-133a, miR-133b, miR-206, miR-208a, miR-208b, miR-486, and miR-499 [76]. The expression patterns of myomiRs are influenced by the type, intensity, and duration of physical exercise, reflecting their dynamic role in regulating skeletal muscle responses (Fig. 2C). For instance, acute endurance exercise upregulates miR-1, miR-133a, miR-486, and miR-133b, which are associated with muscle differentiation, metabolism, stress response, and glucose transport, respectively [77–79]. Conversely, miR-23 expression is downregulated after acute exercise, potentially facilitating muscle remodeling and adaptation. These findings highlight the nuanced regulatory roles of myomiRs in orchestrating exercise-induced muscle changes. Beyond acute responses, miRNAs also exhibit unique expression

profiles based on training status, suggesting their utility as biomarkers for training adaptations and athletic performance. For example, a case-control study identified five miRNAs—miR-126, miR-23b, miR-16, miR-23a, and miR-15a—that distinguish powerlifters from healthy controls, underscoring the potential of miRNA signatures to reflect specific training regimens [80]. While numerous exercise-induced changes in miRNA expression have been identified [77, 78, 81–88], the functional implications of these alterations remain under active investigation. Emerging evidence suggests that individual miRNAs act within complex regulatory networks, influencing signaling pathways, gene expression programs, and adaptive responses in skeletal muscle. These networks may regulate key processes such as muscle growth, metabolism, and responses to stress or injury. The continued exploration of exercise-modulated miRNAs offers promising insights into the molecular mechanisms underlying skeletal muscle plasticity and adaptation.

In the brain

Abundant research indicates that physical exercise has the capacity to reprogram the brain's methylation patterns, thereby regulating gene transcription required for maintaining brain health and motor function (Fig. 3A). For instance, rats with spinal cord injuries that underwent 12 weeks of treadmill exercise exhibited the activation of genes and pathways related to DNA methylation and hydroxymethylation in the brain motor cortex [89]. These mediators encompass 5mC, 5hmC, *Tet1*, *Tet2*, *Tet3*, *Dnmt1*, and *Dnmt3a*; where Dnmt1 and Dnmt3A are capable of converting cytosine into 5mC; and 5mC can be hydroxymethylated to 5hmC by Tet1-3 [90]. In a similar vein, forced running in mice alleviated radiation-induced cognitive dysfunction, which was positively correlated with increased *Tet2* content in the hippocampus and elevated 5hmC levels in the promoter region of the brain-derived neurotrophic factor (BDNF) gene [91]. BDNF is a critical neurotrophic factor that is involved in synaptic plasticity, neuronal survival, and the improvement of depressive symptoms [92, 93]. Exercise's capacity to upregulate *Bdnf* expression in the hippocampus is accompanied by DNA demethylation at the *Bdnf* exon IV promoter. Specifically, exercise significantly reduces methylation at a CpG site (-148 bp) in the promoter, as evidenced by a lower unmethylated-to-total clone ratio [94]. Moreover, studies have shown that swimming in rats enhances DNA methylation in brain regions such as the hippocampus, cortex, and hypothalamus, suggesting that exercise can modulate the brain's response to stress [95]. Another study highlighted that DNA methylation in Agouti-related peptide (AgRP) neurons regulates voluntary physical activity, further emphasizing the role of epigenetic modifications in governing exercise behavior and metabolic processes [96]. Collectively, these findings demonstrate how physical exercise exerts profound effects on the epigenome, influencing gene expression and supporting the brain's adaptive responses to injury, stress, and aging.

Numerous studies have demonstrated that exercise-induced acetylation modification in the hippocampus improves depression and cognitive dysfunction (Fig. 3B). One of the mechanisms underlying this process is the increase in ketone bodies, particularly D-β-hydroxybutyrate (DBHB), produced during exercise. DBHB crosses the blood-brain barrier and influences histone acetylation in the hippocampus. Elevated DBHB levels reduce the binding of HDACs such as HDAC2 and HDAC3 to the promoter region of the *Bdnf* gene, thereby increasing histone H3 acetylation and promoting *Bdnf* expression [97]. Swimming have also been shown to mitigate isoflurane-induced neurocognitive deficits by enhancing hippocampal histone acetylation, specifically at H3K9, H4K5 and H4K12 lysine sites, and increasing cAMP-response element-binding protein (CREB)-binding protein (CBP) expression [98]. Further supporting this, Maejima et al. found that four weeks of aerobic exercise in mice increased both HAT and HDAC activities, which, in turn, enhanced *Bdnf* expression and improved cognitive function [99]. Similarly, exercise-induced changes in histone H3 phospho-acetylation and gene expression in the dentate gyrus of rats were associated with improved stress coping abilities [100]. Additionally, both aerobic and resistance exercise counteract age-related declines in histone modifications such as H3K4me3 at the hippocampal *Bdnf* promoter, and modify H3K9ac or H3K4me3 at the *cFos* promoter, thus enhancing transcription [94, 101–103]. Exercise has also been shown to reverse age-related memory decline and reduce inflammatory markers (e.g., TNFα, IL-1β, and NF-kB) in the rat hippocampus, with a concurrent increase in histone H4 acetylation [104]. These findings suggest that exercise-induced changes in histone acetylation may contribute to the improvement of cognitive function and the reduction of neuroinflammation. Interestingly, the effects of exercise on HAT and HDAC activities vary depending on the frequency, intensity, and type of exercise. For example, a single session of acute treadmill exercise in rats results in an immediate reduction in HDAC activity and an increase in HAT activity in the hippocampus, whereas a 2-week long-term treadmill regimen has no significant effect on these enzymes [105]. Voluntary exercise for 7 days reduces the expression of *Hdac5*, *Hdac7*, and *Hdac8*, while 8 weeks of voluntary exercise leads to decreased transcription of *Hdac3* and *Hdac5* [106, 107]. Notably, long-term aerobic exercise activates both HAT and HDAC activities in the hippocampus, suggesting a potential role for epigenetic

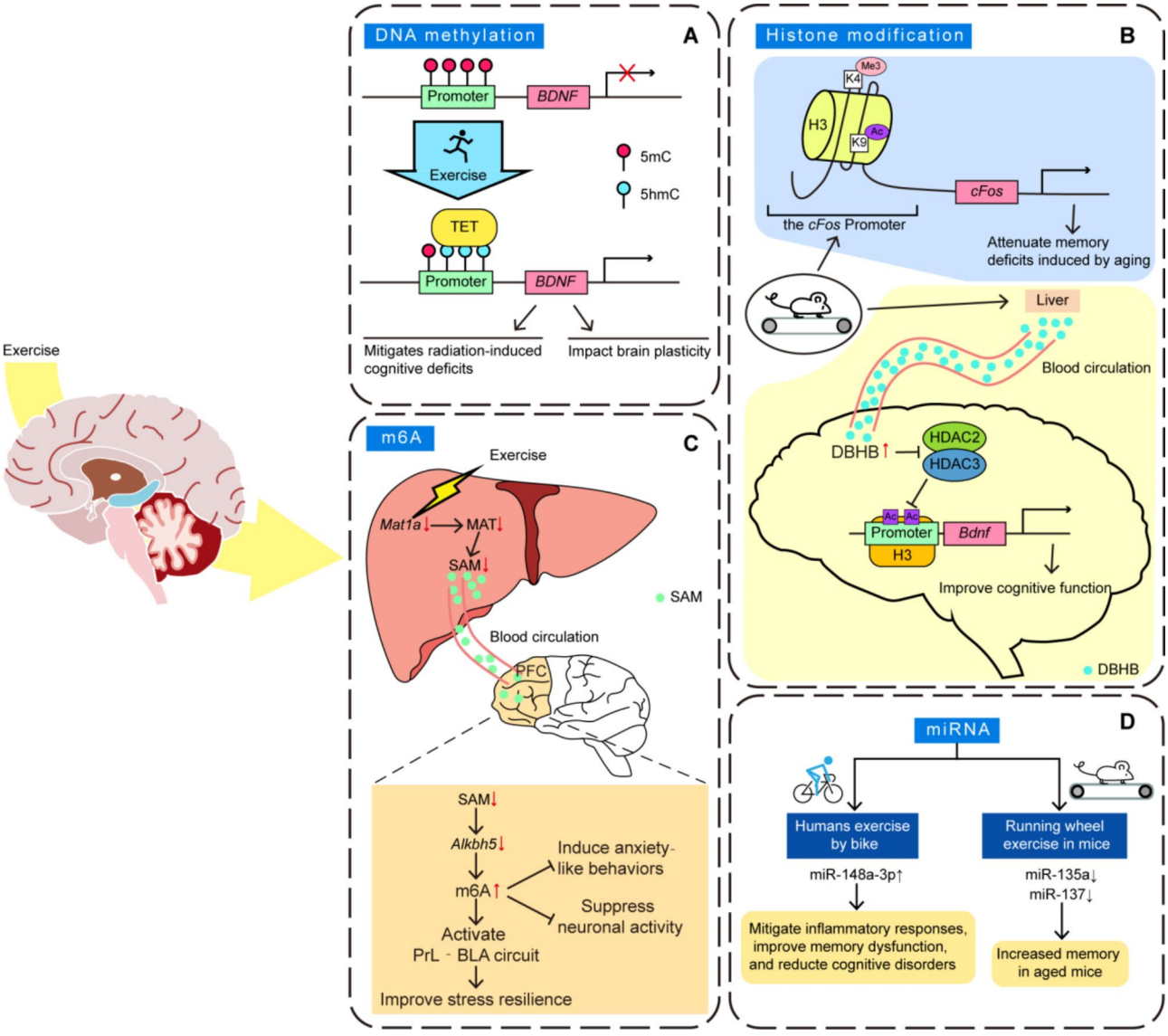

Fig. 3 Exercise-induced epigenetic changes in the brain. (**A**) DNA Methylation: Exercise induces changes in DNA methylation that regulate gene expression, such as in the *BDNF* promoter. (**B**) Histone Modification: Exercise influences histone modifications in various brain regions, such as the *cFos* promoter in the hippocampus, which attenuates memory deficits induced by aging. Additionally, HDAC2 and HDAC3 are involved in promoting *BDNF* expression, enhancing cognitive function via circulating molecules like DBHB. (**C**) m6A RNA Methylation: Exercise affects brain m6A levels through hepatic biosynthesis of SAM, influencing anxiety-like behaviors and neural activity, improving stress resilience. (**D**) miRNA Regulation: Exercise alters the expression of specific miRNAs in the brain

modifications in cognitive improvement [99]. These variations in exercise-induced changes highlight the importance of tailoring exercise modalities to optimize HAT/HDAC activity for cognitive benefits and neuroprotection. Understanding how specific exercise prescriptions affect HAT/HDAC activity and gene expression in the brain offers promising therapeutic avenues for improving brain health, preventing cognitive decline, and mitigating neurodegenerative diseases.

The impact of exercise on RNA modifications, particularly m6A, in the brain is an emerging area of research with significant implications for brain health and function (Fig. 3C). Liu et al. found that long-term exercise training in mice reduces fat mass and obesity-associated protein (FTO) expression in the hypothalamus and hippocampus, increasing m6A-tagged transcripts [108]. Additionally, exercise appears to influence m6A levels in response to environmental stress. For instance, decreased m6A methylation has been linked to anxiety-like behaviors in mice, while physical exercise has been shown to enhance SAM biosynthesis in the liver. This, in turn, increases m6A methylation in the cortex, stabilizing cortical circuits and reducing anxiety-like behaviors [109].

Physical exercise has been recognized for its neuroprotective and cognitive-enhancing effects, with a growing body of research implicating the role of miRNAs in mediating these benefits (Fig. 3D). In individuals with Alzheimer's disease, exercise elevates levels of miR-148a-3p, which is associated with mitigating inflammatory responses, improving memory dysfunction, and reducing cognitive decline [110]. Exercise also downregulates miR-135a, a miRNA that inhibits neural precursor cell proliferation in the dentate gyrus of mice, suggesting a role for exercise in promoting neurogenesis [111]. Another important miRNA, miR-137, is upregulated by exercise, which enhances neurogenesis and memory in aged mice by increasing 5hmC levels at the miR-137 promoter in the hippocampus [112]. This epigenetic modification may boost miR-137 expression, supporting the survival and integration of new neurons and thereby improving memory function. Exercise also influences the hippocampal miRNA-mRNA regulatory network, enhancing memory and upregulating genes that benefit cognitive function [113]. Specific miRNAs, such as miR-409-5p and miR-501-3p, have been identified as key mediators of exercise-induced cognitive improvements, likely by targeting genes involved in synaptic plasticity, neuronal survival, and other processes critical for cognitive health [114].

In the heart

The interplay between exercise, DNA methylation, and cardiac health is a complex and multifaceted area of research that is still being explored. Although direct evidence linking exercise to DNA methylation changes specifically in the heart remains limited, studies in other tissues suggest that exercise-induced epigenetic modifications may confer cardiovascular benefits. One notable example involves the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), a critical component of the inflammasome responsible for activating inflammatory cytokines (Fig. 4A). Dysregulation of the inflammasome and chronic inflammation are strongly associated with various cardiac conditions, including heart failure. Research indicates that the methylation status of the *ASC* gene may play a role in mediating the anti-inflammatory effects of exercise, potentially enhancing aerobic capacity and mitigating inflammation in heart failure patients [115, 116]. Interestingly, an age-related decline in *ASC* gene methylation has been observed, which may contribute to increased systemic inflammation in older individuals. However, long-term moderate exercise appears to counteract this decline by maintaining *ASC* methylation levels, specifically at seven CpG sites preceding exon 1 of *ASC*, thereby reducing excessive secretion of pro-inflammatory cytokine [117]. These findings suggest that regular physical activity not only promotes cardiovascular health but may also mitigate age-associated inflammation by modulating the methylation status of key inflammatory genes like *ASC*, highlighting a potential epigenetic mechanism underlying the cardioprotective effects of exercise.

Physical exercise is increasingly recognized for its ability to modulate cardiac function through the regulation of histone modifications, particularly via the balance of histone acetylation and deacetylation (Fig. 4B). A study by Lehmann et al. highlighted the protective role of the HDAC4 N-terminal fragment (HDAC4-NT) in the heart. They observed that failing hearts exhibit reduced HDAC4-NT levels compared to healthy controls. This fragment suppresses *Nr4a1*, a nuclear orphan receptor, thereby inhibiting the Nr4a1-dependent hexosamine biosynthetic pathway (HBP), which is associated with cardioprotection. Importantly, exercise was shown to enhance HDAC4-NT levels, while deletion of the *Hdac4* gene in cardiomyocytes led to diminished exercise capacity, elevated *Nr4a1* expression, and impaired cardiac contractility [118]. Further evidence links exercise to the regulation of HDACs through O-linked β-N-acetylglucosamine (O-GlcNAc) modifications in the diabetic heart. Exercise increases O-GlcNAc levels and enhances the interaction between the mSin3A/HDAC1/HDAC2 complex and O-linked β-N-acetylglucosamine transferase (OGT) [119]. This interaction suggests a mechanism by which exercise modulates HDAC activity to mitigate diabetic heart hypertrophy. In addition to these findings, recent animal studies have uncovered a novel mechanism by which exercise can improve cardiac function in heart failure. Specifically, the research has shown that during exercise, myocardial AMPK becomes activated and phosphorylates HDAC4. This phosphorylation reduces HDAC4's inhibitory effect on MEF2a, a transcription factor involved in the regulation of cardiac genes. The increased phosphorylation of HDAC4 also leads to an increase in the acetylation level of histone H3K9 at the promoter of the glucose transporter 1 (Glut1) gene, resulting in upregulated *Glut1* expression [120]. This upregulation contributes to the improvement of both cardiac function and glucose metabolism in mice with heart failure.

Exercise has been shown to significantly modulate miRNA expression in cardiac tissues, contributing to beneficial adaptations in heart function (Fig. 4C). Among the most studied miRNAs, miR-1 is upregulated following aerobic exercise in both humans and rats, enhancing cardiac contractility and promoting structural and functional remodeling of the heart [121–123]. Similarly, miR-133a levels increase in response to endurance exercise, such as marathons, and exercise training can mitigate diabetes-induced cardiac damage by modulating the pro-apoptotic and anti-apoptotic balance [124–126]. These

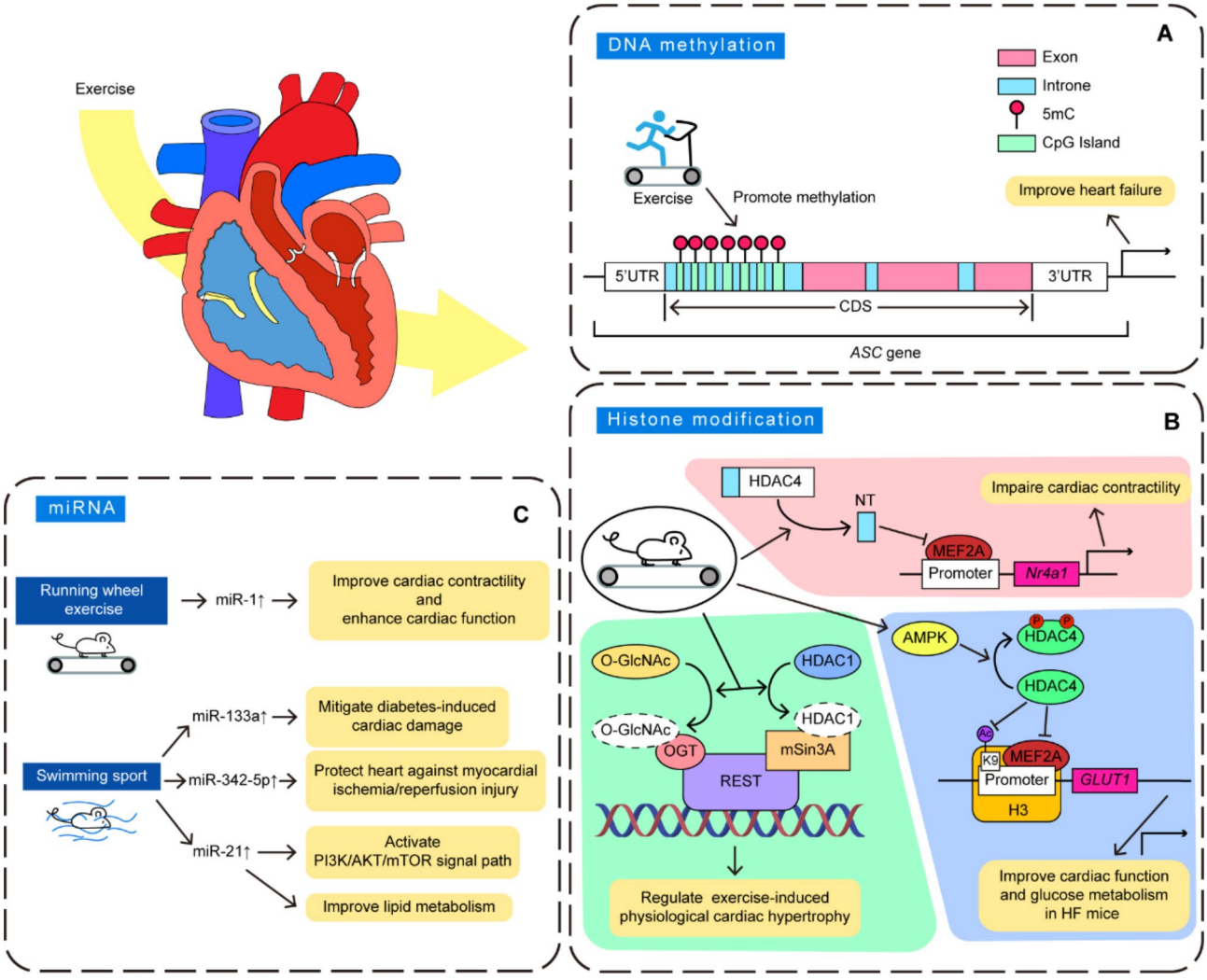

Fig. 4 Exercise-induced epigenetic changes in the heart. (**A**) DNA Methylation: Exercise influences methylation status of the *ASC* gene, thereby regulating its expression and improving heart failure. (**B**) Histone Modification: Exercise triggers histone modifications that affect cardiac function. (**C**) miRNA Regulation: Specific types of exercise, such as running wheel and swimming, modulate the expression of certain miRNAs that play crucial roles in cardiac health

findings suggest miR-133's protective role against pathological cardiac remodeling, particularly under stress conditions like diabetes. MiR-21 is another key miRNA that is upregulated by various forms of exercise, including HIIT and aerobic exercise [127–129]. The upregulation of miR-21 has been associated with several beneficial effects, such as the downregulation of programmed cell death protein 4 (PDCD4), which can mitigate apoptosis, and the improvement of lipid metabolism, which can be particularly beneficial in conditions like hyperlipidemia and heart failure [129, 130]. Furthermore, the cardioprotective effects of miR-21 have been observed in heart failure patients undergoing swim training and cardiopulmonary exercise tests [128, 131]. The increased expression of miR-21 in these contexts suggests that it may contribute to the improvement of cardiac function and the mitigation of heart failure symptoms. Beyond the recognized miRNAs, miR-342-5p, a novel exerkine, is upregulated by long-term exercise and transported to the heart via exosomes, where it protects cardiomyocytes from apoptosis and mitigates ischemia/reperfusion injury [132].

Conclusion

This review emphasizes the pivotal role of physical exercise in modulating the epigenome, with profound effects on skeletal muscle, brain, and heart tissues. Through the induction of DNA methylation, histone modifications, RNA methylation, and alterations in non-coding RNA expression, exercise orchestrates tissue-specific gene expression changes that underpin physiological adaptations essential for metabolic regulation, cognitive function, and cardiovascular health.

The evidence highlights the complexity and context-dependent nature of exercise-induced epigenetic modifications. In skeletal muscle, DNA hypomethylation of key metabolic genes such as *PGC1α* and *GLUT4* enhances metabolic processes and muscle adaptation. Histone modifications, regulated by AMPK and CaMKII, drive chromatin remodeling, supporting long-term muscle health. In the brain, exercise promotes neuroplasticity through DNA demethylation and histone acetylation of BDNF, with miRNAs like miR-137 influencing neurogenesis and memory. In cardiac tissue, exercise modulates HDAC4 activity and miRNAs such as miR-1 and miR-21 to improve cardiac function and mitigate pathological remodeling.

These findings provide compelling evidence for the potential of exercise as a non-pharmacological intervention that modulates the epigenome to promote health. While the correlations between exercise-induced epigenetic changes and health outcomes are well-documented, understanding the causality and variability in these responses remains a challenge. Future research should focus on elucidating the molecular pathways linking these epigenetic modifications to health outcomes, enabling the development of targeted interventions that optimize the benefits of exercise. Longitudinal studies and advanced genomic technologies are essential for capturing the full spectrum of exercise-induced epigenetic changes.

The temporal dynamics of exercise-induced epigenetic changes, particularly across the lifespan, warrant further investigation. Early-life exercise has been shown to provide long-term immunometabolic benefits [133], while maternal exercise may improve vascular health in offspring [134, 135], underscoring the transgenerational effects of physical activity. Optimizing early-life and maternal exercise interventions holds promise for improving long-term health outcomes. Individual variability in epigenetic responses to exercise also presents a significant research challenge. Understanding how factors such as exercise modality, intensity, and duration interact with individual genetic and epigenetic profiles is critical for personalizing exercise interventions.

In conclusion, the epigenetic effects of exercise offer promising avenues for improving health and preventing disease. As research progresses, personalized approaches to exercise may become a cornerstone of preventive healthcare, unlocking the full potential of physical activity in enhancing quality of life and extending healthspan.

Abbreviations

DNMTs	DNA methyltransferases
SAM	S-adenosyl methionine
CpG	Cytosine-phosphate-guanine
m5C	5-methylcytosine
m4C	N4-methylcytosine
m6A	N6-methyladenine
TET	Ten-eleven translocation
5hmC	5-hydroxymethylcytosine
5fC	5-formylcytosine
5caC	5-carboxylcytosine
C	Cytosine
HATs	Histone acetyltransferases
HMTs	Histone methyltransferases
HDACs	Histone deacetylases
HDMs	Histone demethylases
m1A	N1-methyladenosine
m7G	7-methylguanosine
ncRNAs	Non-coding RNAs
miRNAs	microRNAs
lncRNAs	Long non-coding RNAs
circRNAs	Circular RNAs
UTR	Untranslated region
mRNAs	Messenger RNAs
PPARGC1A	Peroxisome proliferator-activated receptor-γ coactivator 1 A
PPAR-δ	Peroxisome proliferator-activated receptor-δ
PDK4	Pyruvate dehydrogenase kinase 4
MEF2	Myocyte enhancer factor 2
GLUT4	Glucose transporter 4
CaMKII	Calcium-calmodulin-dependent protein kinase II
AMPK	AMP-activated protein kinase
BDNF	Brain-derived neurotrophic factor
AgRP	Agouti-related peptide
DBHB	D-β-hydroxybutyrate
CREB	cAMP-response element-binding protein
CBP	CREB-binding protein
FTO	Fat mass and obesity-associated protein
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain
HDAC4-NT	HDAC4 N-terminal fragment
HBP	Hexosamine biosynthetic pathway
O-GlcNAc	O-linked β-N-acetylglucosamine
OGT	O-linked β-N-acetylglucosamine transferase
Mef2a	Myocyte enhancer factor 2a
Glut1	Glucose transporter 1
HIIT	High-intensity interval training
PDCD4	Programmed cell death protein 4

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Declarations

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