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Oxidative stress and metabolism meet epigenetic modulation in physical exercise☆

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ABSTRACT

Physical exercise is established as an important factor of health and generally is recommended for its positive effects on several tissues, organs, and systems. These positive effects come from metabolic adaptations that also include oxidative eustress, in which physical activity increases ROS production and antioxidant mechanisms, although this depends on the intensity of the exercise. Muscle metabolism through mechanisms such as aerobic and anaerobic glycolysis, tricarboxylic acid cycle, and oxidative lipid metabolism can produce metabolites and co-factors which directly impact the epigenetic machinery. In this review, we clearly reinforce the evidence that exercise regulates several epigenetic mechanisms and explain how these mechanisms can be regulated by metabolic products and co-factors produced during exercise. In fact, recent evidence has demonstrated the importance of epigenetics in the gene expression changes implicated in metabolic adaptation after exercise. Importantly, intermediates of the metabolism generated by continuous, acute, moderate, or strenuous exercise control the activity of epigenetic enzymes, therefore turning on or turning off the gene expression of specific programs which can lead to physiological adaptations after exercise.

1. Introduction

A variety of phenomena throughout the life of human beings (e.g., nutrition, disease, infections, physical exercise, environmental conditions, etc.) produce oxidative stress, modify redox homeostasis, and generate metabolic adaptations, and epigenetic changes which in turn directly affect all cells and tissues [1–3]. Several metabolic intermediates generated during glycolysis, the flux of the tricarboxylic acid (TCA) cycle, and mitochondrial oxidative phosphorylation (OXPHOS) have been reported to connect cell metabolism with gene expression regulation through epigenetic mechanisms.

Regular physical exercise, together with a balanced diet and a healthy lifestyle, is established as an important factor of health and is generally recommended for its positive effects on the immune system, musculoskeletal system, and essential metabolic functions [4]. Adversely, oxidative stress and inflammation are recognized as main contributors to disease. However, oxidative stress is also related to physiological adaptation, not only by direct oxidation of biomolecules and enzymes but also by altering redox signaling [5] and cellular metabolism, including the TCA cycle [6,7], the methionine cycle [8], OXPHOS [9], among others. Similarly, inflammation is also a physiological response of the organism to harmful stimuli, but when it persists and becomes chronic it can cause cell and tissue damage. Importantly, both oxidative stress and inflammation are two very related and interdependent processes [10]. Notably, physical exercise, one of the main physiological adaptative processes, has been demonstrated to be one of the strategies to improve and antioxidant defenses, thus physical exercise is recommended for preventing or reducing several pathological disorders [4]. Analogously, physical exercise has been demonstrated to reduce inflammation (*i.e.,* interleukin-6 (IL-6)) at the cellular and tissue level due to the anti-inflammatory effect (*i.e.,* interleukin-10 (IL-10)) of regular and moderate exercise [11,12]. In fact, physical activity has been proposed as a beneficial intervention for several chronic diseases of the pulmonary and cardiovascular system, metabolic disorders, muscle,

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bone, and joint injuries-related diseases, and cancer, as well as neuropsychiatric disorders, among others [4,13,14]. However, intensive exercise can induce fatigue, staleness, and reduced performance along with metabolic alterations [15]; moreover, exhaustive, and extreme amounts of exercise have been associated with negative effects leading to muscle and joint injury and even disease, in part induced by excessive oxidative stress [16], inflammation [17,18] and profound metabolic changes [19]. Here is important to mention that other authors have not found plasma metabolic changes in 147 metabolites between obese subjects under a chronic exercise plan of 24-weeks compared to control groups [20].

Moreover, oxidative stress is influenced by inflammatory processes, contributing to the development of chronic inflammation and age-related diseases [21,22], thus providing adequate treatments for its reduction could majorly benefit aging patients.

Physical activity has been linked to a decrease in age-related oxidative stress and inflammation, simultaneously promoting activation of anabolic and mitochondrial biogenesis pathways, in both skeletal muscle and vascular tissue [23,24]. For example, a study performed by Gomarasca et al. showed the impact of moderate-intensity aerobic exercise in elderly women, finding a reduced expression of IL-1β, IL-6, and TNF-α, also affecting the inflammasome (mainly NLRP3 and TLR4) [25]. Interestingly, active elder people were found to have lower levels of IL-6 and higher levels of IL-10, than their non-active counterparts [26].

As it is well known, physical exercise produces alterations in the expression of several genes, mainly ones related to antioxidant defense, fission and fusion mitochondrial proteins, mitochondrial biogenesis as well as those genes required to facilitate cellular adaptation to metabolic changes [27,28], and genes related with inflammatory and anti-inflammatory response [11]. Importantly, epigenetics is an important switch that controls the expression of most of these genes [2,29,30].

Epigenetics is the study of the mechanisms able to regulate gene expression through changes that are independent of the nucleotide sequence of DNA [31–34]. Generally, non-genetic alterations in gene expression and also in the chromatin state are tightly regulated by three major mechanisms: the methylation of the cytosine residues of DNA, the transcriptional regulation by non-coding RNAs (*i.e.,* microRNAs, long non-coding RNAs, circular RNAs, among others), and the chemical modifications of specific residues of histone tails, which set the basis of the histone code (*e.g.*, acetylation, methylation, phosphorylation, etc.) [31–34]. Epigenetic changes are currently under study for their potential in precision medicine. Identifying epigenetic signatures of immune cells and their possible modifications could help determine patients with a risk of metabolic complications [30].

DNA methylation is the most studied and characterized epigenetic mechanism. It consists of the addition of a methyl group at the 5′ position of the cytosine base from S-adenosylmethionine (SAM) mediated by the enzymes DNA methyltransferases (also known as Cytosine-5-methyltransferases) DNMT1, 3A, and 3B [34,35]. The chromatin compaction also controls gene regulation, but the conformation of the chromatin is regulated by histone variants and by histone post-translational modifications (PTMs), which control the compaction of the DNA across several nucleosome domains. Nucleosomes are formed by an octamer of histone proteins in which every 147 base pairs of DNA are wrapped around it. The so-called histone tails, consisting of a chain of several amino acids that protrude from the histone core (formed by two proteins of each canonical histone H2A, H2B, H3, and H4) are accessible to chromatin-modifying enzymes [31,34].

Although non-coding RNAs (ncRNAs) are key elements in the epigenetic and epitranscriptomic regulation, in this review we will not focus on epigenetic regulation mediated by ncRNAs. It is important to indicate that ncRNAs have been closely related to epigenetic regulation and metabolic adaptations associated with physical exercise [36–38]. Also, we will not describe epigenetic mechanisms related to sirtuins, which are NAD^+-dependent deacetylases that have been associated with physical exercise, since there are already interesting reviews focused on this topic [39,40].

These last decades have served to obtain evidence that training and exercise have a direct impact on the epigenetic control of genes involved in mitochondrial biogenesis, metabolic adaptations, and muscle adaptation among others. Particularly, chronic moderate-intensity exercise induces hypomethylation of genes involved in many aspects of muscle adaptation, such as mitochondrial and lipid metabolism (i.e., *Stard10, Slc20a1, RUNX1, MEF2A, NDUFC2, ADIPOR1, ADIPOR2*, and *BDKRB2*), glucose metabolism (*Gfpt2* and *Cab39*) [41], muscle growth and differentiation (*Igfbp4* and *Plxna2*) [42] as well as angiogenesis (*Cds2*) and muscle innervation (*Dok7*) [43,44]. However, high-intensity acute exercise has demonstrated to produce hypomethylation of genes involved in the correct functioning of mitochondria and energy supply optimization, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PGC1A*), pyruvate dehydrogenase kinase, isozyme 4 (*PDK4*), mitochondrial transcription factor A (*TFAM*), peroxisome proliferator-activated receptor d (*PPARD*), as well as citrate synthase and myocyte enhancer factor 2A (*MEF2A*), among others [45].

Both resistance and endurance exercise in humans can induce epigenetic changes in pathways associated with energy metabolism, insulin sensitivity, and mitochondrial biogenesis, thus contributing to physiological adaptations [46], not only in the skeletal muscle but also in other tissues and systems (i.e., cardiovascular, neuromuscular, respiratory, as well as the immune system).

Although in recent years a lot of research has demonstrated the importance of epigenetics in the gene expression changes implicated in metabolic adaptation after exercise, it is not completely known what mechanisms can take place at different intensities of physical exercise, and specifically how the metabolic alterations that occur at different levels of training can affect epigenetic mechanisms and, in turn, gene expression. However, increasing evidence shows the relevance of epigenetic mechanisms regulation for metabolic plasticity in muscle during exercise. Despite this, it is currently a challenge to identify how these mechanisms can be imprinted after exercise in the muscle cells and how long these epigenetic changes remain stored in our epigenome.

2. Exercise produces free radical species which can impact epigenetic regulation

Free radical species, mainly reactive oxygen species (ROS) and reactive nitrogen species (RNS) have a relevant physiological role by activating and regulating several signaling pathways. Therefore, maintaining redox homeostasis is important for normal cell function. In this regard, an appropriate balance between oxidants and antioxidants (both enzymatic and non-enzymatic) is essential for maintaining normal physiology in the cells and organisms [47]. However, free radical species, especially at high concentrations, also have negative effects by oxidizing key biological molecules such as proteins, lipids, and nucleic acids [5]. Helmut Sies coined the term oxidative stress to define the disbalance between oxidative and antioxidative molecules produced by different sources and causes, though generally with either an increase in the oxidants, a decrease in the antioxidants, or both [48,49]. Maintenance of redox homeostasis is a continuously ongoing challenge, denoted as oxidative eustress [50]. When stress enhances certain biological functions (such as during exercise), it is eustress (conventionally known as “good” stress). Conversely, persistent stress that is not resolved through coping or adaptation is distress [51]. As indicated above, Sies has also used the term “oxidative eustress” which consists of oxidative stress that operates at a physiological range [50].

Fortunately, physical exercise not only increases the production of free radicals and associated molecules but also antioxidant responses. In this regard, all types of training and exercise including aerobic, anaerobic, or mixed training, provoke changes in the redox balance and oxidative eustress, which is controlled by changes in the expression of the antioxidant system in response to the increase in production of ROS and RNS [52–55]. As inferred, biological systems, and cellular, and

organic processes may tend to homeostasis, so they will require oxidative eustress to reach physiological and metabolic adaptations during training [1,50]. Obviously, external interferences to reach oxidative eustress may alter physiological adaptations promoted by exercise. This may explain some of the findings described by Gómez-Cabrera et al., in which antioxidant supplementations can blunt the benefits of exercise training [56].

As indicated above, physical activity not only increases ROS production but also antioxidant utilization [57], although this depends on the intensity of the exercise. In fact, moderate exercise can produce moderate levels of ROS, which are considered vital in the adaptive response, but high ROS and RNS production is a serious threat to cellular homeostasis [58]. Among the different pathways that can produce oxidative stress during exercise, ROS formation by oxygen metabolism is the most noteworthy (mitochondria can generate ROS in complex I and complex III, and in a proportional way to the respiratory chain activity) [59,60].

Importantly, intense exercise requires the recruitment of all available energy pathways, (*i.e.,* ATP and phosphocreatine, glycogenolysis, glycolysis, and OXPHOS) and both the aerobic and anaerobic energy pathways are important sources of ROS and RNS [61,62]. Moreover, intense exercise can also act as a powerful stimulus for mitochondrial biogenesis and thus increase mitochondrial density and oxidative capacity.

Both short-term and intense exercise in previously untrained healthy subjects induce oxidative stress, which in turn can inactivate aconitase leading to decreased mitochondrial respiration and additional ROS production [63]. Oxidative stress increases substantially during periods of intensive training [64,65]. This also occurs during exhaustive exercise in humans, when ROS production increases exorbitantly through a mechanism mediated by the xanthine oxidase enzyme [66], which can lead to oxidative distress.

Larsen et al. found a substantial reduction in mitochondrial respiration with oxidative alterations of mitochondrial proteins in high-intensity exercise [63], which is in line with previous observations related to the increase in ROS production during intense aerobic exercise [67], a process in which biomolecules oxidation is also generated, such as proteins [68], DNA [69], and increased levels of malondialdehyde and oxidized glutathione [66].

A recent systematic review showed how high-intensity exercise (mainly cycling and running exercise) increases oxidative stress, regardless of the type of exercise. It was shown that the time of the strenuous exercise was also directly related to the level of oxidative stress [70]. Importantly, high oxidative stress has been shown to correlate with an increase in inflammatory mediators, such as tumor necrosis factor- α (TNF-α), interleukin-6 (IL-6), and NF-kB under conditions of strenuous exercise [11,12,71]. However, it is noteworthy that regular exercise and the intrinsic characteristics (i.e., gender, age, fitness, previous training, and nutrition, etc.) of everyone who is performing a specific type of exercise are directly related to the generation of oxidative and nitrosative stress, as well as the activation of the antioxidant defense mechanisms [72]. For example, a recent review showed differences in inflammation of oxidative stress markers, depending on the type of exercise and the type of person performing it (*i.e.* professional athletes versus non-professional people), even suggesting the use of these markers as a means of measuring if the training has been completed properly [73].

In addition, during exhaustive or anaerobic exercise ischemia-reperfusion occurs due to the reduction of the blood supply to the skeletal muscles because of muscle contraction. This effect may limit the supply of high O_2 requirements of the muscle tissue. However, when the exercise is finalized, a high amount of O_2 arrives again to ischemic tissues producing high levels of ROS (in a mechanism that activates xanthine oxidase) [74,75]. Moreover, during exhaustive or anaerobic exercise, ROS can also be generated during hemoglobin and myoglobin oxidation, the increased central temperature of the body, and the rise of catecholamines and lactate, which have the potential to convert $O^{2\bullet-}$ into •OH [76], increase oxidative stress and alter the redox balance.

At this level, ROS directly oxidizes some of the substrates required for epigenetic modifications. This is the case of methionine which can be oxidized by the hydroxyl radical to give rise to methionine sulphoxide, which in turn can directly transfer the methyl group to the cysteine to produce 5-methyl cysteine through a non-enzymatic reaction [77]. Importantly, redox balance alteration affects the levels of the methyl donor SAM because methionine adenosyl transferase (MAT), the enzyme that synthesizes SAM, contains redox-sensitive cysteine residues in their catalytic sites [78], therefore decreasing the levels of the substrate required for DNA methylation. Other mechanisms that are redox-dependent described originally by our group consisted of the S-glutathionylation of histone H3, which directly impacts in the conformation of the chromatin [79]. However, not only histone H3-glutathionylation can occur under conditions of oxidative stress, but other redox changes have also been described such as histone cysteine S-nitrosylation (as observed by Riccio et al., [80]) and histone tyrosine nitration, mediated by peroxynitrite [81]. In this regard, it has been shown how NO affects dozens of histone modifications indirectly by modifying epigenetic enzymes such as histone acetyltransferases and histone methyltransferases [82].

Other oxidative post-translational modifications, such as histone carbonylation, have also been found in histone proteins [83,84]. Up to 21 modification sites for the formation of aldehyde adducts have been described in all core histones and the linker histone H1, mainly in residues such as Cys, Lys, and His. Carbonylation is another redox modification found in histones, which can occur directly by the nucleophilic attack of hydroxyl radicals, or indirectly by the attack of the acyl chains of polyunsaturated lipids leading to the formation of reactive aldehydes. These aldehydes, such as 4-hydroxynonenal (4-HNE) and 4-hydroxyhexenal (4-HHE), are subject to nucleophilic attack by the side chains of lysine, cysteine, and histidine residues, giving rise to histone carbonylation.

Importantly, histone carbonylation has been identified in the terminal histone tail including in key regulatory sites of gene expression H3K4, H3K9, H3K36, and H2BK5 [85]. As mentioned, these oxidative post-translational modifications occur on histone bodies or histone tails, therefore affecting chromatin compaction and gene expression (Fig. 1) [86].

Importantly, histone S-glutathionylation, which was found by us and also identified by other authors, occurs under different physiological and pathological conditions [61,87] and shows the relevance of this oxidative modification as an important PTM in the control of chromatin compaction. Particularly, histone H3 S-glutathionylation has been described at least in H3.1 and H3.3 variants. It may also occur in the testis variant H3.t which also contains two Cys (Cys96 and Cys110), as occurs in the histone H3 variant H3.1 [79]. But importantly, the susceptibility of histone H3 to be glutathionylated and therefore modify the state of the chromatin may depend on the redox balance, as we demonstrated [79].

The other process by which oxidative stress can potentially affect epigenetic regulation is by altering the activity of the epigenetic machinery. In this regard, GSH, as the major intracellular non-enzymatic antioxidant, can be oxidized to glutathione disulfide (GSSG) under oxidative stress conditions, and this change in the redox balance of GSH/GSSG can directly impact the control of several epigenetic enzymes, as we reviewed previously [88,89]. In fact, GSH/GSSG balance can also alter the activity of histone demethylase, Class I/II histone deacetylase, TET, and PAD4 activity. These mechanisms will be described in more detail in the following sections.

It has been shown in a model of mice how fatiguing contractions in muscle produce significant increase of S-glutathionylation of proteins such mitochondrial complex I and II, GAPDH, MDH1, ACO2, and mitochondrial complex V, RYR1, SERCA1, titin, and troponin I2 [90] As we present at the final section of this review, there is an intricate

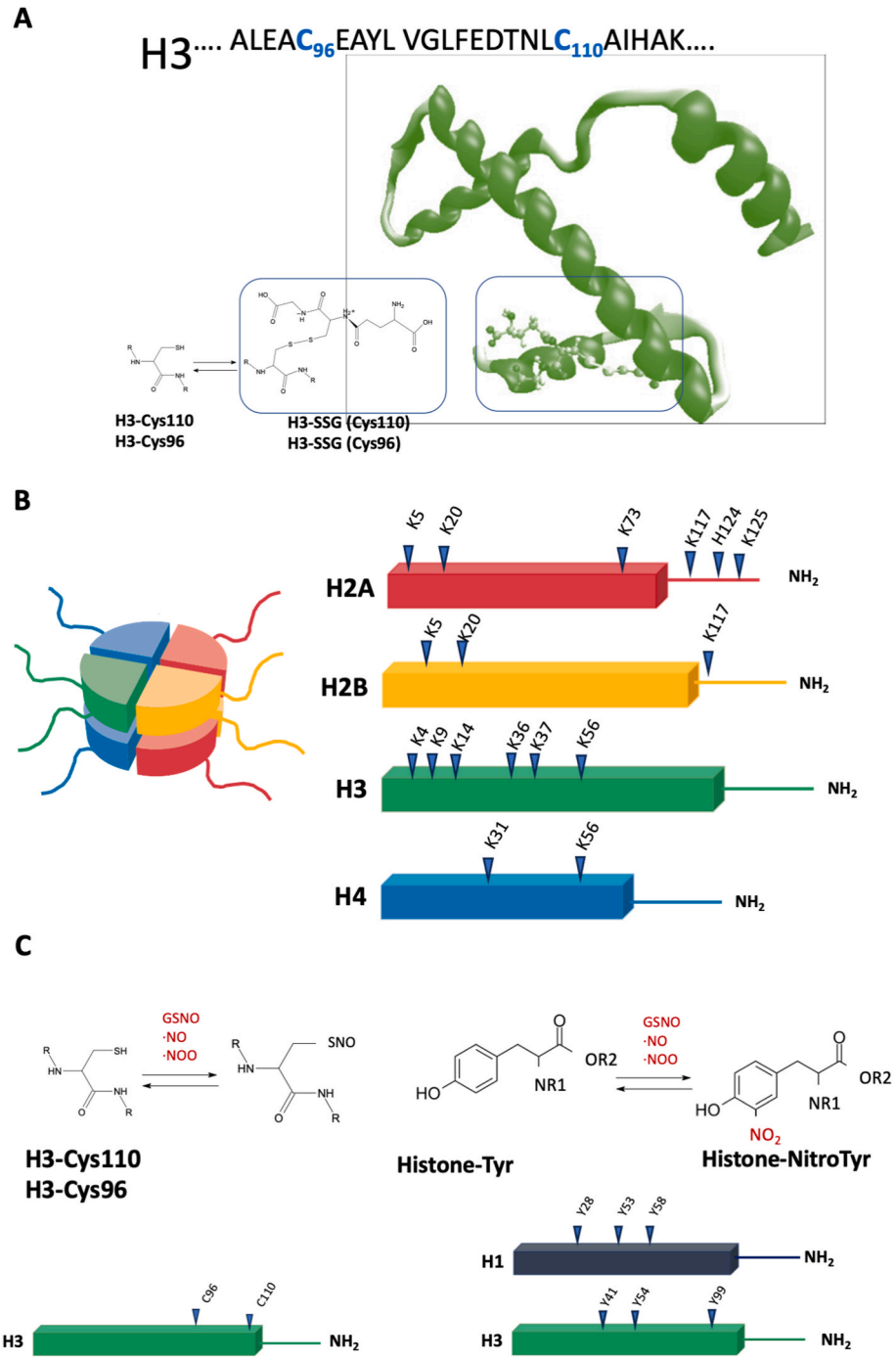

Fig. 1. Representation of oxidative post-translational modifications on histone bodies and histone tails. A) Histone H3 S-glutathionylation. Histone H3 family contains 5 histone variants. Among them, at least variants H3.1 and the testis variant H3.t contain two Cys (Cys96 and Cys110) which are susceptible to being S-glutathionylated. Note that the other majority variants H3.2 and H3.3 contain only Cys110; B) Identification of carbonylation sites in vivo. These sites, mainly Cys, Lys, and His, can suffer covalent modification by reactive lipid aldehydes or direct oxidation; C) Histones are highly susceptible to being nitrated. Particularly histone H3 can be modified by S-nitrosylation at Cys. Among histone proteins, H1 and H3 are the most susceptible histones to suffer nitration at the tyrosine residues shown in the figure.

connection between the mitochondria and the nucleus at redox level, so it is plausible to find S-glutathionylated proteins in the nucleus as the histone H3, which in turn may connect the redox balance with the gene expression.

3. Exercise induces metabolic adaptations with a direct impact on epigenetic mechanisms

Exercise induces several metabolic adaptations within muscle tissue, which are produced to provide the appropriate substrates and fuel requirements to the cells [91]. These metabolic adaptations require the regulation of the expression of specific genes (codifying proteins that may provide the appropriate substrates and cofactors required during

the process of metabolic adaptation in different cells and tissues, including antioxidant enzymes).

Mitochondria is the major source of cellular energy production (Fig. 2), but it is also closely related to metabolic homeostasis, thus disruption in the mitochondrial function may induce oxidative distress and negative metabolic outcomes in health. In this regard, several authors have hypothesized that there is a close relationship between exercise training load and mitochondrial function, glucose metabolism, redox balance, and physiological adaptation of the tissues to exercise [15](63).

Interestingly, a recent work by Flockhart et al. has shown how high training intensity in healthy volunteers produced a notable reduction in intrinsic mitochondrial function and elevated oxidative stress which concur with a disturbance in glucose tolerance and insulin secretion [15] and therefore can cause changes in the normal metabolic flux.

Metabolites shown in Fig. 2, such as citrate, $FADH_2$, succinate, malate, and fumarate, produce inhibitory effects in the epigenetic and epitranscriptomic regulation, thus controlling physiological responses to extracellular stimuli [92]. Therefore, the deregulation of the cellular metabolism, and particularly of specific interconnected pathways, by physical exercise can lead to profound consequences in the epigenetic control of gene expression.

3.1. *The glycolytic control and production of lactate as a regulator of epigenetic mechanisms*

High-intensity exercise is enabled through the activation of the glycolytic energy pathway [93,94]. In fact, both the intensity of physical exercise and its duration directly correlate to muscle glycogen degradation rate, with the limiting factor being the finite nature of this carbohydrate stored within the skeletal muscles [95]. Importantly, the glycolysis of glycogen in skeletal muscle is the main source of lactate, a crucial intermediate in energy metabolism. Lactate produced in the skeletal muscles is transferred through the bloodstream to the liver where it undergoes gluconeogenesis to generate glucose [96]. This glucose produced in the liver from lactate can re-enter the bloodstream and then, return to the skeletal muscles where it is used in the glycolysis to generate lactate, which in turn is the major gluconeogenic precursor, a process which is known as the Cori cycle. Interestingly, lactate has been proposed to be a circulating fuel that can be used as a carbon source in the TCA cycle and thereby constitutes a fundamental way for the distribution of mitochondrial fuel across the circulation [97]. Flockhart et al. have recently found that blood lactate concentration measured in healthy volunteers under excessive training decreases. Although Flockhart et *al.* did not identify feasible mechanisms explaining this decrease in lactate concentration during intense training, they propose that this effect cannot be explained by reduced glycogen availability but suggests that other metabolic changes likely would take place in the lactate reduction [15]. During prolonged exercise, obtaining other extra-muscular carbohydrates as a source of energy through liver glycogenolysis and from lactate is of special relevance, as described by Coyle [98]. On the other hand, the concentration of lactate positively correlates to exercise intensity [99] as well as to prolonged endurance exercise [100,101]. Linking all these processes, it is likely that glycemia may be supported by gluconeogenesis from lactate during physical exercise [102–104].

Recently, lactate has been considered as a signaling molecule with autocrine-, paracrine-, and endocrine-like effects. Importantly, lactate

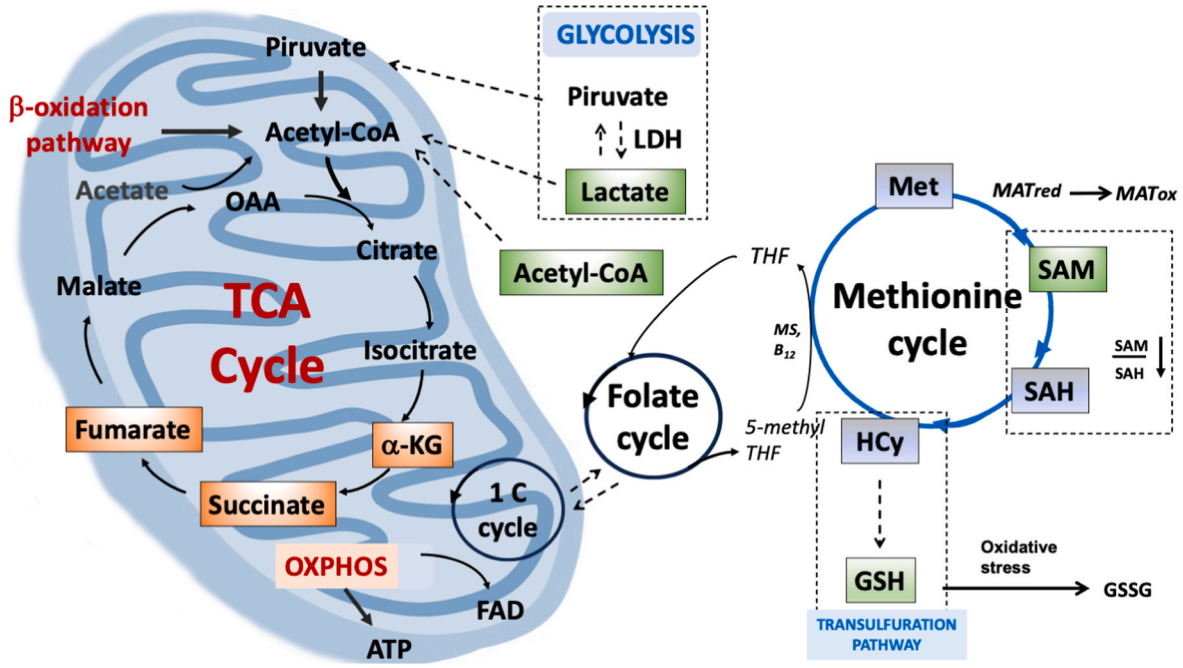

Fig. 2. Cellular metabolism is related to exercise and epigenetic control. Metabolic processes include specific cellular intermediates participating in the glycolysis, tricarboxylic acid (TCA) cycle, the mitochondrial oxidative phosphorylation (OXPHOS) to produce ATP, and methionine cycle which recycles methionine (Met). The methionine cycle is intrinsically connected with the one-carbon metabolism through the folate cycle, and downstream with the transsulfuration pathway to finally produce glutathione (GSH) which can be oxidized to glutathione disulfide (GSSG) because of oxidative stress. The glycolytic pathway, which will produce pyruvate to generate acetyl-CoA, is required downstream by the TCA cycle to produce relevant intermediates and co-factors such as α-ketoglutarate and NADH, which directly impact the function of epigenetic enzymes. Among the diverse metabolites participating in the TCA cycle, such as citrate, $FADH_2$, succinate, malate, and fumarate, these metabolites particularly malate and fumarate which are produced during exercise are characterized by their inhibitory effects in the epigenetic machinery. Importantly, the major epigenetic metabolite is S-adenosyl methionine (SAM), a key molecule of the methionine cycle, which is required by the DNA methyltransferases and histone methyltransferases to incorporate the methyl group to DNA or specific amino acids in the histones contributing to the epigenetic control. Furthermore, S-adenosyl homocysteine (SAH), another intermediate of the methionine cycle, controls the bioavailability of SAM as a substrate for the DNA and histone methylation machinery. Green-colored squares indicate metabolites that are directly required to modify the DNA or histones, while orange-colored squares mark important metabolites that have been described to regulate epigenetic mechanisms or epigenetic enzyme functions.

has been linked to epigenetic regulation by controlling epigenetic mechanisms, both directly and indirectly, therefore controlling gene expression for adaptative responses. In fact, lactate acts as an epi-metabolic reprogrammer, by producing a-KG, activating TETs, and catalyzing DNA hypomethylation as it has been found in several cell types [105], as well as directly producing histone lactylation, which has demonstrated its capacity to regulate gene expression in some cellular models of cancer [106–108], and regulate specific active enhancers [109]. If histone lactylation is activating gene transcription of genes related to metabolic adaptations due to physical exercise remains unknown at this moment. However, its correlation with changes in the expression of homeostatic genes involved in maintaining biological homeostasis [110], activation of reparative genes (*e.g. LRG1*), angiogenic genes (*e.g. VGEF*), and anti-inflammatory genes (e.g. IL-10) [111], and its immunomodulatory effects [112], as well as its function linking metabolism and gene expression [107], make us propose that histone lactylation may occur during physical exercise (Fig. 3).

3.2. The tricarboxylic acid cycle as a source of key metabolites of epigenetic control

As a central core of cellular aerobic metabolism, the tricarboxylic acid (TCA) cycle plays a key role in the production of several metabolites which are used directly by specific epigenetic enzymes to control DNA and histone methylation, as shown in Fig. 2. Importantly, the TCA cycle is a redox-sensitive cycle [6], being its function crucial to provide several essential epigenetic substrates and cofactors, such as α-KG, succinate, fumarate, and of course NAD+/NADH. In fact, intermediates of the TCA cycle can control DNA and histone methylation [113], parsylation (also known as poly(ADP-ribosyl)ation) [114], and acetylation, among other PTMs, and these modifications are strongly dependent on the redox status of the cells [115] (Fig. 4).

The normal metabolic flux in the TCA cycle during high oxidative stress is halted since aconitase can be completely inactivated. However, α-ketoglutarate dehydrogenase (α-KGDH) is still functional under oxidative stress conditions, so it can continue the flux in the TCA, thanks to the supply of glutamate, which is converted to α-KG via transamination. This bypass of the TCA cycle can function until α-KGDH is finally inhibited by high levels of ROS [6] (Fig. 4).

NAD^+ and NADH, which are generated in the TCA cycle, are essential coenzymes that provide the required oxidoreductive power for the generation of ATP by mitochondria through the OXPHOS mechanism. As generally established, the NAD^+/NADH ratio represents a balance of the redox state and integrates several networks of NAD^+-consuming pathways and NAD^+ biosynthetic and salvage pathways [116]. NAD^+ and NADH are found in several compartments of the cell, such as the cytosol, the mitochondria, and the nucleus. Moreover, NAD^+ and NADH can move freely across pores in the nuclear membrane, so it is considered that concentrations of NAD^+ and NADH are similar in the nucleus and the cytosol [116]. This is consistent with the fact that the NAD^+ salvage pathway occurs in both the cytosol and the nucleus. Here it is important to mention that most NAD^+ is recycled from nicotinamide, nicotinic acid, nicotinamide riboside, and nicotinamide mononucleotide in the salvage pathway to maintain the cellular NAD^+ levels [117]. Additionally, NAD^+/NADH metabolism is strictly controlled by several pathways of biosynthesis, recycling, and metabolic regeneration through the TCA cycle and degradation. This is of note since NAD^+ also contributes directly to the epigenetic metabolism through a post-translational modification catalyzed by poly(ADP-ribosyl) polymerases (PARPs), which introduce poly(ADP-ribosyl) chains in the histone tails [86,115,118–120], to finaly produce parsylation of histones.

When the human muscle is not working, it can be considered that the nuclear-to-cytosolic NAD^+(H) concentrations are balanced and that the nuclear NAD^+ and NADH levels would be in equilibrium with those found in the cytosol [116].

During high-intensity exercise and submaximal isometric muscle

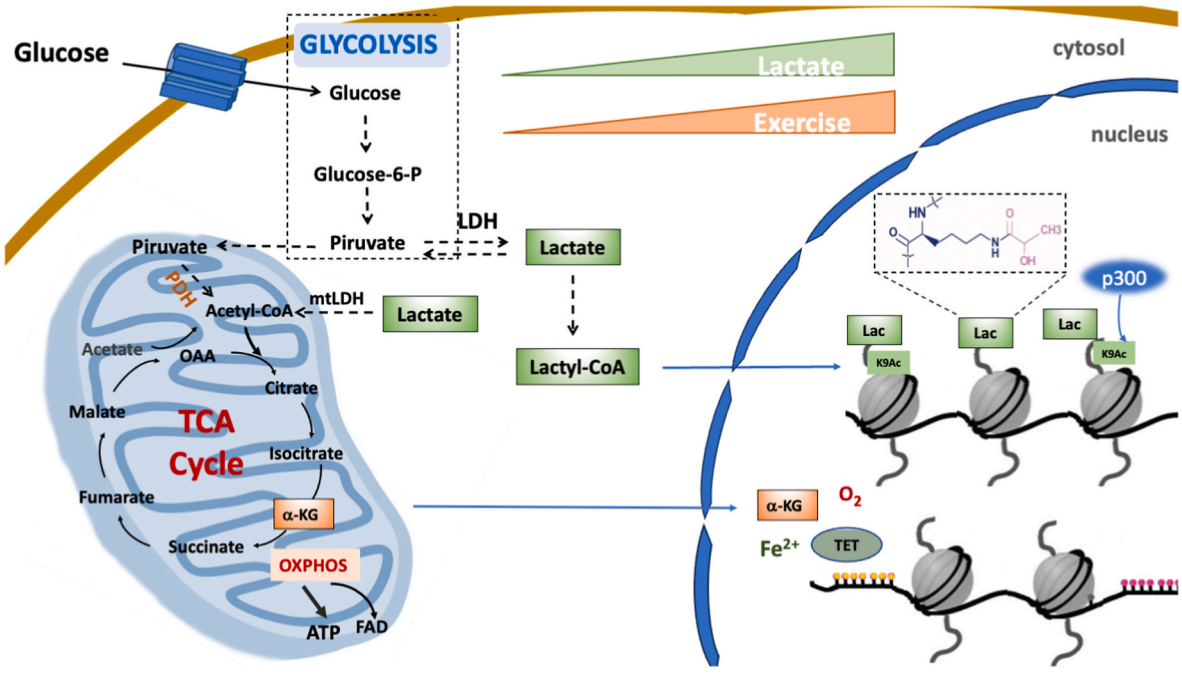

Fig. 3. Histone lactylation acts as a new epigenetic post-translational modification. Lactate metabolism can be considered as an epimodulator participating in the chromatin conformation by altering histone post-translational modifications. The main biochemical player in lactate generation is the glycolytic pathway, which increases the levels of intracellular lactate. Therefore, stimuli that activates glycolysis, such as the increase in the intensity of physical exercise, can result in the increase of lactate and the intermediate molecule lactyl-CoA, which enters the nucleus to produce histone lactylation (through enzymatic mechanisms that still have not been completely elucidated). Moreover, re-entering lactate to the mitochondria and the action of the mitochondrial lactate dehydrogenase (mtLDH) can fuel the tricarboxylic acid (TCA) cycle to produce new molecules of alpha-ketoglutarate (a-KG), which acts as co-factor of ten-eleven translocases (TET) to produce the demethylation of DNA. This process is linked to histone lactylation and contributes to the activation of gene expression.

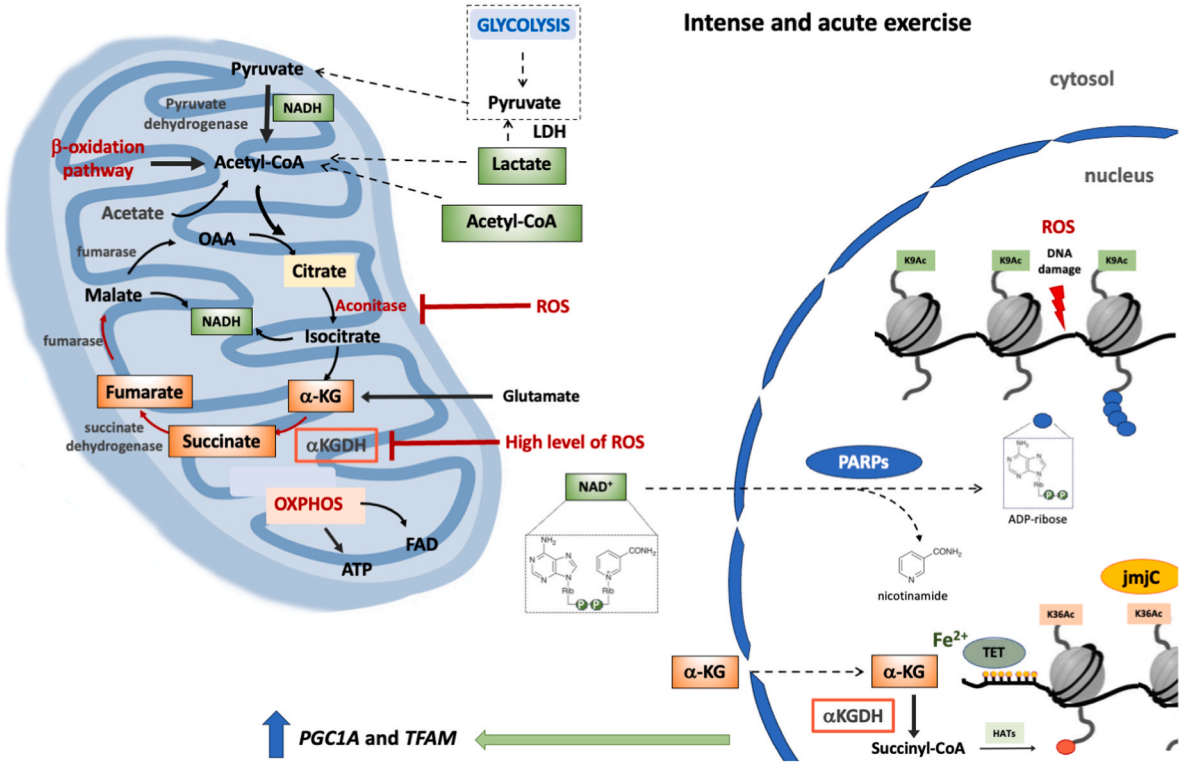

Fig. 4. Metabolic flux in the tricarboxylic cycle (TCA) when oxidative stress occurs during intense exercise. During exercise, in the mitochondria of skeletal muscle, the principal function of the TCA cycle is to oxidize acetyl-CoA derived from the oxidative decarboxylation of pyruvate and from the β-oxidation of fatty acids to generate reducing equivalents (NADH, FADH2) for the synthesis of ATP, which is the energy fuel of the muscular cells. Intense exercise also promotes lactate dehydrogenase (LDH) to produce pyruvate through oxidative mechanisms [140], then pyruvate is reincorporated into the mitochondria to fuel the TCA. Intense exercise and oxygen radical species and oxidant molecules such as hydrogen peroxide (H_2O_2), superoxide radical anion ($O_2^{\cdot-}$), and hydroxyl radical (·OH) can produce the complete inhibition of aconitase, which produces the accumulation of citrate. However, other enzymes such as α-ketoglutarate dehydrogenase (α-KGDH) can still function under oxidative stress and maintain the flux of the TCA cycle by the continuous supply of glutamate [6], which is converted to α-ketoglutarate via transamination. The increased levels of α-KG provide the substrate for ten-eleven translocase (TET) proteins to generate 5-hydroxy-methylcytosine (5-hmeC; marked as yellow circles in the figure) and the substrate for jmjC to demethylate histone H3K36 (light orange rectangles). In addition, the subsidiary pathway involves α-KGDH continuing the TCA cycle, which can be also inhibited under conditions of high oxidative stress. Moreover, nuclear α-KGDH can produce succinyl-CoA from α-KG [141], which can produce succinylation of histones (orange circle) through a process mediated by histone acetyltransferases (HATs). NAD + produced during intense exercise can enter the nucleus after this intense exercise and act as a substrate of PARP1 to produce PARsylation of histones (dark blue circles) and mark sites of single strand breaks produced as a result of oxidative stress. All these events may contribute to avoiding DNA damage and increase the expression of key genes related to mitochondrial biogenesis, such as *PGC1A* and *TFAM*. Interestingly, the hypomethylation of these genes was directly related to the intensity of the exercise [45].

contractions, NADH can increase up to ~140 % above resting levels, whereas NAD^+ levels remain constant [121,122]. Regarding the NAD^+/NADH ratio, it decreases during exercise at 50 % V̇ O2 max because of the NADH increase [123] but increases above resting values when the intensity of the exercises reaches 75 % and 100 % V̇ O2 max [124]. Therefore, considering that concentrations of NAD^+ and NADH are similar in the nucleus and the cytosol, it is expected that the NAD^+/NADH ratio may also decrease in the nucleus in the same manner.

Research has demonstrated that the NAD^+/NADH ratio controls the enzymatic activity of sirtuins (SIRT1, -2, -3, -4, -5, -6, -7) a Class III histone deacetylases (HDACs) family which uses NAD^+ as an essential cofactor for its activity [125]. It is noteworthy, that Class III HDACs are NAD^+-dependent deacetylases, so they may function as a redox sensor in muscle cells. Particularly, Sirt6 improves muscle fitness and exercise capacity [126]. In any case, as indicated in the introduction of this review, we have not focused our attention on the regulation of sirtuins in our review because of the high number of reviews describing this issue. However, we have focused our attention on relevant PTMs, such as the PARsylation, lactylation, and succinylation of histones.

Particularly, histone PARsylation is a process occurring as a response to oxidative stress, after the recognition of DNA lesions, by PARPs, which allows the removal of histones immediately after DNA damage [127], thus facilitating single and double-strand break repair [128]. In skeletal muscle, global PARsylation increases after electrically evoked isometric contractions in mice models [129]. It is well known that physical activity induces mild musculoskeletal injuries, not only at the tissue level but also at cellular level, that requires rapid and efficient repair to preserve muscle homeostasis and function. In human beings, it is known that a single and acute bout of exercise induces single and double-strand breaks [130] because of mitochondrial ROS and inflammation mediators (*i.e.,* catecholamines and cytokines) released during physical activity. ROS and subsequent DNA damage are significantly increased after excessive exercise [131]. Interestingly, studies performed by Moreno-Villanueva et al., indicated that acute exercise induces DNA strand breaks in lymphocytes of untrained individuals. Interestingly a recent work by Roman et al., showed how myofibers of adult mice after eccentric exercise can response to damage by mobilizing and aggregating myonuclei and subsequently activating transcriptional and translational programs to the site of injury to promote myofibers self-repairing [132].

Importantly, differences in the DNA strand breaks and the activity of PARP are found following acute exercise and it depends on the physical fitness of the subjects studied. In this regard, trained individuals

repaired radiation-induced DNA strand breaks faster than untrained individuals, through a process involving PARP1 activity after acute exercise [133]. This is an important finding since PARP1 activity responds to exercise and PARP1 levels of the muscle *vastus lateralis* do not change in young trained but increase in young untrained individuals in response to an acute exercise bout [134]. Stocks et al. showed how PARP1 displayed a trend to increase after exercise performed at moderate intensity in a healthy cohort of subjects [135]. Conversely, the work performed by Cobley et al., showed how PARP1 levels in muscle remained unchanged in young and trained participants after exercise. However, the authors found in old both, trained and untrained, subjects decreased levels of PARP1 [136], which may compromise the capacity of signaling the chromatin for DNA repair. Conversely, in young untrained subjects, the levels of PARP1 substantially increased after exercise, demonstrating that DNA damage could be more severe in these subjects. Although the previous papers apparently found contradictory results, the evidence suggests that physical exercise may attenuate genomic instability, not only by modulating ROS and antioxidant activity, but also by regulating the expression levels of PARP1 [136] (Fig. 4).

The accumulation of ADP-ribose within the nucleus could induce a glycation reaction that ultimately can produce carbonylation. In fact, carbonylation is a consequence of poly(ADP-ribosyl)ation (PARsylation) [84]. It is important to consider that histone carbonylation is a post-translational mark that can accumulate after the increase of oxidative stress but, additionally, we showed how this PTM specifically increases in cells during active replication [137]. Since skeletal muscle mass is regulated by dynamic control of protein synthesis and degradation [138], and it has been proposed that proteasome activity increases in human muscles following intense exercise [139], there is a possibility that histone carbonylation may increase in the muscle during intense exercise.

Particularly, the enzyme aconitase decreases its activity by over 50 % in parallel with mitochondrial respiration after sprint training [63]. During intensive exercise, mitochondrial stress response may contribute not only to produce more ROS but also to accumulate citrate which may help to preserve the redox status of the cell [63]. Nonetheless, it should be considered that accumulation of citrate during intense exercise may inhibit phosphofructokinase, which is essential in the glycolytic pathway [142].

As indicated above, the TCA cycle supplies the intermediates and co-factors required for the epigenetic machinery [143], but the TCA flux depends on the intensity of physical exercise [144](145). In fact, one of the intermediates of the TCA is the α-KG, which, together with succinate and fumarate, regulates the enzymatic activity of α-KG-dependent dioxygenases [145], mainly TETs and Jumonji C (jmjC), which are relevant enzymes in the epigenetic control.

A single activity of exercise is enough to increase TCA cycle flux and increase TCA cycle intermediates, such as citrate, isocitrate, succinate, and fumarate [145], which directly can impact epigenetic control by regulating epigenetic enzymes. Most of these metabolites contribute to the function of important epigenetic modifiers that control methylation of the DNA and histone PTMs introduced or erased by histone acetyltransferases (HATs) and HDACs, respectively. In addition, other enzymes are involved in the elimination of DNA methylation, such as ten-eleven-translocation proteins (TETs), and the removal of methylation in histones, which is mediated by histone demethylases such as jmjC and lysine-specific histone demethylases (LSD, etc.), among others (Fig. 3).

The *TET* family of proteins (TET1, TET2, and TET3) are dioxygenases that produce the hydroxylation of the 5-methylcytosine to generate 5-hydroxy-methylcytosine (5-hmeC) [146], through an oxidative process that requires alpha-ketoglutarate (α-KG) and Fe(II)-dependent mechanism [146]. 5-hmC is an intermediate, being deaminated by cytidine deaminases to 5-hydroxymethyluracil, which finally produces DNA demethylation [147].

On the other hand, histone demethylases are essential enzymes involved in histone code regulation through histone lysine demethylation. Specifically, histone demethylase jmj proteins also require α-KG and Fe(II) for their demethylase activity. Among jmj family proteins, jmjC can demethylate specifically histone H3 lysine 36 (H3K36me2) [148].

It is noteworthy that α-KG has recently been linked to the response to resistance exercise by stimulating muscle hypertrophy [149]. This, in part, may be facilitated by the hyperactivation of TETs and subsequent demethylation of key genes that may activate downstream pathways such as AKTm/mTOR signaling pathways [150], which can promote protein synthesis into the muscle.

However, the bioavailability of other intermediates of the TCA metabolism produced during exercise may affect the activity of epigenetic enzymes, by increasing the ATP-citrate lyase activity, and acetyl-CoA concentration, which subsequently enhances the acetylation of histones thus affecting the expression of genes related to antioxidant activity, mitochondrial biogenesis, muscle protein synthesis, AMPK, and the peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) [151]. Particularly, it has been described how CpG sites in the *PRKAA2* gene, which codifies for the catalytic subunit of AMPK, were modified in whole blood cells of subjects due to 4-week rehabilitation training [46]. Moreover, Barrés et al., found that acute exercise (reaching 80 % of the VO2max) induced DNA hypomethylation at the promoters of genes required in mitochondrial biogenesis, such as *PPARGC1A* and *TFAM* (Fig. 4). Interestingly, the hypomethylation of these genes was directly related to the intensity of the exercise [45]. Together, all these processes indicate that exercise can promote the acetylation of histones and hypomethylation of CpG sites in key genes related to mitochondrial and muscle protein synthesis needed for muscle adaptation to exercise.

As indicated above, intermediates of the TCA metabolism produced during exercise affect the activity of epigenetic enzymes. In fact, jmjs and TETs are inhibited by 2-hydroxyglutarate (2-HG), fumarate, and succinate, thus affecting the activity of these epigenetic enzymes and consequently histone and DNA methylation, respectively [152]. In line with these observations, the 2-HG, a secondary metabolite produced from the TCA cycle and produced from α-KG, takes an important role in the regulation of the activity of key epigenetic enzymes. Moreover, 2-HG can alter the activity of TET demethylases and jmjC histone demethylases to compete with the α-KG as a co-factor of these Fe(II) dioxygenases. Subsequently, this entails low histone demethylation and low levels of 5-hmeC, which may contribute to chromatin compaction and inhibition of gene expression [153]. Importantly, 2-HG can also accumulate by the inhibition of the NADP + -specific isocitrate dehydrogenase (IDH), which is responsible for converting isocitrate to α-KG. Interestingly, an upregulation of IDH has been described after metabolic stress produced with endurance training in the skeletal muscle of trained rats [154]. This may produce the downregulation of 2-HG and increase the levels of α-KG after physical exercise, therefore providing increased levels of this co-factor needed to promote the activity of a-KG and Fe (II)-dependent dioxygenases. In fact, plasmatic levels of α-KG have been observed to increase after resistance exercise [155]. However, it is important to consider that intramuscular and interstitial α-KG levels are decreased during cycling exercise compared to the resting state [156, 157], which suggests that the skeletal muscle is not the main source of a-KG production during exercise.

As indicated above, a-KG and Fe(II) dependent dioxygenases, TETs and jmjCs, can be inhibited by succinate and fumarate accumulation, which compete with a-KG by the catalytic site of these enzymes [158]. The effect of succinate on jmjC histone demethylases is confirmed by the observations of Cervera et al., who treated human cells with succinate dehydrogenase inhibitors, producing the accumulation of succinate and increasing histone methylation [159]. Besides its effect on histone methylation, histone succinylation has also been described as a PTM participating in the histone code, particularly in the succinylation of H3K122, which may produce activation of gene transcription. In this

regard, succinyl-CoA can be produced from α-KG in a process mediated by α-KGDH into the nucleus [141] (Fig. 4).

The accumulation of succinate and fumarate can be caused by physical exercise [144]. Regarding succinate, both endurance and resistance exercise induce an elevation of succinate concentration not only in plasma [155] but also in skeletal muscle [160]. The concentration of succinate depends on the intensity and duration of the physical exercise and decreases rapidly after the recovery phase [160,161], although it remains higher at the end of exercise than resting levels [156].

Concerning fumarate, it has been shown that after endurance exercise, such as a marathon and cycling, the plasma levels of fumarate increased about 2.5-fold and remained elevated about 1 h after finalizing the exercise [156,162,163]. Interestingly, fumarate is also elevated in muscles after performing cycling tests (60–75 % VO2max) [164]. Since, fumarate has been described as a potent inhibitor of histone H3 demethylation by counteracting the activity of Fe(II)-ketoglutarate dioxygenases (*i.e.,* TET and jmjC) [165], it is feasible that the accumulation of fumarate into muscle cells during intense exercise can control the levels of this epigenetic mark, and specifically contribute to enhanced levels H3K36me2 and promotion of DNA repair [166,167].

4. Other important epigenetic mechanisms regulated by oxygen and energetic metabolism produced during exercise

As described in the previous sections, any stress capable of inducing a boost of free radicals or continuous production of an excess of ROS and RNS should affect the regulation of α-KG and Fe(II)-oxygen-dependent enzymes like JmjC and TETs [168], as in the case of physical exercise.

One of the most interesting metabolites in the cell is *β*-hydroxybutyrate which has demonstrated its potential to boost the production of ATP and its ability to regulate the ratio NAD+/NADH, NADP+/NADPH, acetyl-CoA/CoA, as well as to exert antioxidant effects [169,170]. Importantly, *β*-hydroxybutyrate is also a potent regulator of epigenetic mechanisms [171,172]. This molecule is produced from fatty acids and ketogenic amino acids, and it is produced at millimolar levels after prolonged or strenuous exercise [173]. It derives from acetoacetate, which is catabolized by *β*-hydroxybutyrate dehydrogenase in an NAD + -dependent reaction, and both are products of the normal metabolism of fatty acid oxidation, serving as metabolic fuels in extrahepatic tissues such as muscle cells. In a protocol involving twenty subjects who completed two 36-h fasts and completed a treadmill exercise session at the beginning of the fast, *β* -hydroxybutyrate levels increased substantially in blood [174]. Kwak et al., also found the beneficial effects of *β*-hydroxybutyrate levels released by skeletal muscle to the blood following endurance exercise, which may improve muscle function in both animals and elderly humans [175]. This observation is reinforced by other results obtained in animal models, in which *β*-hydroxybutyrate supplementation increased exercise capacity, thanks to the improvement of mitochondrial morphology and function in mouse skeletal muscle [176].

From a chemical point of view, *β*-hydroxybutyrate is the oxidized form of butyrate, and it has demonstrated its capacity to reduce oxidative stress [177]. Importantly, and related to its epigenetic potential, *β*-hydroxybutyrate inhibits HDAC1, HDAC3, and HDAC4 in a dose-dependent manner in human cells and in mice models during fasting and calorie restriction, which can lead to increased levels of histone H3 lysine 9 acetylation (H3K9ac) and histone H3 lysine 14 acetylation (H3K14ac) [172]. These results indicate that *β*-hydroxybutyrate can regulate the epigenetic state of the chromatin by inhibiting the activity of class I and class II HDACs [172].

5. Mitochondria-nuclear metabolic interconnection via epigenetic pathways

It is well-established that exercise induces changes in the mitochondrial biogenesis. Among the different processes that can be activated by exercise, one with great importance involves the transcriptional peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) which is proposed to coordinate mitochondrial biogenesis in the skeletal muscle through the interconnection of a well-coordinated nuclear- and mitochondrial-encoded gene transcription mechanisms. Furthermore, PGC-1α is hypomethylated after exercise, further promoting its expression and impact on gene expression [178]. Previous evidence has demonstrated that PGC-1α is responsible for the activation of various nuclear transcription factors that increase the expression of mitochondrial genes. Moreover, PGC-1α directly interacts with mitochondrial transcription factor (TFAM) within mitochondria to increase the transcription of mitochondrial genes and produce an increase in mitochondrial protein content [179]. This fact is of special relevance since it is regulated in a training intensity-dependent manner and effectively produces training-induced changes in mitochondrial content and morphology [180] through the induction of mitochondrial biogenesis.

To generate a well-coordinated cellular response to various environmental cues, both mitochondrial and nuclear genomes, as well as, mitochondrial and nuclear compartments, must communicate with each other through a bi-directional circuit using a wide array of metabolites that control epigenetic mechanisms, which in turn may regulate gene expression. As described above, many metabolites are generated in specific pools throughout the cell, mainly the mitochondria. In addition, these metabolites also involve the intricate mechanisms of transport and enzymes that catalyze epigenetic modifications in both nuclear and mitochondrial genomes [92]. Specifically, promoters of genes related to the TCA cycle have shown differential DNA methylation patterns in skeletal muscle related to life-long exercise [181]. Furthermore, several TCA cycle metabolites have been studied in the context of epigenetics [182,183].

As described in the previous sections, the accumulation of succinate and fumarate can be due to physical exercise [144] as well as the increase in α-KG, which can migrate to the nucleus to produce succinyl-CoA into the nucleus in a process mediated by α-KGDH [141]. Importantly, fumarate, succinate, succinyl-CoA, and α-KG may maintain an intricate equilibrium in the nucleus to regulate the activity of DNA methyltransferases or α-KG-Fe(II) dioxygenases, such as lysine demethylases, jmjC, and TETs to control the methylation state of the chromatin, as we described in the previous section. Both succinate and fumarate have been shown to inhibit the activity of α-KG-dependent dioxygenases, such as histone demethylases and TETs of 5-methylcytosine (5 mC) hydroxylases [184–186]. Furthermore, mutation of succinate dehydrogenase (SDH) impacted DNA methylation [187], while fumarate has been thoroughly studied as both a modifier of epigenetic modifications, as well as interacting with factors involved in DNA repair [188,189] through inhibition of H3 demethylation [166,190]. Thus, the accumulation of succinate and fumarate in the context of exercise may have a direct impact on the methylation pattern.

Interestingly, a recent study by Liu et al. has described the presence in the nucleus of all enzymes participating in the TCA cycle except for SDH [191]. Moreover, despite it has not been yet described the mechanisms of translocation of succinyl-CoA synthetase (SCS) to the nucleus from the mitochondria, SCS is also found in the nucleus. Importantly, nuclear KGDH and SCS, as well as the entrance of succinate into the nucleus, may control the availability of succinyl-CoA, which is also the source of specific acetyltransferases to produce histone succinylation (Fig. 5) [192]. As described in the previous section, succinate levels increase after exercise, so it is expected that histone succinylation may occur after physical activity, therefore controlling the expression of specific enzymes [144]. Current evidence has demonstrated that high-intensity exercise can alter the acetylation and succinylation marks, so it is plausible that a nuclear proteome, and specifically chromatin, is directly impacted by these modifications after exercise [193]. This would imply that exercise could have a direct impact on this

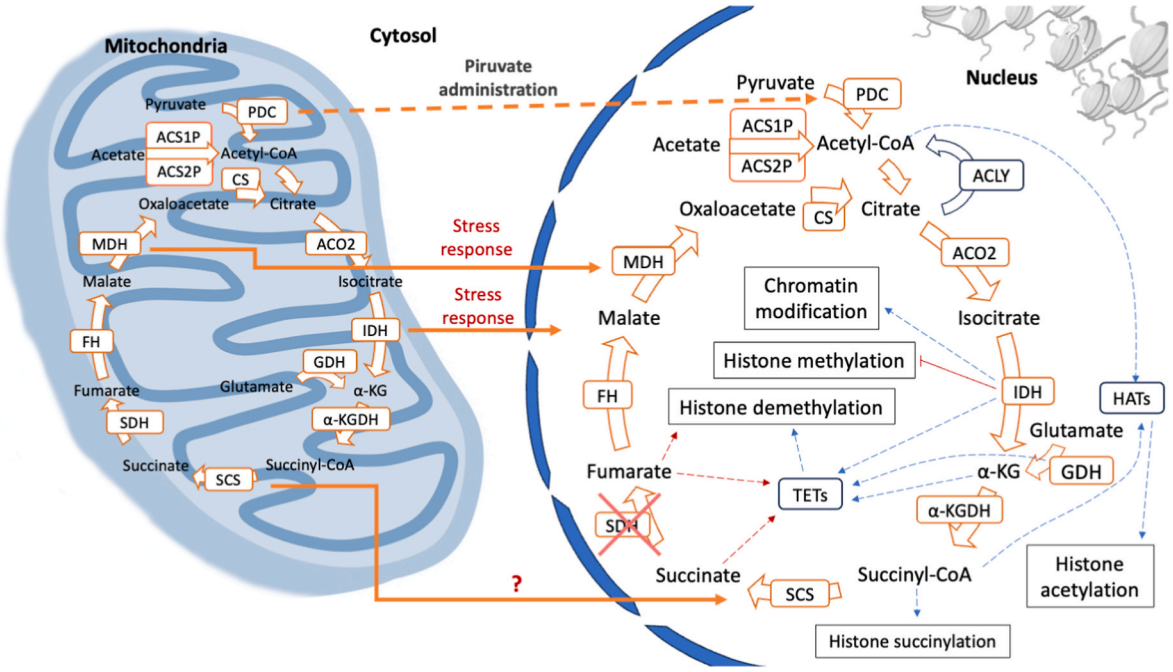

Fig. 5. Schematization of the presence of the classical mitochondrial TCA-cycle enzymes and products in the nucleus, and their impact on epigenetic modifications. Enzymes are marked with rounded squares, where orange-coded enzymes are classically mitochondrial associated, and other enzymes are dark blue-coded. Processes are indicated by broad arrows, with the classical mitochondrial TCA cycle orange-coded, and the rest in dark blue. Epigenetic modifications are squared with black corners. Blue-dotted thin arrows indicate a direct relation or promotion of the epigenetic processes, while red-dotted thin arrows indicate an indirect relation. Moreover, the inhibition of histone methylation by IDH is marked with a red blunt arrow. Since some studies have suggested that SDH is not present in the nucleus, it is crossed from the non-classical nucleus TCA cycle. Currently, it is unknown if SCS can be translocated from the mitochondria to the nucleus, so a question mark symbol above this arrow denotes this. However, IDH and MDH enzymes have been found to migrate to the nucleus after a stress stimulus. PDC, ACS1P, and ACS2P can also migrate to the nucleus to contribute to the production of acetyl-CoA. Abbreviations: α-ketoglutarate (α-KG), alpha-ketoglutarate dehydrogenase (α-KGDH), ATP-citrate lysate (ACLY), aconitase 2 (ACO2), acetyl-CoA synthetases 1P and 2P (ACS1P and ACS2P), citrate synthase (CS), fumarase hydratase (FH), glutamate dehydrogenase (GDH), histone acetyl-transferases (HATs), isocitrate dehydrogenase (IDH), malate dehydrogenase (MDH), pyruvate dehydrogenase complex (PDC), succinyl-CoA synthetase (SCS), succinate dehydrogenase (SDH), ten-eleven translocations (TETs).

nuclear TCA cycle as with the classical TCA cycle described in the mitochondria. Furthermore, Liu et al. also evaluated the role of this incomplete cycle, showing a direct impact on epigenetic mechanisms, further confirming the effect of the non-classical TCA cycle functions on the nucleus (Fig. 5).

Other studies have also noted the presence of the TCA cycle enzymes in the nucleus. Nagara et al. confirmed the existence of part of the pyruvate dehydrogenase complex (PDC), pyruvate dehydrogenase (PDH) E1 subunit alpha 1 (PDH-A1), pyruvate carboxylase, citrate synthase (CS), aconitase 2 (ACO2), isocitrate dehydrogenase (IDH)-3 [194]. Meanwhile, Traube et al. described the presence of glutamate dehydrogenase (GDH) in the nucleus and showed its impact on TET3 [195].

A recent study performed on cardiomyocytes describes that TCA cycle dehydrogenases, specifically pyruvate dehydrogenase subunit 1 (PDH-E1), malate dehydrogenase 2 (MDH-2), and isocitrate dehydrogenase 2 (IDH-2), translocated from the mitochondria to the nucleus as a stress response, but were absent in nuclei subcellular fractioning in cardiomyocytes in the control group [196]. After stress induction and confirmation of IDH-2 expression in the nucleus, some were treated with succinate, which significantly increased cell apoptosis, thus the inhibition of α-KG dependent enzymes (*i.e.,* TET and jmjC) by succinate [197] resulted in increased cell death, indicating the relevant role of the optimal α-KG, fumarate, and succinate levels in the nucleus. Additionally, nuclear-expressed IDH-2 was indirectly correlated with DNA and histone methylation, resulting in decreased methylation when cells were subjected to stress induction. Finally, IDH-2 expression showed a significant increase in accessibility and expression of cardioprotective genes, showing a chromatin-modification function. Meanwhile, mutant IDH-1 has been linked to DNA hypermethylation [198]. In acute myeloid leukemia, mutations of both IDH-1 and IDH-2 impaired TET2 function [199].

PDH-A1, MDH-2, IDH-3a, and KGDH, were identified in the nucleus during somatic cell programming. Specifically, nuclear PDH-A1 was found to increase nuclear acetyl-CoA which resulted in the increase of H3 acetylation levels [200], which directly impacts in gene expression programs.

Additional studies have specifically highlighted the translocation of the PDC. The experiments carried out by Sutendra et al., showed *de novo* production of acetyl-CoA as well as co-localization of PDC in the nuclei after pyruvate administration (Fig. 5) [201]. Additionally, histone acetylation was assessed and was found to be significantly decreased. This is mainly due to the impact acetyl-CoA has on HATs. Other studies have confirmed the localization of mitochondrial PDC in the nucleus, with interaction with STAT5 [202].

The nuclear translocation of selected mitochondrial TCA cycle dehydrogenases seems to be a relevant mechanism for adaptive stress response, as described by Srivastava et al. [203]. Exercise has been shown as an activator of PDC in muscle cells [204], although scarce literature exists related to this issue. Moreover, whether physical exercise can lead PDC components into the nucleus or activate nuclear PDC remains unknown at this moment.

Having established the importance of nuclear acetyl-CoA in the nucleus for epigenetic modulation through HATs, it is important to note the different nuclear sources that this molecule has. ATP-citrate lysate (ACLY) has been described in the nucleus and impacts histone methylation through the generation of acetyl-CoA [205]. Acetyl-CoA synthetases, including ACS1P and ACS2P, have also been described in the nucleus, being another source of acetyl-CoA for HATs [206].

As deduced from this section, scarce scientific evidence exists yet describing how mitochondrial TCA enzymes can migrate to the nucleus

or how the nuclear TCA can be regulated by physical exercise. So, how these nuclear processes and reactions related to nuclear TCA may impact epigenetic regulation remains at this moment elusive. Therefore, further research is needed to clarify these intriguing mechanisms which may relate mitochondrial to nucleus metabolic connection with epigenetic control during exercise, which could clearly have an impact on the neuromuscular adaptations to exercise. In fact, although not demonstrated at the moment, all these processes may be closely related with several phenomena involved in sarcomere repair by which transcriptional programs are activated together nuclear migration to the injury site in myofibers produced after physical exercise [132].

6. Conclusions and future perspectives

It appears that our knowledge of the precise epigenetic-related mechanisms of regulation that are induced by oxidative stress during physical exercise is far from being completely understood. In this review, we have presented an overview of our current understanding of metabolic regulation and integration during exercise and the utilization of its intermediates as regulators of epigenetic mechanisms. A recent work by Qiu et al. has tried to deep insight into the positive effects of physical exercise on the healthy status of people and showed how moderate-intensity exercise affects the major hallmarks of health [207]. Among other processes, physical exercise induces musculoskeletal injuries that requires efficient repair to preserve muscle homeostasis. It has been recently shown how cellular damage in the skeletal muscle can be repaired after myonuclei movement to injured sites and locally deliver of the messenger RNA for cellular repair and reconstruction [132]. As deduced from our review, for this process may be required the activation of transcriptional programs which require of changes in the epigenetic regulation, which can be modulated by metabolic and redox-dependent processes.

In any case, it is important to bear in mind the heterogeneity, complexity, and wide array of physical activities and specific training procedures. Currently, from the outcomes described in the current literature, it is not possible to propose a specific type of physical activity, exercise, intensity, and duration of training that could be beneficial for different subsets of the population. In any case, the genetic background, the metabolic control, and the epigenetic control of specific mechanisms that may facilitate the physiological adaptations during physical exercise seem to be carefully orchestrated and thus the different protocols of training must be studied in detail to understand the epigenetic-induce processes of metabolic adaptation that take place during physical exercise.

As shown in this review, oxidative stress, glycolytic mechanism, and TCA cycle are closely interconnected with epigenetic machinery. In fact, some of these important systems involved in the adaptation to physical exercise are specific epigenetic mechanisms that use metabolic intermediates, including oxygen, to regulate epigenetic signals [1,2].

Epigenetic modifications and many epigenetic enzymes are potentially dependent on changes in the levels of intermediate metabolites and products of the glycolysis (*i.e.,* lactate and acetyl-CoA) and the TCA cycle (*i.e.,* a-KG, 2-hydroxyglutarate, succinate and succinyl-CoA, fumarate, NAD^+/NADH and $FADH_2$), as well as other metabolic intermediates from the fatty acid oxidation such as β-hydroxybutyrate. In addition, at least mitochondrial TCA cycle enzymes can translocate to the nucleus in some conditions to produce a nuclear TCA cycle, which can provide the epigenetic machinery of appropriate substrates for the epigenetic modifications. In summary, this is an exciting field and in the future years, we will have relevant information about how physical exercise can modulate the epigenetic machinery and substrates and how they depend not only on the intensity and duration of the exercise, but also on the age, physical fitness, and health status of the person who is performing the physical activity.

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CRediT authorship contribution statement

José Luis García-Giménez: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Irene Cánovas-Cervera:** Formal analysis, Investigation, Writing – original draft. **Federico V. Pallardó:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jose Luis Garcia Gimenez reports a relationship with EpiDisease S.L. (Spin-Off from the University of Valencia) that includes: board membership and equity or stocks. Federico V. Pallardo reports a relationship with EpiDisease S.L. (Spin-Off from the University of Valencia) that includes: equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] F. Sanchis-Gomar, J.L. Garcia-Gimenez, C. Perez-Quilis, M.C. Gomez-Cabrera, F. V. Pallardo, G. Lippi, Physical exercise as an epigenetic modulator: eustress, the "positive stress" as an effector of gene expression, J. Strength Condit Res. 26 (2012), https://doi.org/10.1519/JSC.0b013e31825bb594.

[2] H. Pareja-Galeano, F. Sanchis-Gomar, J.L. García-Giménez, Physical exercise and epigenetic modulation: elucidating intricate mechanisms, Sports Med. (2014) 44, https://doi.org/10.1007/s40279-013-0138-6.

[3] J.A. Alegría-Torres, A. Baccarelli, V. Bollati, Epigenetics and lifestyle, Epigenomics 3 (2011) 267–277, https://doi.org/10.2217/epi.11.22.

[4] J. Vina, F. Sanchis-Gomar, V. Martinez-Bello, M. Gomez-Cabrera, Exercise acts as a drug; the pharmacological benefits of exercise, Br. J. Pharmacol. 167 (2012) 1–12, https://doi.org/10.1111/j.1476-5381.2012.01970.x.

[5] H.J. Forman, H. Zhang, Targeting oxidative stress in disease: promise and limitations of antioxidant therapy, Nat. Rev. Drug Discov. 20 (2021) 689–709, https://doi.org/10.1038/s41573-021-00233-1.

[6] L. Tretter, V. Adam-Vizi, Alpha-ketoglutarate dehydrogenase: a target and generator of oxidative stress, Phil. Trans. Biol. Sci. 360 (2005) 2335–2345, https://doi.org/10.1098/rstb.2005.1764.

[7] A.-L. Bulteau, M. Ikeda-Saito, L.I. Szweda, Redox-dependent modulation of aconitase activity in intact mitochondria, Biochemistry 42 (2003) 14846–14855, https://doi.org/10.1021/bi0353979.

[8] J.M. Mato, S.C. Lu, Role of S-adenosyl-L-methionine in liver health and injury, Hepatology 45 (2007) 1306–1312, https://doi.org/10.1002/hep.21650.

[9] J.S. Bhatti, G.K. Bhatti, P.H. Reddy, Mitochondrial dysfunction and oxidative stress in metabolic disorders — a step towards mitochondria based therapeutic strategies, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1863 (2017) 1066–1077, https://doi.org/10.1016/j.bbadis.2016.11.010.

[10] S.K. Biswas, Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxid. Med. Cell. Longev. 2016 (2016) 1–9, https://doi.org/10.1155/2016/5698931.

[11] M. Gleeson, N.C. Bishop, D.J. Stensel, M.R. Lindley, S.S. Mastana, M.A. Nimmo, The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease, Nat. Rev. Immunol. 11 (2011) 607–615, https://doi.org/10.1038/nri3041.

[12] K.M. Beavers, T.E. Brinkley, B.J. Nicklas, Effect of exercise training on chronic inflammation, Clin. Chim. Acta 411 (2010) 785–793, https://doi.org/10.1016/j.cca.2010.02.069.

[13] D.E.R. Warburton, Health benefits of physical activity: the evidence, Can. Med. Assoc. J. 174 (2006) 801–809, https://doi.org/10.1503/cmaj.051351.

[14] B.K. Pedersen, B. Saltin, Evidence for prescribing exercise as therapy in chronic disease, Scand. J. Med. Sci. Sports 16 (2006) 3–63, https://doi.org/10.1111/j.1600-0838.2006.00520.x.
[15] M. Flockhart, L.C. Nilsson, S. Tais, B. Ekblom, W. Apró, F.J. Larsen, Excessive exercise training causes mitochondrial functional impairment and decreases glucose tolerance in healthy volunteers, Cell Metabol. 33 (2021) 957–970.e6, https://doi.org/10.1016/j.cmet.2021.02.017.
[16] C.E. Cooper, N.B. Vollaard, T. Choueiri, M.T. Wilson, Exercise, free radicals and oxidative stress, Biochem. Soc. Trans. 30 (2002) 280–285.
[17] F. Baygutalp, Y. Buzdağlı, M. Ozan, M. Koz, N. Kılıç Baygutalp, G. Atasever, Impacts of different intensities of exercise on inflammation and hypoxia markers in low altitude, BMC Sports Sci. Med. Rehabil. 13 (2021) 145, https://doi.org/10.1186/s13102-021-00375-0.
[18] É. Cerqueira, D.A. Marinho, H.P. Neiva, O. Lourenço, Inflammatory effects of high and moderate intensity exercise—a systematic review, Front. Physiol. (2020) 10, https://doi.org/10.3389/fphys.2019.01550.
[19] J.P. Karl, L.M. Margolis, N.E. Murphy, C.T. Carrigan, J.W. Castellani, E. H. Madslien, H. Teien, S. Martini, S.J. Montain, S.M. Pasiakos, Military training elicits marked increases in plasma metabolomic signatures of energy metabolism, lipolysis, fatty acid oxidation, and ketogenesis, Phys. Rep. (2017) 5, https://doi.org/10.14814/phy2.13407.
[20] A.M. Brennan, M. Benson, J. Morningstar, M. Herzig, J. Robbins, R.E. Gerszten, R. Ross, Plasma metabolite profiles in response to chronic exercise, Med. Sci. Sports Exerc. 50 (2018) 1480–1486, https://doi.org/10.1249/MSS.0000000000001594.
[21] Q. Ding, Z. Gao, K. Chen, Q. Zhang, S. Hu, L. Zhao, Inflammation-related epigenetic modification: the bridge between immune and metabolism in type 2 diabetes, Front. Immunol. (2022) 13, https://doi.org/10.3389/fimmu.2022.883410.
[22] N. Khansari, Y. Shakiba, M. Mahmoudi, Chronic inflammation and oxidative stress as a major cause of age- related diseases and cancer, Recent Pat. Inflamm. Allergy Drug Discov. 3 (2009) 73–80, https://doi.org/10.2174/187221309787158371.
[23] K. Fisher-Wellman, R.J. Bloomer, Acute exercise and oxidative stress: a 30 year history, Dyn. Med. 8 (2009) 1, https://doi.org/10.1186/1476-5918-8-1.
[24] M. El Assar, A. Álvarez-Bustos, P. Sosa, J. Angulo, L. Rodríguez-Mañas, Effect of physical activity/exercise on oxidative stress and inflammation in muscle and vascular aging, Int. J. Mol. Sci. 23 (2022) 8713, https://doi.org/10.3390/ijms23158713.
[25] M. Gomarasca, K. Micielska, M. Faraldi, M. Flis, S. Perego, G. Banfi, E. Ziemann, G. Lombardi, Impact of 12-week moderate-intensity aerobic training on inflammasome complex activation in elderly women, Front. Physiol. (2022) 13, https://doi.org/10.3389/fphys.2022.792859.
[26] R. Jankord, B. Jemiolo, Influence of physical activity on serum IL-6 and IL-10 levels in healthy older men, Med. Sci. Sports Exerc. 36 (2004) 960–964, https://doi.org/10.1249/01.MSS.0000128186.09416.18.
[27] J. Norrbom, E.K. Sällstedt, H. Fischer, C.J. Sundberg, H. Rundqvist, T. Gustafsson, Alternative splice variant PGC-1α-b is strongly induced by exercise in human skeletal muscle, Am. J. Physiol. Endocrinol. Metabol. 301 (2011) E1092–E1098, https://doi.org/10.1152/ajpendo.00119.2011.
[28] J. Norrbom, S.E. Wallman, T. Gustafsson, H. Rundqvist, E. Jansson, C. J. Sundberg, Training response of mitochondrial transcription factors in human skeletal muscle, Acta Physiol. 198 (2010) 71–79, https://doi.org/10.1111/j.1748-1716.2009.02030.x.
[29] J. Ntanasis-Stathopoulos, J.G. Tzanninis, A. Philippou, M. Koutsilieris, Epigenetic regulation on gene expression induced by physical exercise, J. Musculoskelet. Neuronal Interact. 13 (2013) 133–146.
[30] S. Raghuraman, I. Donkin, S. Versteyhe, R. Barrès, D. Simar, The emerging role of epigenetics in inflammation and immunometabolism, Trends Endocrinol. Metabol. 27 (2016) 782–795, https://doi.org/10.1016/j.tem.2016.06.008.
[31] T. Jenuwein, D.C. Allis, Translating the histone code, Science 11 (2001) 1074–1080, 1979.
[32] A.D. Goldberg, C.D. Allis, E. Bernstein, Epigenetics: a landscape takes shape, Cell 128 (2007) 635–638, https://doi.org/10.1016/j.cell.2007.02.006.
[33] A. Bird, DNA methylation patterns and epigenetic memory, Genes Dev. 16 (2002) 6–21, https://doi.org/10.1101/gad.947102.
[34] H.G. Stunnenberg, M. Hirst, S. Abrignani, D. Adams, M. de Almeida, L. Altucci, V. Amin, I. Amit, S.E. Antonarakis, S. Aparicio, et al., The international human epigenome consortium: a blueprint for scientific collaboration and discovery, Cell 167 (2016) 1145–1149, https://doi.org/10.1016/j.cell.2016.11.007.
[35] P.A. Jones, R. Martienssen, A blueprint for a human epigenome project: the AACR human epigenome workshop, Cancer Res. 65 (2005) 11241–11246, https://doi.org/10.1158/0008-5472.CAN-05-3865.
[36] L. Wang, X. Zhao, Y. Lu, J. Xiao, Noncoding RNAs: a new frontier in regulation of exercise-induced physiological cardiac hypertrophy, Curr. Opin Physiol. 33 (2023) 100653, https://doi.org/10.1016/j.cophys.2023.100653.
[37] C.C.M. Correia, L.F. Rodrigues, B.R. de Avila Pelozin, E.M. Oliveira, T. Fernandes, Long non-coding RNAs in cardiovascular diseases: potential function as biomarkers and therapeutic targets of exercise training, Noncoding RNA 7 (2021) 65, https://doi.org/10.3390/ncrna7040065.
[38] B. Bonilauri, B. Dallagiovanna, Long non-coding RNAs are differentially expressed after different exercise training programs, Front. Physiol. (2020) 11, https://doi.org/10.3389/fphys.2020.567614.
[39] K. Vargas-Ortiz, V. Pérez-Vázquez, M.H. Macías-Cervantes, Exercise and sirtuins: a way to mitochondrial health in skeletal muscle, Int. J. Mol. Sci. 20 (2019) 2717, https://doi.org/10.3390/ijms20112717.
[40] Z. Radak, E. Koltai, A.W. Taylor, M. Higuchi, S. Kumagai, H. Ohno, S. Goto, I. Boldogh, Redox-regulating sirtuins in aging, caloric restriction, and exercise, Free Radic. Biol. Med. 58 (2013) 87–97, https://doi.org/10.1016/j.freeradbiomed.2013.01.004.
[41] M.D. Nitert, T. Dayeh, P. Volkov, T. Elgzyri, E. Hall, E. Nilsson, B.T. Yang, S. Lang, H. Parikh, Y. Wessman, et al., Impact of an exercise intervention on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes, Diabetes 61 (2012) 3322–3332, https://doi.org/10.2337/db11-1653.
[42] T. Kanzleiter, M. Jähnert, G. Schulze, J. Selbig, N. Hallahan, R.W. Schwenk, A. Schürmann, Exercise training alters DNA methylation patterns in genes related to muscle growth and differentiation in mice, Am. J. Physiol. Endocrinol. Metabol. 308 (2015) E912–E920, https://doi.org/10.1152/ajpendo.00289.2014.
[43] S. Voisin, N. Eynon, X. Yan, D.J. Bishop, Exercise training and DNA methylation in humans, Acta Physiol. 213 (2015) 39–59, https://doi.org/10.1111/apha.12414.
[44] J. Ntanasis-Stathopoulos, J.G. Tzanninis, A. Philippou, M. Koutsilieris, Epigenetic regulation on gene expression induced by physical exercise, J. Musculoskelet. Neuronal Interact. 13 (2013) 133–146.
[45] R. Barrès, J. Yan, B. Egan, J.T. Treebak, M. Rasmussen, T. Fritz, K. Caidahl, A. Krook, D.J. O'Gorman, J.R. Zierath, Acute exercise remodels promoter methylation in human skeletal muscle, Cell Metabol. 15 (2012) 405–411, https://doi.org/10.1016/j.cmet.2012.01.001.
[46] E. Barrón-Cabrera, O. Ramos-Lopez, K. González-Becerra, J.I. Riezu-Boj, F. I. Milagro, E. Martínez-López, J.A. Martínez, Epigenetic modifications as outcomes of exercise interventions related to specific metabolic alterations: a systematic review, Lifestyle Genom. 12 (2019) 25–44, https://doi.org/10.1159/000503289.
[47] F. Ursini, M. Maiorino, Lipid peroxidation and ferroptosis: the role of GSH and GPx4, Free Radic. Biol. Med. 152 (2020) 175–185, https://doi.org/10.1016/j.freeradbiomed.2020.02.027.
[48] H. Sies, Biochemistry of oxidative stress, Angew Chem. Int. Ed. Engl. 25 (1986) 1058–1071, https://doi.org/10.1002/anie.198610581.
[49] H. Sies, On the history of oxidative stress: concept and some aspects of current development, Curr Opin Toxicol 7 (2018) 122–126, https://doi.org/10.1016/j.cotox.2018.01.002.
[50] H. Sies, Oxidative eustress: on constant alert for redox homeostasis, Redox Biol. 41 (2021) 101867, https://doi.org/10.1016/j.redox.2021.101867.
[51] H. Selye, Stress and distress, Compr. Ther. 1 (1975) 9–13.
[52] J.N. Cobley, G.K. Sakellariou, D.J. Owens, S. Murray, S. Waldron, W. Gregson, W. D. Fraser, J.G. Burniston, L.A. Iwanejko, A. McArdle, et al., Lifelong training preserves some redox-regulated adaptive responses after an acute exercise stimulus in aged human skeletal muscle, Free Radic. Biol. Med. 70 (2014) 23–32, https://doi.org/10.1016/j.freeradbiomed.2014.02.004.
[53] I.A. Samjoo, A. Safdar, M.J. Hamadeh, S. Raha, M.A. Tarnopolsky, The effect of endurance exercise on both skeletal muscle and systemic oxidative stress in previously sedentary obese men, Nutr. Diabetes 3 (2013), https://doi.org/10.1038/nutd.2013.30 e88–e88.
[54] C. Brinkmann, N. Chung, U. Schmidt, T. Kreutz, E. Lenzen, T. Schiffer, S. Geisler, C. Graf, G. Montiel-Garcia, R. Renner, et al., Training alters the skeletal muscle antioxidative capacity in non-insulin-dependent type 2 diabetic men, Scand. J. Med. Sci. Sports 22 (2012) 462–470, https://doi.org/10.1111/j.1600-0838.2010.01273.x.
[55] A. Linke, V. Adams, P.C. Schulze, S. Erbs, S. Gielen, E. Fiehn, S. Möbius-Winkler, A. Schubert, G. Schuler, R. Hambrecht, Antioxidative effects of exercise training in patients with chronic heart failure, Circulation 111 (2005) 1763–1770, https://doi.org/10.1161/01.CIR.0000165503.08661.E5.
[56] M.C. Gomez-Cabrera, A. Salvador-Pascual, H. Cabo, B. Ferrando, J. Viña, Redox modulation of mitochondriogenesis in exercise. Does antioxidant supplementation blunt the benefits of exercise training? Free Radic. Biol. Med. 86 (2015) 37–46, https://doi.org/10.1016/j.freeradbiomed.2015.04.006.
[57] J. Finaud, G. Lac, E. Filaire, Oxidative stress, Sports Med. 36 (2006) 327–358, https://doi.org/10.2165/00007256-200636040-00004.
[58] M. Ristow, K. Zarse, How increased oxidative stress promotes longevity and metabolic health: the concept of mitochondrial hormesis (mitohormesis), Exp. Gerontol. 45 (2010) 410–418, https://doi.org/10.1016/j.exger.2010.03.014.
[59] G. Lenaz, Role of mitochondria in oxidative stress and ageing, Biochim. Biophys. Acta Bioenerg. 1366 (1998) 53–67, https://doi.org/10.1016/S0005-2728(98)00120-0.
[60] B. Sjödin, Y.H. Westing, F.S. Apple, Biochemical mechanisms for oxygen free radical formation during exercise, Sports Med. 10 (1990) 236–254, https://doi.org/10.2165/00007256-199010040-00003.
[61] S.K. Powers, M.J. Jackson, Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production, Physiol. Rev. 88 (2008) 1243–1276, https://doi.org/10.1152/physrev.00031.2007.
[62] D. Morales-Alamo, J.A.L. Calbet, Free radicals and sprint exercise in humans, Free Radic. Res. 48 (2014) 30–42, https://doi.org/10.3109/10715762.2013.825043.
[63] F.J. Larsen, T.A. Schiffer, N. Ørtenblad, C. Zinner, D. Morales-Alamo, S.J. Willis, J.A. Calbet, H. Holmberg, R. Boushel, High-intensity sprint training inhibits mitochondrial respiration through aconitase inactivation, Faseb. J. 30 (2016) 417–427, https://doi.org/10.1096/fj.15-276857.
[64] D.C. Mckenzie, Markers of excessive exercise, Can. J. Appl. Physiol. 24 (1999) 66–73, https://doi.org/10.1139/h99-007.
[65] C. Petibois, G. Cazorla, J.-R. Poortmans, D??l??ris G. Biochemical aspects of overtraining in endurance sports, Sports Med. 32 (2002) 867–878, https://doi.org/10.2165/00007256-200232130-00005.

[66] A.G.J.S.J. Viña, Mechanism of free radical production in exhaustive exercise in humans and rats; role of xanthine oxidase and protection by allopurinol, IUBMB Life 49 (2000) 539–544, https://doi.org/10.1080/15216540050167098.
[67] K.J.A. Davies, A.T. Quintanilha, G.A. Brooks, L. Packer, Free radicals and tissue damage produced by exercise, Biochem. Biophys. Res. Commun. 107 (1982) 1198–1205, https://doi.org/10.1016/S0006-291X(82)80124-1.
[68] Y. Kobayashi, A. Nakatsuji, W. Aoi, S. Wada, M. Kuwahata, Y. Kido, Intense exercise increases protein oxidation in spleen and liver of mice, Nutr. Metab. Insights 7 (2014) S13668, https://doi.org/10.4137/NMI.S13668. NMI.
[69] D.V. Tryfidou, C. McClean, M.G. Nikolaidis, G.W. Davison, DNA damage following acute aerobic exercise: a systematic review and meta-analysis, Sports Med. 50 (2020) 103–127, https://doi.org/10.1007/s40279-019-01181-y.
[70] Y. Lu, H.D. Wiltshire, J.S. Baker, Q. Wang, Effects of high intensity exercise on oxidative stress and antioxidant status in untrained humans: a systematic review, Biology 10 (2021) 1272, https://doi.org/10.3390/biology10121272.
[71] A.L. Bessa, V.N. Oliveira, G. Agostini G, R.J.S. Oliveira, A.C.S. Oliveira, G. E. White, G.D. Wells, D.N.S. Teixeira, F.S. Espindola, Exercise intensity and recovery, J. Strength Condit Res. 30 (2016) 311–319, https://doi.org/10.1519/JSC.0b013e31828f1ee9.
[72] A. Thirupathi, M. Wang, J.K. Lin, G. Fekete, B. István, J.S. Baker, Y. Gu, Effect of different exercise modalities on oxidative stress: a systematic review, BioMed Res. Int. 2021 (2021) 1–10, https://doi.org/10.1155/2021/1947928.
[73] S. Luti, A. Modesti, P.A. Modesti, Inflammation, peripheral signals and redox homeostasis in athletes who practice different sports, Antioxidants 9 (2020) 1065, https://doi.org/10.3390/antiox9111065.
[74] E. Fehrenbach, H. Northoff, Free radicals, exercise, apoptosis, and heat shock proteins, Exerc. Immunol. Rev. 7 (2001) 66–89.
[75] S. Di Meo, P. Venditti, Mitochondria in exercise-induced oxidative stress, Neurosignals 10 (2001) 125–140, https://doi.org/10.1159/000046880.
[76] P.M. Clarkson, H.S. Thompson, Antioxidants: what role do they play in physical activity and health? Am. J. Clin. Nutr. 72 (2000) 637S–646S, https://doi.org/10.1093/ajcn/72.2.637S.
[77] K. Kawai, Y.-S. Li, M.-F. Song, H. Kasai, DNA methylation by dimethyl sulfoxide and methionine sulfoxide triggered by hydroxyl radical and implications for epigenetic modifications, Bioorg. Med. Chem. Lett 20 (2010) 260–265, https://doi.org/10.1016/j.bmcl.2009.10.124.
[78] S.K. Goswami, Cellular Redox, Epigenetics and Diseases, 2013, pp. 527–542, https://doi.org/10.1007/978-94-007-4525-4_23.
[79] J.L. García-Giménez, G. Olaso, S.B. Hake, C. Bönisch, S.M. Wiedemann, J. Markovic, F. Dasí, A. Gimeno, C. Pérez-Quilis, O. Palacios, et al., Histone H3 glutathionylation in proliferating mammalian cells destabilizes nucleosomal structure, Antioxidants Redox Signal. (2013) 19, https://doi.org/10.1089/ars.2012.5021.
[80] A. Riccio, R.S. Alvania, B.E. Lonze, N. Ramanan, T. Kim, Y. Huang, T.M. Dawson, S.H. Snyder, D.D. Ginty, A nitric oxide signaling pathway controls CREB-mediated gene expression in neurons, Mol. Cell. 21 (2006) 283–294, https://doi.org/10.1016/j.molcel.2005.12.006.
[81] K. Dixit, M.A. Khan, Y.D. Sharma, Alam K. Moinuddin, Physicochemical studies on peroxynitrite-modified H3 histone, Int. J. Biol. Macromol. 46 (2010) 20–26, https://doi.org/10.1016/j.ijbiomac.2009.10.009.
[82] R.C. Bovee, J.R. Hickok, D. Vasudevan, D.D. Thomas, Mechanisms of epigenetic regulation by nitric oxide, Nitric Oxide (2017) 255–270, https://doi.org/10.1016/B978-0-12-804273-1.00020-X. Elsevier.
[83] J.L. García-Giménez, A.M.V. Ledesma, I. Esmoris, C. Romá-Mateo, P. Sanz, J. Viña, F.V. Pallardó, Histone carbonylation occurs in proliferating cells, Free Radic. Biol. Med. 52 (2012) 1453–1464, https://doi.org/10.1016/j.freeradbiomed.2012.01.022.
[84] G.T. Wondrak, D. Cervantes-Laurean, E.L. Jacobson, M.K. Jacobson, Histone carbonylation in vivo and in vitro, Biochem. J. 351 (Pt 3) (2000) 769–777.
[85] A.K. Hauck, T. Zhou, A. Upadhyay, Y. Sun, M.B. O'Connor, Y. Chen, D. A. Bernlohr, Histone carbonylation is a redox-regulated epigenomic mark that accumulates with obesity and aging, Antioxidants 9 (2020) 1210, https://doi.org/10.3390/antiox9121210.
[86] J.L. García-Giménez, C. Romá-Mateo, F.V. Pallardó, Oxidative post-translational modifications in histones, Biofactors (2019) 45, https://doi.org/10.1002/biof.1532.
[87] A. de Luca, N. Moroni, A. Serafino, A. Primavera, A. Pastore, J.Z. Pedersen, R. Petruzzelli, M.G. Farrace, P. Pierimarchi, G. Moroni, et al., Treatment of doxorubicin-resistant MCF7/Dx cells with nitric oxide causes histone glutathionylation and reversal of drug resistance, Biochem. J. 440 (2011) 175–183, https://doi.org/10.1042/BJ20111333.
[88] J.L. García-Giménez, C. Romá-Mateo, G. Pérez-Machado, L. Peiró-Chova, F. V. Pallardó, Role of glutathione in the regulation of epigenetic mechanisms in disease, Free Radic. Biol. Med. 112 (2017) 36–48, https://doi.org/10.1016/j.freeradbiomed.2017.07.008.
[89] Y. Niu, T.L. DesMarais, Z. Tong, Y. Yao, M. Costa, Oxidative stress alters global histone modification and DNA methylation, Free Radic. Biol. Med. 82 (2015) 22–28, https://doi.org/10.1016/j.freeradbiomed.2015.01.028.
[90] P.A. Kramer, J. Duan, M.J. Gaffrey, A.K. Shukla, L. Wang, T.K. Bammler, W.-J. Qian, D.J. Marcinek, Fatiguing contractions increase protein S-glutathionylation occupancy in mouse skeletal muscle, Redox Biol. 17 (2018) 367–376, https://doi.org/10.1016/j.redox.2018.05.011.
[91] J.O. Holloszy, E.F. Coyle, Adaptations of skeletal muscle to endurance exercise and their metabolic consequences, J. Appl. Physiol. 56 (1984) 831–838, https://doi.org/10.1152/jappl.1984.56.4.831.
[92] M. Wiese, A.J. Bannister, Two genomes, one cell: mitochondrial-nuclear coordination via epigenetic pathways, Mol. Metabol. 38 (2020) 100942, https://doi.org/10.1016/j.molmet.2020.01.006.
[93] K.A. Burgomaster, N.M. Cermak, S.M. Phillips, C.R. Benton, A. Bonen, M. J. Gibala, Divergent response of metabolite transport proteins in human skeletal muscle after sprint interval training and detraining, Am. J. Physiol. Regul. Integr. Comp. Physiol. 292 (2007) R1970–R1976, https://doi.org/10.1152/ajpregu.00503.2006.
[94] S.L. McGee, M. Hargreaves, Exercise and skeletal muscle glucose transporter 4 expression: molecular mechanisms, Clin. Exp. Pharmacol. Physiol. 33 (2006) 395–399, https://doi.org/10.1111/j.1440-1681.2006.04362.x.
[95] T.E. Graham, K.B. Adamo, J. Shearer, I. Marchand, B. Saltin, Pro- and macroglycogenolysis: relationship with exercise intensity and duration, J. Appl. Physiol. 90 (2001) 873–879, https://doi.org/10.1152/jappl.2001.90.3.873.
[96] A. Facey, R. Irving, L. Dilworth, Overview of lactate metabolism and the implications for athletes, American J. Sports Sci. Med. 1 (2013) 42–46.
[97] S. Hui, J.M. Ghergurovich, R.J. Morscher, C. Jang, X. Teng, W. Lu, L.A. Esparza, T. Reya, Le Zhan, J. Yanxiang Guo, et al., Glucose feeds the TCA cycle via circulating lactate, Nature 551 (2017) 115–118, https://doi.org/10.1038/nature24057.
[98] E.F. Coyle, Physical activity as a metabolic stressor, Am. J. Clin. Nutr. 72 (2000) 512S–520S, https://doi.org/10.1093/ajcn/72.2.512S.
[99] L.J.C. Loon, P.L. Greenhaff, D. Constantin-Teodosiu, W.H.M. Saris, A.J. M. Wagenmakers, The effects of increasing exercise intensity on muscle fuel utilisation in humans, J. Physiol. 536 (2001) 295–304, https://doi.org/10.1111/j.1469-7793.2001.00295.x.
[100] G. van Hall, Lactate kinetics in human tissues at rest and during exercise, Acta Physiol. 199 (2010) 499–508, https://doi.org/10.1111/j.1748-1716.2010.02122.x.
[101] R.S. Mazzeo, G.A. Brooks, D.A. Schoeller, T.F. Budinger, Disposal of blood [1-13C]lactate in humans during rest and exercise, J. Appl. Physiol. 60 (1986) 232–241, https://doi.org/10.1152/jappl.1986.60.1.232.
[102] T. Jenssen, N. Nurjhan, A. Consoli, J.E. Gerich, Dose-response effects of lactate infusions on gluconeogenesis from lactate in normal man, Eur. J. Clin. Invest. 23 (1993) 448–454, https://doi.org/10.1111/j.1365-2362.1993.tb00789.x.
[103] A. Consoli, N. Nurjhan, J.J. Reilly, D.M. Bier, J.E. Gerich, Contribution of liver and skeletal muscle to alanine and lactate metabolism in humans, Am. J. Physiol. Endocrinol. Metabol. 259 (1990) E677–E684, https://doi.org/10.1152/ajpendo.1990.259.5.E677.
[104] B.C. Bergman, M.A. Horning, G.A. Casazza, E.E. Wolfel, G.E. Butterfield, G. A. Brooks, Endurance training increases gluconeogenesis during rest and exercise in men, Am. J. Physiol. Endocrinol. Metabol. 278 (2000) E244–E251, https://doi.org/10.1152/ajpendo.2000.278.2.E244.
[105] T.D. Bhagat, D. Von Ahrens, M. Dawlaty, Y. Zou, J. Baddour, A. Achreja, H. Zhao, L. Yang, B. Patel, C. Kwak, et al., Lactate-mediated epigenetic reprogramming regulates formation of human pancreatic cancer-associated fibroblasts, Elife (2019) 8, https://doi.org/10.7554/eLife.50663.
[106] D. Zhang, Z. Tang, H. Huang, G. Zhou, C. Cui, Y. Weng, W. Liu, S. Kim, S. Lee, M. Perez-Neut, et al., Metabolic regulation of gene expression by histone lactylation, Nature 574 (2019) 575–580, https://doi.org/10.1038/s41586-019-1678-1.
[107] L.T. Izzo, K.E. Wellen, Histone lactylation links metabolism and gene regulation, Nature 574 (2019) 492–493, https://doi.org/10.1038/d41586-019-03122-1.
[108] J. Jiang, D. Huang, Y. Jiang, J. Hou, M. Tian, J. Li, L. Sun, Y. Zhang, T. Zhang, Z. Li, et al., Lactate modulates cellular metabolism through histone lactylation-mediated gene expression in non-small cell lung cancer, Front. Oncol. (2021) 11, https://doi.org/10.3389/fonc.2021.647559.
[109] E. Galle, C.-W. Wong, A. Ghosh, T. Desgeorges, K. Melrose, L.C. Hinte, D. Castellano-Castillo, M. Engl, J.A. de Sousa, F.J. Ruiz-Ojeda, et al., H3K18 lactylation marks tissue-specific active enhancers, Genome Biol. 23 (2022) 207, https://doi.org/10.1186/s13059-022-02775-y.
[110] M.V. Liberti, J.W. Locasale, Histone lactylation: a new role for glucose metabolism, Trends Biochem. Sci. 45 (2020) 179–182, https://doi.org/10.1016/j.tibs.2019.12.004.
[111] N. Wang, W. Wang, X. Wang, G. Mang, J. Chen, X. Yan, Z. Tong, Q. Yang, M. Wang, L. Chen, et al., Histone lactylation boosts reparative gene activation post–myocardial infarction, Circ. Res. 131 (2022) 893–908, https://doi.org/10.1161/CIRCRESAHA.122.320488.
[112] D. Zhang, Z. Tang, H. Huang, G. Zhou, C. Cui, Y. Weng, W. Liu, S. Kim, S. Lee, M. Perez-Neut, et al., Metabolic regulation of gene expression by histone lactylation, Nature 574 (2019) 575–580, https://doi.org/10.1038/s41586-019-1678-1.
[113] A. Salminen, A. Kauppinen, M. Hiltunen, K. Kaarniranta, Krebs cycle intermediates regulate DNA and histone methylation: epigenetic impact on the aging process, Ageing Res. Rev. 16 (2014) 45–65, https://doi.org/10.1016/j.arr.2014.05.004.
[114] R. Gupte, Z. Liu, W.L. Kraus, PARPs and ADP-ribosylation: recent advances linking molecular functions to biological outcomes, Genes Dev. 31 (2017) 101–126, https://doi.org/10.1101/gad.291518.116.
[115] J.L. García-Giménez, J.S. Ibañez-Cabellos, M. Seco-Cervera, F.V. Pallardó, Glutathione and cellular redox control in epigenetic regulation, Free Radic. Biol. Med. 75 (2014) S3, https://doi.org/10.1016/j.freeradbiomed.2014.10.828.
[116] A.T. White, S. Schenk, NAD $^{+}$/NADH and skeletal muscle mitochondrial adaptations to exercise, Am. J. Physiol. Endocrinol. Metabol. 303 (2012) E308–E321, https://doi.org/10.1152/ajpendo.00054.2012.

[117] N. Xie, L. Zhang, W. Gao, C. Huang, P.E. Huber, X. Zhou, C. Li, G. Shen, B. Zou, NAD+ metabolism: pathophysiologic mechanisms and therapeutic potential, Signal Transduct. Targeted Ther. 5 (2020) 227, https://doi.org/10.1038/s41392-020-00311-7.
[118] J.L. García-Giménez, F.V. Pallardó, Maintenance of glutathione levels and its importance in epigenetic regulation, Front. Pharmacol. (2014), https://doi.org/10.3389/fphar.2014.00088, 5 MAY.
[119] J. Markovic, J.L. García-Gimenez, A. Gimeno, J. Viña, F.V. Pallardó, Role of glutathione in cell nucleus, Free Radic. Res. 44 (2010), https://doi.org/10.3109/10715762.2010.485989.
[120] J.L. García-Giménez, A.M.V. Ledesma, I. Esmoris, C. Romá-Mateo, P. Sanz, J. Viña, F.V. Pallardó, Histone carbonylation occurs in proliferating cells, Free Radic. Biol. Med. (2012) 52, https://doi.org/10.1016/j.freeradbiomed.2012.01.022.
[121] J. Henriksson, A. Katz, K. Sahlin, Redox state changes in human skeletal muscle after isometric contraction, J. Physiol. 380 (1986) 441–451, https://doi.org/10.1113/jphysiol.1986.sp016296.
[122] K. Sahlin, NADH in human skeletal muscle during short-term intense exercise, Pflügers Archiv Eur. J. Physio. 403 (1985) 193–196, https://doi.org/10.1007/BF00584099.
[123] A. Katz, K. Sahlin, Effect of decreased oxygen availability on NADH and lactate contents in human skeletal muscle during exercise, Acta Physiol. Scand. 131 (1987) 119–127, https://doi.org/10.1111/j.1748-1716.1987.tb08213.x.
[124] K. Sahlin, A. Katz, J. Henriksson, Redox state and lactate accumulation in human skeletal muscle during dynamic exercise, Biochem. J. 245 (1987) 551–556, https://doi.org/10.1042/bj2450551.
[125] S. Imai, C.M. Armstrong, M. Kaeberlein, L. Guarente, Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase, Nature 403 (2000) 795–800, https://doi.org/10.1038/35001622.
[126] H. Tian, S. Liu, J. Ren, J.K.W. Lee, R. Wang, P. Chen, Role of histone deacetylases in skeletal muscle physiology and systemic energy homeostasis: implications for metabolic diseases and therapy, Front. Physiol. (2020) 11, https://doi.org/10.3389/fphys.2020.00949.
[127] G. Yang, Y. Chen, J. Wu, S.-H. Chen, X. Liu, A.K. Singh, X. Yu, Poly(ADP-ribosyl)ation mediates early phase histone eviction at DNA lesions, Nucleic Acids Res. 48 (2020) 3001–3013, https://doi.org/10.1093/nar/gkaa022.
[128] M. Moreno-Villanueva, A. Kramer, T. Hammes, M. Venegas-Carro, P. Thumm, A. Bürkle, M. Gruber, Influence of acute exercise on DNA repair and PARP activity before and after irradiation in lymphocytes from trained and untrained individuals, Int. J. Mol. Sci. 20 (2019) 2999, https://doi.org/10.3390/ijms20122999.
[129] J.S. Mohamed, J.C. Wilson, M.J. Myers, K.J. Sisson, S.E. Alway, Dysregulation of SIRT-1 in aging mice increases skeletal muscle fatigue by a PARP-1-dependent mechanism, Aging 6 (2014) 820–834, https://doi.org/10.18632/aging.100696.
[130] E. Danese, G. Lippi, F. Sanchis-Gomar, G. Brocco, M. Rizzo, M. Banach, M. Montagnana, Physical Exercise and DNA Injury, 2017, pp. 193–230, https://doi.org/10.1016/bs.acc.2017.01.005.
[131] J.N. Cobley, N.V. Margaritelis, J.P. Morton, G.L. Close, M.G. Nikolaidis, J. K. Malone, The basic chemistry of exercise-induced DNA oxidation: oxidative damage, redox signaling, and their interplay, Front. Physiol. (2015) 6, https://doi.org/10.3389/fphys.2015.00182.
[132] W. Roman, H. Pinheiro, M.R. Pimentel, J. Segalés, L.M. Oliveira, E. García-Domínguez, M.C. Gómez-Cabrera, A.L. Serrano, E.R. Gomes, P. Muñoz-Cánoves, Muscle repair after physiological damage relies on nuclear migration for cellular reconstruction, Science 2021 (374) (1979) 355–359, https://doi.org/10.1126/science.abe5620.
[133] M. Moreno-Villanueva, A. Kramer, T. Hammes, M. Venegas-Carro, P. Thumm, A. Bürkle, M. Gruber, Influence of acute exercise on DNA repair and PARP activity before and after irradiation in lymphocytes from trained and untrained individuals, Int. J. Mol. Sci. 20 (2019) 2999, https://doi.org/10.3390/ijms20122999.
[134] J.N. Cobley, G.K. Sakellariou, S. Murray, S. Waldron, W. Gregson, J.G. Burniston, J.P. Morton, L.A. Iwanejko, G.L. Close, Lifelong endurance training attenuates age-related genotoxic stress in human skeletal muscle, Longev. Heal. 2 (2013) 11, https://doi.org/10.1186/2046-2395-2-11.
[135] B. Stocks, S.P. Ashcroft, S. Joanisse, L.C. Dansereau, Y.C. Koay, Y.S. Elhassan, G. G. Lavery, L. Quek, J.F. O'Sullivan, A.M. Philp, et al., Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise, J. Physiol. 599 (2021) 1513–1531, https://doi.org/10.1113/JP280825.
[136] J.N. Cobley, G.K. Sakellariou, S. Murray, S. Waldron, W. Gregson, J.G. Burniston, J.P. Morton, L.A. Iwanejko, G.L. Close, Lifelong endurance training attenuates age-related genotoxic stress in human skeletal muscle, Longev. Heal. 2 (2013) 11, https://doi.org/10.1186/2046-2395-2-11.
[137] A.K. Hauck, T. Zhou, A. Upadhyay, Y. Sun, M.B. O'Connor, Y. Chen, D. A. Bernlohr, Histone carbonylation is a redox-regulated epigenomic mark that accumulates with obesity and aging, Antioxidants 9 (2020) 1210, https://doi.org/10.3390/antiox9121210.
[138] T.G. Anthony, Mechanisms of protein balance in skeletal muscle, Domest. Anim. Endocrinol. 56 (2016) S23–S32, https://doi.org/10.1016/j.domaniend.2016.02.012.
[139] J.J.S. VerPlank, S. Lokireddy, J. Zhao, A.L. Goldberg, 26S Proteasomes are rapidly activated by diverse hormones and physiological states that raise cAMP and cause Rpn6 phosphorylation, Proc. Natl. Acad. Sci. USA 116 (2019) 4228–4237, https://doi.org/10.1073/pnas.1809254116.
[140] X. Liang, L. Liu, T. Fu, Q. Zhou, D. Zhou, L. Xiao, J. Liu, Y. Kong, H. Xie, F. Yi, et al., Exercise inducible lactate dehydrogenase B regulates mitochondrial function in skeletal muscle, J. Biol. Chem. 291 (2016) 25306–25318, https://doi.org/10.1074/jbc.M116.749424.
[141] L. Zorro Shahidian, M. Haas, S. Le Gras, S. Nitsch, A. Mourão, A. Geerlof, R. Margueron, J. Michaelis, S. Daujat, R. Schneider, Succinylation of H3K122 destabilizes nucleosomes and enhances transcription, EMBO Rep. (2021) 22, https://doi.org/10.15252/embr.202051009.
[142] G.D. Wells, H. Selvadurai, I. Tein, Bioenergetic provision of energy for muscular activity, Paediatr. Respir. Rev. 10 (2009) 83–90, https://doi.org/10.1016/j.prrv.2009.04.005.
[143] O. Matilainen, P.M. Quirós, J. Auwerx, Mitochondria and epigenetics – crosstalk in homeostasis and stress, Trends Cell Biol. 27 (2017) 453–463, https://doi.org/10.1016/j.tcb.2017.02.004.
[144] M.J. Gibala, D.A. MacLean, T.E. Graham, B. Saltin, Tricarboxylic acid cycle intermediate pool size and estimated cycle flux in human muscle during exercise, Am. J. Physiol. Endocrinol. Metabol. 275 (1998) E235–E242, https://doi.org/10.1152/ajpendo.1998.275.2.E235.
[145] J. Maurer, M. Hoene, C. Weigert, Signals from the circle: tricarboxylic acid cycle intermediates as myometabokines, Metabolites 11 (2021) 474, https://doi.org/10.3390/metabo11080474.
[146] M. Tahiliani, K.P. Koh, Y. Shen, W.A. Pastor, H. Bandukwala, Y. Brudno, S. Agarwal, L.M. Iyer, D.R. Liu, L. Aravind, et al., Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1, Science 2009 (324) (1979) 930–935, https://doi.org/10.1126/science.1170116.
[147] M. Hirsilä, P. Koivunen, V. Günzler, K.I. Kivirikko, J. Myllyharju, Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor, J. Biol. Chem. 278 (2003) 30772–30780, https://doi.org/10.1074/jbc.M304982200.
[148] Y. Tsukada, J. Fang, H. Erdjument-Bromage, M.E. Warren, C.H. Borchers, P. Tempst, Y. Zhang, Histone demethylation by a family of JmjC domain-containing proteins, Nature 439 (2006) 811–816, https://doi.org/10.1038/nature04433.
[149] Y. Yuan, P. Xu, Q. Jiang, X. Cai, T. Wang, W. Peng, J. Sun, C. Zhu, C. Zhang, D. Yue, et al., Exercise-induced α-ketoglutaric acid stimulates muscle hypertrophy and fat loss through OXGR1-dependent adrenal activation, EMBO J. (2020) 39, https://doi.org/10.15252/embj.2019103304.
[150] Y. Sekita, Y. Sugiura, A. Matsumoto, Y. Kawasaki, K. Akasaka, R. Konno, M. Shimizu, T. Ito, E. Sugiyama, T. Yamazaki, et al., AKT signaling is associated with epigenetic reprogramming via the upregulation of TET and its cofactor, alpha-ketoglutarate during iPSC generation, Stem Cell Res. Ther. 12 (2021) 510, https://doi.org/10.1186/s13287-021-02578-1.
[151] H. Barbosa, W. Ramadan, J. Matzenbacher dos Santos, S.A. Benite-Ribeiro, Effects of physical exercise on mitochondrial biogenesis of skeletal muscle modulated by histones modifications in type 2 diabetes, Open Access Maced. J. Med. Sci. 10 (2022) 590–599, https://doi.org/10.3889/oamjms.2022.10095.
[152] E.M. Martin, R.C. Fry, Environmental influences on the epigenome: exposure-associated DNA methylation in human populations, Annu. Rev. Publ. Health 39 (2018) 309–333, https://doi.org/10.1146/annurev-publhealth-040617-014629.
[153] R. Janke, A.T. Iavarone, J. Rine, Oncometabolite D-2-Hydroxyglutarate enhances gene silencing through inhibition of specific H3K36 histone demethylases, Elife (2017) 6, https://doi.org/10.7554/eLife.22451.
[154] J.M. Lawler, S.K. Powers, D.S. Criswell, Inducibility of NADP-specific isocitrate dehydrogenase with endurance training in skeletal muscle, Acta Physiol. Scand. 149 (1993) 177–181, https://doi.org/10.1111/j.1748-1716.1993.tb09610.x.
[155] T. Morville, R.E. Sahl, T. Moritz, J.W. Helge, C. Clemmensen, Plasma metabolome profiling of resistance exercise and endurance exercise in humans, Cell Rep. 33 (2020) 108554, https://doi.org/10.1016/j.celrep.2020.108554.
[156] M.J. Gibala, M.A. Tarnopolsky, T.E. Graham, Tricarboxylic acid cycle intermediates in human muscle at rest and during prolonged cycling, Am. J. Physiol. Endocrinol. Metabol. 272 (1997) E239–E244, https://doi.org/10.1152/ajpendo.1997.272.2.E239.
[157] J. Zhang, S. Bhattacharyya, R.C. Hickner, A.R. Light, C.J. Lambert, B.K. Gale, O. Fiehn, S.H. Adams, Skeletal muscle interstitial fluid metabolomics at rest and associated with an exercise bout: application in rats and humans, Am. J. Physiol. Endocrinol. Metabol. 316 (2019) E43–E53, https://doi.org/10.1152/ajpendo.00156.2018.
[158] M. Xiao, H. Yang, W. Xu, S. Ma, H. Lin, H. Zhu, L. Liu, Y. Liu, C. Yang, Y. Xu, et al., Inhibition of α-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors, Genes Dev. 26 (2012) 1326–1338, https://doi.org/10.1101/gad.191056.112.
[159] A.M. Cervera, J.-P. Bayley, P. Devilee, K.J. McCreath, Inhibition of succinate dehydrogenase dysregulates histone modification in mammalian cells, Mol. Cancer 8 (2009) 89, https://doi.org/10.1186/1476-4598-8-89.
[160] A. Reddy, L.H.M. Bozi, O.K. Yaghi, E.L. Mills, H. Xiao, H.E. Nicholson, M. Paschini, J.A. Paulo, R. Garrity, D. Laznik-Bogoslavski, et al., pH-gated succinate secretion regulates muscle remodeling in response to exercise, Cell 183 (2020) 62–75.e17, https://doi.org/10.1016/j.cell.2020.08.039.
[161] P.W. Hochachka, R.H. Dressendorfer, Succinate accumulation in man during exercise, Eur. J. Appl. Physiol. Occup. Physiol. 35 (1976) 235–242, https://doi.org/10.1007/BF00423282.
[162] G.D. Lewis, L. Farrell, M.J. Wood, M. Martinovic, Z. Arany, G.C. Rowe, A. Souza, S. Cheng, E.L. McCabe, E. Yang, et al., Metabolic signatures of exercise in human plasma, Sci. Transl. Med. 2 (2010), https://doi.org/10.1126/scitranslmed.3001006.

[163] Z. Stander, L. Luies, L.J. Mienie, K.M. Keane, G. Howatson, T. Clifford, E. J. Stevenson, D.T. Loots, The altered human serum metabolome induced by a marathon, Metabolomics 14 (2018) 150, https://doi.org/10.1007/s11306-018-1447-4.
[164] K. Sahlin, A. Katz, S. Broberg, Tricarboxylic acid cycle intermediates in human muscle during prolonged exercise, Am. J. Physiol.: Cell Physiol. 259 (1990) C834–C841, https://doi.org/10.1152/ajpcell.1990.259.5.C834.
[165] M. Xiao, H. Yang, W. Xu, S. Ma, H. Lin, H. Zhu, L. Liu, Y. Liu, C. Yang, Y. Xu, et al., Inhibition of α-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors, Genes Dev. 26 (2012) 1326–1338, https://doi.org/10.1101/gad.191056.112.
[166] Y. Jiang, X. Qian, J. Shen, Y. Wang, X. Li, R. Liu, Y. Xia, Q. Chen, G. Peng, S.-Y. Lin, et al., Author Correction: local generation of fumarate promotes DNA repair through inhibition of histone H3 demethylation, Nat. Cell Biol. 20 (2018), https://doi.org/10.1038/s41556-018-0074-7, 1226–1226.
[167] Y. Jiang, X. Qian, J. Shen, Y. Wang, X. Li, R. Liu, Y. Xia, Q. Chen, G. Peng, S.-Y. Lin, et al., Local generation of fumarate promotes DNA repair through inhibition of histone H3 demethylation, Nat. Cell Biol. 17 (2015) 1158–1168, https://doi.org/10.1038/ncb3209.
[168] E. Berra, A. Ginouvès, J. Pouysségur, The hypoxia-inducible-factor hydroxylases bring fresh air into hypoxia signalling, EMBO Rep. 7 (2006) 41–45, https://doi.org/10.1038/sj.embor.7400598.
[169] R.L. Veech, M. Todd King, R. Pawlosky, Y. Kashiwaya, P.C. Bradshaw, W. Curtis, The "great" controlling nucleotide coenzymes, IUBMB Life 71 (2019) 565–579, https://doi.org/10.1002/iub.1997.
[170] L. Wang, P. Chen, W. Xiao, β-Hydroxybutyrate as an anti-aging metabolite, Nutrients 13 (2021) 3420, https://doi.org/10.3390/nu13103420.
[171] B.A. Zinker, K. Britz, G.A. Brooks, Effects of a 36-hour fast on human endurance and substrate utilization, J. Appl. Physiol. 69 (1990) 1849–1855, https://doi.org/10.1152/jappl.1990.69.5.1849.
[172] T. Shimazu, M.D. Hirschey, J. Newman, W. He, K. Shirakawa, N. Le Moan, C. A. Grueter, H. Lim, L.R. Saunders, R.D. Stevens, et al., Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor, Science 2013 (339) (1979) 211–214, https://doi.org/10.1126/science.1227166.
[173] J.H. Koeslag, T.D. Noakes, A.W. Sloan, Post-exercise ketosis, J. Physiol. 301 (1980) 79–90, https://doi.org/10.1113/jphysiol.1980.sp013190.
[174] L.S. Deru, B.T. Bikman, L.E. Davidson, L.A. Tucker, G. Fellingham, C. L. Bartholomew, H.L. Yuan, B.W. Bailey, The effects of exercise on β-hydroxybutyrate concentrations over a 36-h fast: a randomized crossover study, Med. Sci. Sports Exerc. 53 (2021) 1987–1998, https://doi.org/10.1249/MSS.0000000000002655.
[175] S.E. Kwak, J.H. Bae, J.H. Lee, H.E. Shin, D. Zhang, S.C. Cho, W. Song, Effects of exercise-induced beta-hydroxybutyrate on muscle function and cognitive function, Phys. Rep. (2021) 9, https://doi.org/10.14814/phy2.14497.
[176] M. Monsalves-Alvarez, P.E. Morales, M. Castro-Sepulveda, C. Sepulveda, J. M. Rodriguez, M. Chiong, V. Eisner, S. Lavandero, R. Troncoso, β-Hydroxybutyrate increases exercise capacity associated with changes in mitochondrial function in skeletal muscle, Nutrients 12 (2020) 1930, https://doi.org/10.3390/nu12071930.
[177] T. Shimazu, M.D. Hirschey, J. Newman, W. He, K. Shirakawa, N. Le Moan, C. A. Grueter, H. Lim, L.R. Saunders, R.D. Stevens, et al., Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor, Science 2013 (339) (1979) 211–214, https://doi.org/10.1126/science.1227166.
[178] Barrè R, Yan J, Egan B, Treebak JT, Rasmussen M, Fritz T, Caidahl K, Krook A, O'gorman DJ, Zierath JR. Cell Metabolism Acute Exercise Remodels Promoter Methylation in Human Skeletal Muscle.doi: 10.1016/j.cmet.2012.01.001.
[179] H. Islam, B.A. Edgett, B.J. Gurd, Coordination of mitochondrial biogenesis by PGC-1α in human skeletal muscle: a re-evaluation, Metabolism 79 (2018) 42–51, https://doi.org/10.1016/j.metabol.2017.11.001.
[180] C. Granata, N.A. Jamnick, D.J. Bishop, Principles of exercise prescription, and how they influence exercise-induced changes of transcription factors and other regulators of mitochondrial biogenesis, Sports Med. 48 (7) (2018) 1541–1559, https://doi.org/10.1007/S40279-018-0894-4 (2018) 48.
[181] M.R. Sailani, J.F. Halling, H.D Møller, H. Lee, P. Plomgaard, H. Pilegaard, M. P. Snyder, B. Regenberg, Lifelong physical activity is associated with promoter hypomethylation of genes involved in metabolism, myogenesis, contractile properties and oxidative stress resistance in aged human skeletal muscle 9 (2019) 3272, https://doi.org/10.1038/s41598-018-37895-8.
[182] Martínez-Reyes I, Chandel NS. Mitochondrial TCA Cycle Metabolites Control Physiology and Disease.doi: 10.1038/s41467-019-13668-3.
[183] A. Castegna, V. Iacobazzi, V. Infantino, The mitochondrial side of epigenetics, Physiol. Genom. 47 (2015) 299–307, https://doi.org/10.1152/PHYSIOLGENOMICS.00096.2014.
[184] Xiao M, Yang H, Xu W, Ma S, Lin H, Zhu H, Liu L, Liu Y, Yang C, Xu Y, et al. Inhibition of A-KG-dependent Histone and DNA Demethylases by Fumarate and Succinate that Are Accumulated in Mutations of FH and SDH Tumor Suppressors. doi: 10.1101/gad.191056.112.
[185] T. Laukka, C.J. Mariani, T. Ihantola, J.Z. Cao, J. Hokkanen, W.G. Kaelin, L. A. Godley, P. Koivunen, Fumarate and Succinate Regulate Expression of Hypoxia-Inducible Genes via TET Enzymes *, 2015, https://doi.org/10.1074/jbc.M115.688762.
[186] M. Sciacovelli, E. Gonçalves, T.I. Johnson, V.R. Zecchini, A.S.H. Da Costa, E. Gaude, A.V. Drubbel, S.J. Theobald, S.R. Abbo, M.G.B. Tran, et al., Fumarate is an epigenetic modifier that elicits epithelial-to-mesenchymal transition, Nature 537 (2016) 544, https://doi.org/10.1038/NATURE19353.
[187] J.K. Killian, S.Y. Kim, M. Miettinen, C. Smith, M. Merino, M. Tsokos, M. Quezado, W.I. Smith, M.S. Jahromi, P. Xekouki, et al., Succinate Dehydrogenase Mutation Underlies Global Epigenomic Divergence in Gastrointestinal Stromal Tumor, 2013, https://doi.org/10.1158/2159-8290.CD-13-0092.
[188] S. Giallongo, F. Costa, L. Longhitano, C. Giallongo, J. Ferrigno, E. Tropea, N. Vicario, G. Li Volti, R. Parenti, I. Barbagallo, et al., The pleiotropic effects of fumarate: from mitochondrial respiration to epigenetic rewiring and DNA repair mechanisms, Metabolites (2023) 13, https://doi.org/10.3390/METABO13070880.
[189] D.R. Crooks, N. Maio, M. Lang, C.J. Ricketts, C.D. Vocke, S. Gurram, S. Turan, Y. Y. Kim, G.M. Cawthon, F. Sohelian, et al., Mitochondrial DNA alterations underlie an irreversible shift to aerobic glycolysis in fumarate hydratase-deficient renal cancer, Sci. Signal. 14 (2021) 4436, https://doi.org/10.1126/SCISIGNAL.ABC4436.
[190] Y. Jiang, X. Qian, J. Shen, Y. Wang, X. Li, R. Liu, Y. Xia, Q. Chen, G. Peng, S.Y. Lin, et al., Local generation of fumarate promotes DNA repair through inhibition of histone H3 demethylation, Nat. Cell Biol. 17 (2015) 1158, https://doi.org/10.1038/NCB3209.
[191] X. Liu, W. Si, L. He, J. Yang, Y. Peng, J. Ren, X. Liu, T. Jin, H. Yu, Z. Zhang, et al., The existence of a nonclassical TCA cycle in the nucleus that wires the metabolic-epigenetic circuitry, Signal Transduct. Targeted Ther. (2021) 6, https://doi.org/10.1038/S41392-021-00774-2.
[192] G. Yang, Y. Yuan, H. Yuan, J. Wang, H. Yun, Y. Geng, M. Zhao, L. Li, Y. Weng, Z. Liu, et al., Histone acetyltransferase 1 is a succinyltransferase for histones and non-histones and promotes tumorigenesis, EMBO Rep. (2021) 22, https://doi.org/10.15252/embr.202050967.
[193] M. Hostrup, A.K. Lemminger, B. Stocks, A. Gonzalez-Franquesa, J.K. Larsen, J. P. Quesada, M. Thomassen, B.T. Weinert, J. Bangsbo, A.S. Deshmukh, High-intensity interval training remodels the proteome and acetylome of human skeletal muscle, Elife (2022) 11, https://doi.org/10.7554/eLife.69802.
[194] R. Nagaraj, M.S. Sharpley, F. Chi, R. Kim, A.T. Clark, U. Banerjee Correspondence, Nuclear localization of mitochondrial TCA cycle enzymes as a critical step in mammalian zygotic genome activation in brief mitochondrial enzymes in the nucleus synthesize metabolites for epigenetic remodeling during zygote activation, Cell 168 (2017) 210–223, https://doi.org/10.1016/j.cell.2016.12.026.
[195] Traube FR, Özdemir D, Sahin H, Scheel C, Glück AF, Geserich AS, Oganesian S, Kostidis S, Iwan K, Rahimoff R, et al. Redirected Nuclear Glutamate Dehydrogenase Supplies Tet3 with α-ketoglutarate in Neurons.doi: 10.1038/s41467-021-24353-9.
[196] S. Srivastava, P. Gajwani, J. Jousma, H. Miyamoto, Y. Kwon, A. Jana, P.T. Toth, G. Yan, S.G. Ong, J. Rehman, Nuclear translocation of mitochondrial dehydrogenases as an adaptive cardioprotective mechanism, Nat. Commun. 14 (1) (2023) 1–15, https://doi.org/10.1038/s41467-023-40084-5 (2023) 14.
[197] E.H. Smith, R. Janknecht, L.J. Maher, Succinate inhibition of α-ketoglutarate-dependent enzymes in a yeast model of paraganglioma, Hum. Mol. Genet. 16 (2007) 3136–3148, https://doi.org/10.1093/hmg/ddm275.
[198] S. Turcan, D. Rohle, A. Goenka, L.A. Walsh, F. Fang, E. Yilmaz, C. Campos, A.W. M. Fabius, C. Lu, P.S. Ward, et al., IDH1 Mutation Is Sufficient to Establish the Glioma Hypermethylator Phenotype, 2012, https://doi.org/10.1038/nature10866.
[199] Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, Li Y, Bhagwat N, Vasanthakumar A, Fernandez HF, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, Disrupt TET2 Function, Impair Hematopoietic Different.. doi: 10.1016/j.ccr.2010.11.015.
[200] Li W, Long Q, Wu H, Zhou Y, Duan L, Yuan H, Ding Y, Huang Y, Wu Y, Huang J, et al. Nuclear Localization of Mitochondrial TCA Cycle Enzymes Modulates Pluripotency via Histone Acetylation.doi: 10.1038/s41467-022-35199-0.
[201] G. Sutendra, A. Kinnaird, P. Dromparis, R. Paulin, T.H. Stenson, A. Haromy, K. Hashimoto, N. Zhang, E. Flaim, E.D. Michelakis, A nuclear pyruvate dehydrogenase complex is important for the generation of Acetyl-CoA and histone acetylation, Cell 158 (2014) 84–97, https://doi.org/10.1016/j.cell.2014.04.046.
[202] F.-Y. Chueh, K.-F. Leong, R.J. Cronk, S. Venkitachalam, S. Pabich, C.-L. Yu, Nuclear localization of pyruvate dehydrogenase complex-E2 (PDC-E2), a mitochondrial enzyme, and its role in signal transducer and activator of transcription 5 (STAT5)-dependent gene transcription, Cell. Signal. 23 (2011) 1170–1178, https://doi.org/10.1016/j.cellsig.2011.03.004.
[203] S. Srivastava, P. Gajwani, J. Jousma, H. Miyamoto, Y. Kwon, A. Jana, P.T. Toth, G. Yan, S.-G. Ong, J. Rehman, Nuclear translocation of mitochondrial dehydrogenases as an adaptive cardioprotective mechanism, Nat. Commun. 14 (2023) 4360, https://doi.org/10.1038/s41467-023-40084-5.
[204] D. Constantin-Teodosiu, Regulation of muscle pyruvate dehydrogenase complex in insulin resistance: effects of exercise and dichloroacetate, Diabetes Metab. J 37 (2013) 301, https://doi.org/10.4093/dmj.2013.37.5.301.
[205] K.E. Wellen, G. Hatzivassiliou, U.M. Sachdeva, T.V. Bui, J.R. Cross, C. B. Thompson, ATP-citrate lyase links cellular metabolism to histone acetylation, Science 324 (2009) 1076, https://doi.org/10.1126/SCIENCE.1164097.
[206] H. Takahashi, J.M. Mccaffery, R.A. Irizarry, J.D. Boeke, Nucleocytosolic acetyl-coenzyme A synthetase is required for histone acetylation and global transcription, Mol. Cell. 23 (2006) 207–217, https://doi.org/10.1016/j.molcel.2006.05.040.
[207] Y. Qiu, B. Fernández-García, H.I. Lehmann, G. Li, G. Kroemer, C. López-Otín, J. Xiao, Exercise sustains the hallmarks of health, J. Sport Health Sci. 12 (2023) 8–35, https://doi.org/10.1016/j.jshs.2022.10.003.