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Review

Pleiotropic and multi-systemic actions of physical exercise on PGC-1α signaling during the aging process

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ABSTRACT

Physical training is a potent therapeutic approach for improving mitochondrial health through peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) signaling pathways. However, comprehensive information regarding the physical training impact on PGC-1α in the different physiological systems with advancing age is not fully understood. This review sheds light on the frontier-of-knowledge data regarding the chronic effects of exercise on the PGC-1α signaling pathways in rodents and humans. We address the molecular mechanisms involved in the different tissues, clarifying the precise biological action of PGC-1α, restricted to the aged cell type. Distinct exercise protocols (short and long-term) and modalities (aerobic and resistance exercise) increase the transcriptional and translational PGC-1α levels in adipose tissue, brain, heart, liver, and skeletal muscle in animal models, suggesting that this versatile molecule induces pleiotropic responses. However, PGC-1α function in some human tissues (adipose tissue, heart, and brain) remains challenging for further investigations. PGC-1α is not a simple transcriptional coactivator but supports a biochemical environment of mitochondrial dynamics, controlling physiological processes (primary metabolism, tissue remodeling, autophagy, inflammation, and redox balance). Acting as an adaptive mechanism, the long-term effects of PGC-1α following exercise may reflect the energy demand to coordinate multiple organs and contribute to cellular longevity.

1. Introduction

Aging is a multifaceted biological course related to accumulating molecular and cellular detrimental alterations, potentially decreasing function and the regenerative response in organs, tissues, and systems (Mc Auley et al., 2017). This reduction is related to progressive macromolecular damage, genomic instability, and diminished physiological reserve in reaction to stress, accompanied by the failure of multiple mechanisms responsible for overall homeostasis (Edifizi and Schumacher, 2015). Mitochondrial dysfunction is a general feature in many aging facets, leading to dysregulated metabolism (Chistiakov et al., 2014). Accumulation of mutations in deoxyribonucleic acid (DNA), oxidized proteins, and imbalance between fission and fusion of mitochondria are characteristic of advancing age (Lima et al., 2022). Hence, understanding the molecular phenomena driving the complex processes underlying mitochondria function could clarify common disorders over the life course.

The genes implicated in mitochondrial energy metabolism and the electron transport system are dysregulated with aging, including peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α). PGC-1α is a transcription coactivator governing mitochondrial biogenesis in most tissues. It is also related to several vital functions, such as cell differentiation (Huang et al., 2016), primary metabolism (Summermatter et al., 2013), adaptive thermogenesis (Puigserver et al., 1998), and respiratory function (Broskey et al., 2014). The interplay between PGC-1α and other downstream factors mediates the communication between external stimuli and tissue function, integrating endocrine events and bioenergetic states (Lin et al., 2004). Clinical trials and animal experiments suggest PGC-1α expression is reduced during age-associated diseases such as obesity, diabetes, cardiomyopathy, and neurodegenerative disorders (Botta et al., 2013; Schilling and Kelly, 2011; Soyal et al., 2006; Wohlgemuth et al., 2011). However, PGC-1α is considered a powerful molecule for repairing the harmful impact of aging on mitochondrial activity, integrity, and quality

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(Liang and Ward, 2006).

Mounting evidence has shown exercise attenuates aging from cellular to clinical levels in several physiological systems. The main biological effects of exercise include an increase in blood flow and capillary density (Huang et al., 2016), along with enhanced skeletal muscle remodeling (Ribeiro et al., 2017), neurogenesis (E et al., 2014), as well as cardiorespiratory and vascular functions (Gu et al., 2014). Moreover, exercise activates anti-inflammatory responses, sympathetic and endocrine regulations (release of catecholamines, exercise hormones, myokine, and cytokines), which robustly improve impaired metabolism associated with age (Kadoglou et al., 2007). Mechanistically, physical exercise alleviates the aging-linked worsening in the cellular housekeeping system (DNA repair and proteasome), positively impacting organ integrity (Radak et al., 2019). Physical exercise represents a positive physiological stimulus modulating organelles involved in repair and quality control, restoring overall homeostasis, mitochondrial dynamics, and autophagy process that removes dysfunctional mitochondria (Halling et al., 2017). These beneficial adaptations are due to temporary rises in energy expenditure affecting metabolism, turnover, and network morphology, including mitochondrial fusion (Konopka et al., 2014), synthesis, and bioenergetic flux, besides improvements in respiration capacity (Broskey et al., 2014) and antioxidant defense system (Bayod et al., 2012).

Notably, energy resource adjustments and metabolic processes inherent to exercise are orchestrated by PGC-1α signaling pathways, which improves aging mitochondrial health (Halling et al., 2019). Regular training as a mechanical stimulus initiates many actions converging on PGC-1α (Bayod et al., 2012; Gu et al., 2014). PGC-1α can be activated by β-adrenergic stimulation, cellular stressors, nutrient sensors, and oxidative damage through multi-branched metabolic pathways, including AMP-activated protein kinase (AMPK), p38 mitogen-activated protein kinases (p38 MAPK), silent mating type information regulation 2 homolog 1 (SIRT1) (Lin et al., 2020), Ca^{2+}/calmodulin-dependent protein kinase IV, calcineurin A, cAMP response element-binding protein (CREB), and ROS production (Fernandez-Marcos et al., 2011). Once activated, PGC-1α upregulates other essential transcription factors on DNA promoters to control genes encoding proteins involved in bioenergetic homeostasis and mitochondria integrity (Kristensen et al., 2017; Leveille et al., 2020). This transcriptional coordination is necessary for proper functional proteome maintenance and improves the capacity of mitochondria to argument ATP supply during aging (Sun et al., 2021; Thirupathi et al., 2019). After physical exercise, increased protein contents of PGC-1α in different tissues of rodents (i.e., adipose tissue, brain, heart, liver, and skeletal muscle) can reduce cell damage, apoptosis, and proteasome degradation, which in turn lessens inflammation and oxidative stress in the aged state, besides improving tissue plasticity and remodeling (Kang et al., 2013; Chen et al., 2018; Lin et al., 2020; Bianchi et al., 2021; Sun et al., 2021). Furthermore, the combination of elevated muscle PGC-1α and exercise improves lipid metabolism and glucose homeostasis, in addition to increasing Krebs cycle activity in mice (Summermatter et al., 2013). These versatile mechanisms potentially provide healthier phenotypes and improve the innate ability of cellular recovery, impacting longevity.

Although the many functions of PGC-1α are well described, signaling pathways in response to exercise training that dictates unique tissue-specific properties are poorly understood. For the first time, examining the influence of different physical exercise modalities on various physiological systems, especially in the aging context, may increase the understanding of beneficial exercise effects, particulars, and restraints, as well as provide significant evidence for therapeutic approaches. Identifying a tissue-particular molecular signature could offer new points of view regarding the pleiotropic impacts of PGC-1α and the intricacy of the response at the molecular level. Of note, these aspects may suggest a more practical lifestyle intervention design that prevents the harmful effects inherent to cellular senescence. Exploring new perspectives to understand how PGC-1α acts as a central effector to integrate vital physiological responses could explain the protective exercise properties against age-related degeneration.

Thus, in the present integrative review, we discuss the chronic effects of exercise on the PGC-1α signaling pathways in rodents and humans during the aging process. We addressed the primary physiological and molecular mechanisms involved in the different organs and tissues. These aspects are valuable in clarifying the precise function and biological action of PGC-1α restricted to a cell type. In learning the exact adaptational mechanisms controlling PGC-1α, we will be closer to optimizing exercise prescription parameters. Moreover, we provide additional insights and guidance that warrant attention in basic and clinical investigations. Since there is substantial growth in the aging population worldwide (Dogra et al., 2022), our remarks have applicability in exercise physiology, medicine, and biogerontology.

2. The complex mechanisms triggered by aging on mitochondrial dynamics, structure, and activity

The aging process provokes abnormal mitochondrial fission and fusion, leading to biogenesis impairment and degradation events, including reducing the mitochondrial biomass, function, number, and shape (Liu et al., 2020; Vezza et al., 2022). Senescent cells display defects and reductions in mitochondria-associated membrane couples/-fractions, besides a gradual decrease in mitochondrial calcium uptake and lipid fluxes (Janikiewicz et al., 2018). Moreover, aging impairs mtDNA polymerase, inducing a significant accumulation of mitochondrial DNA (mtDNA) mutations (Sharma et al., 2019). These harmful effects are linked to point mutations or deletions in the genome, mainly due to random errors during replication (Sharma et al., 2019). Moreover, reactive oxygen species (ROS) production can induce errors in the mtDNA-encoded polypeptides, which are conducted through mitochondrial division (Kumaran et al., 2004). As shown in *C. elegans*, these adaptive variations affect mitochondrial and cytosolic translation (Molenaars et al., 2020). Chronic ineffective repair mechanisms accompany this harmful process.

Subsequently, autophagy dysregulation is one intrinsic cause of mitochondrial malfunction and retards the quality maintenance of organelles (Seo et al., 2010). There is an overall shift towards more fission events, fragmented mitochondria, and apoptosis accompanied by less fusion during the aging of *Drosophila* ovarian germline stem cells (Amartuvshin et al., 2020). Moreover, aging reduces mitochondria clearance through autophagy, which explains why selective degradation capacity diminishes with aging (Seo et al., 2010). Oxidative damage and the apoptosis process superimpose optimal lysosomal autophagy in the aging context. These aspects establish the mitochondrial stress-response network associated with key metabolite dysregulation, proteotoxicity, and damage-associated molecular patterns (Lima et al., 2022).

In response to mitochondria dysfunction, detrimental alterations in energy metabolism occur. The primary biological fuels (i.e., carbohydrates, amino acids, and fatty acids) are disrupted due to defects in primary energy metabolism homeostasis (Lima et al., 2022). First, reduced cytosolic phosphoenolpyruvate carboxykinase (PEPCK) (Lima et al., 2022) following the reproductive peak and a mutual rise in pyruvate kinase decrease ATP efficiency and total energy production in aged organisms (Yuan et al., 2016). PEPCK is a central enzyme connecting the tricarboxylic acid cycle with the metabolism of amino acids, carbohydrates, fatty acids, and additional vital metabolites, besides increasing mitochondrial respiration (Feng et al., 2016). In addition to this harmful process, disturbed glucose homeostasis, fat deposition, reduction in enzymes of the citric acid cycle, and biosynthesis associated with cataplerosis promote a decline in energy production during aging (Feng et al., 2016). In addition, aging reduces succinate dehydrogenase activity in rat diaphragm muscle and yeast strains (Fogarty et al., 2020; Berlowska et al., 2006).

Finally, the consequence of these modifications impacts the four-mitochondrial complexes (I, III, and IV) and ATPase (complex V)

involved in energy conservation and reserve. The decline in enzymatic activity and overall nicotinamide adenine dinucleotide (NAD^+) production and defective electron transfer induce a decrease in ATP production (Choksi et al., 2011; Tatarkova et al., 2011). Furthermore, ROS production can cause a conformational rearrangement of catalytically active sites of these complexes and subunits, establishing electron transport chain disruption in a vicious circle (Emelyanova et al., 2018) (Fig. 1).

3. The regulation of the PGC-1α-signaling cascade is negatively impacted by cellular stress signals inherent to aging

The variety of dysfunctional mechanisms intrinsic to aging delivers immense versatility to modify PGC-1α activity rapidly. Of note, PGC-1α modulates multiple stimuli, including mitochondrial biogenesis and remodeling, fatty acid transport and oxidation, inflammatory responses, antioxidant metabolism, and glucose metabolic regulation (Anderson and Prolla, 2009). Although the precise cause of the aging-induced PGC-1α reduction is unknown, it is reasonable to hypothesize that a general decrease in beta-adrenergic sensitivity would influence PGC-1α expression to be suppressed (Cheng et al., 2018). Furthermore, the

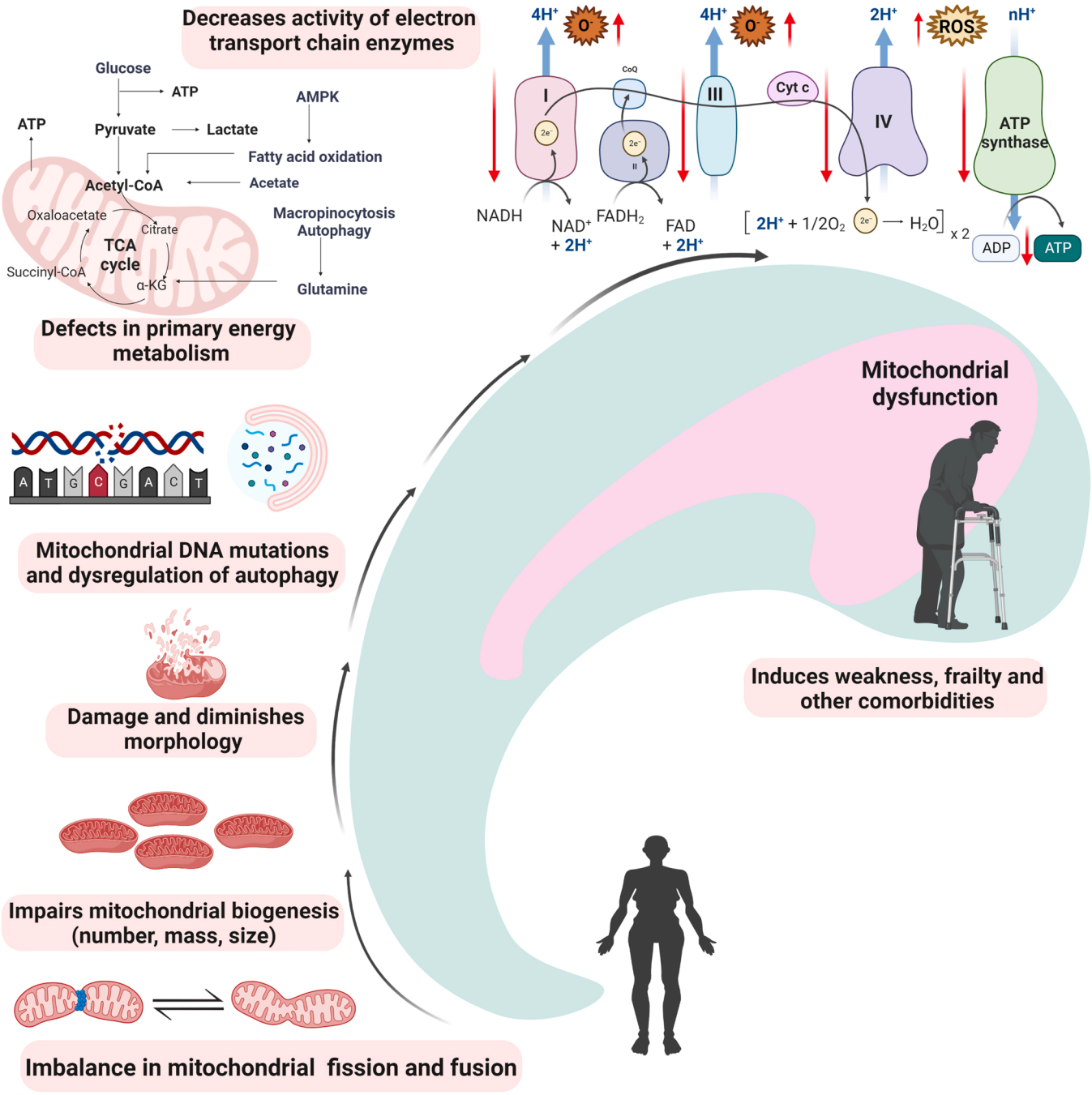

Fig. 1. Schematic description of the complex mechanisms involved in mitochondrial dysfunction during the aging process impacting weakness, frailty, and related comorbidities. Impairment of dynamics (fission and fusion), Mitochondrial biogenesis (number, mass, and size), Structure and function, DNA mutations and autophagy, Primary energy metabolism, and Electron chain transport activity. Biorender webbased software was used to create the figure (License Number AG24O7FRXZ).

telomerase reverse transcriptase deficiency-induced PGC-1α down-regulation leads to mitochondrial impairment, showing a possible relationship between telomere dysfunction and organelle impairment during aging (Sahin et al., 2011). Mechanistic linkages are incompletely understood, but somatic mtDNA mutations (Dillon et al., 2012), chronic tissue disuse, and aging-related diseases can also contribute directly or indirectly to the decline of PGC-1α during the aging process (Anderson and Prolla, 2009). All of the functions modulated by PGC-1α are interconnected and depend on the integrity of individual mitochondria, whole cells, and the organelle network.

In the *Drosophila* model, PGC-1α overexpression in the digestive tract progenitor cells displays a delay in ROS production compared to controls, leading to upgraded tissue homeostasis and extended lifespan in the old flies (Rera et al., 2011). In addition, unexercised flies overexpressing PGC-1α in the heart improved negative geotaxis ability, cardiac stress resistance, and longevity, mimicking some beneficial effects elicited by exercise (Tinkerhess et al., 2012). Transgenic mice with high muscle levels of PGC-1α also prolonged their lifespan, which was associated with increased expression of mRNA levels related to energy metabolism pathways, muscle integrity, and regeneration (Garcia et al., 2018).

In many cell types (muscle, nerve, fat, cardiac, and pancreatic cells), PGC-1α metabolic managers are negatively regulated with aging. These include the following signaling pathways: insulin/insulin-like growth factor 1 (IGF-1), mammalian target of rapamycin (mTOR), and AMP-activated kinase (AMPK), as well as sirtuin 1 (SIRT1) activity (Anderson and Prolla, 2009). Reduced activity of these pathways is linked to impaired fatty-acid oxidation and age-related insulin resistance (Rowe and Arany, 2014). The stimulation of numerous transcription factors by PGC-1α, including the nuclear respiratory factors (NRF-1 and 2), mitochondrial transcription factor A (TFAM) binding, and estrogen receptor-related receptor α (ERRα), is impaired with advanced age (Picca et al., 2013a; Picca et al., 2013b). Additionally, aged rats had reduced responsiveness to catecholamine, documenting a decrease in β-adrenergic receptors in the liver (Shi et al., 2018), brain (Greenberg et al., 1978), heart (Chevalier et al., 1991) and skeletal muscle (Ryall et al., 2004), which potentially reduces PGC-1α levels. Furthermore, aging decreases the intracellular Ca^{2+} signaling system in rat myocardium (Xu and Narayanan, 1998) and thoracic muscles of *Drosophila* (Delrio-Lorenzo et al., 2020), which is recognized as a primary mechanism of PGC-1α activation.

Due to its potent ability as a transcriptional coactivator, PGC-1α connects to targets such as peroxisome proliferator-activated receptors (PPARα, PPARβ/δ, and PPARγ), which are responsible for fatty acid transport and utilization (Cheng et al., 2018). Subsequently, PGC-1α deacetylation is necessary to activate mitochondrial fatty acid oxidation genes. Hence, the metabolic reprogramming in response to PGC-1α overexpression potentializes an alteration from partial to complete β-oxidation (Koves et al., 2005). Furthermore, PGC-1α activation induced by elevated p38 mitogen-activated protein kinase (MAPK) seems necessary to stimulate liver gluconeogenesis from free fatty acids (Fernandez-Marcos and Auwerx, 2011). Aging-induced βAR-regulated activation leads to lower transfer of fat storage and, consequently, downregulation of PGC-1α (Cheng et al., 2018). Furthermore, the loss of PGC-1α did not modify brown fat differentiation but reduced the induction of critical thermogenic genes (Uldry et al., 2006). The loss of PGC-1α expression linked to aging may contribute considerably to impaired glucose tolerance, increasing fat mass, insulin resistance, and inflammation in the liver and white adipose tissues (Sczelecki et a, 2014).

Previously published investigations indicate that PGC-1α connects redox control and inflammatory pathways during aging (Palomer et al., 2009; Rius-Perez et al., 2020). The loss of PGC-1α during aging causes local or systemic inflammation and might control the expression of pro-inflammatory cytokines via nuclear factor kappa B (NF-κB) activation and p38 MAPK (Palomer et al., 2009; Planavila et al., 2005). Activating pro-inflammatory cytokines and toll-like receptors decrease PGC-1α levels in isolated macrophage cells (Feingold et al., 2004; Maitra et al., 2009). The complex function of PGC-1α and its capacity to induce a proper balance of energy supplies with the redox state in the brain and muscle may be controlled by antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) (Aquilano et al., 2013; Huang et al., 2019). Furthermore, PGC-1α stimulates Nrf2 in human renal cells by suppressing glycogen synthase kinase-3 beta (GSK3β) (Choi et al., 2017).

In the aged state, oxidative stress induces GSK3β activation by p38. As an outcome, the Nrf2 antioxidant effects are suppressed (Huang et al., 2019). Subsequently, aging-associated PGC-1α and Nrf2 downregulation decrease mitochondrial antioxidant gene expressions, such as glutathione peroxidase (GPX), manganese superoxide dismutase (SOD), catalase (CAT), peroxiredoxins, uncoupling protein 2 (UCP-2), and thioredoxin reductase (TRXR), inducing oxidative injury in multiple tissues of rodents (heart, brain, liver) (Valle et al., 2005; Aquilano et al., 2013; Gu et al., 2014; Gioscia-Ryan et al., 2016; Rius-Perez et al., 2020).

ROS accumulation also induces insulin/IGF-1 pathway suppression, impairing insulin sensitivity (Papaconstantinou, 2009). Some evidence indicates that improvements in β-cell survival, islet function, and insulin secretion with aging are associated with higher pancreatic levels of PGC-1α (Soesanto et al., 2011; Xu et al., 2020). Regarding plausible mechanisms, PGC-1α hypothetically regulates the insulin receptor substrates 1 (IRS1)/IRS2 ratio, which is fundamental for modulating the precise insulin signal (Besse-Patin et al., 2019). Furthermore, a lack of PGC-1α in muscle induces systemic inflammation and insulin resistance onset (Sczelecki et al., 2014). Mechanistically, decreasing muscle transforming growth factor β (TGF-β) signaling pathways and AMPK activity reduces mice muscle glucose uptake and may impact whole-body glucose homeostasis (Sczelecki et al., 2014).

After cellular damage accumulation, inflammation, oxidative stress, and impaired glucose metabolism, the autophagic pathways can become overwhelmed (Rubinsztein et al., 2011). The optimal autophagy process is impaired with senescence, which hampers the degradation of old and dysfunctional cellular components, such as mitochondria (Rubinsztein et al., 2011). Cell culture and aged mice experiments described that PGC-1α deficiency promotes down-regulation of microtubule-associated protein 1 A/1B-light chain 3 II (LC3-II), lysosomal-associated membrane protein 2 (LAMP2), sequestosome 1 (SQSTM1), and transcription factor EB (TFEB) levels, besides abnormal and reduced autophagosomes (Salazar et al., 2020; Vainshtein et al., 2015; Wu et al., 2009; Yuan et al., 2021). Although aging reduces autophagic potential, PGC-1α is a potent molecular candidate to mediate the anti-aging effects on defective autophagy (Fig. 2).

Interestingly, published data showed that PGC-1α signaling could modulate premature senescence through p21 and p16 pathways that regulate DNA damage and cell cycle arrest. It is established that *Ppargc1a* deficiency in the mouse vascular smooth cells displayed augmented senescent target expression (Cyclin-dependent kinase inhibitor 1 A/p21) and DNA damage while reducing cell proliferation and autophagy (Salazar et al., 2020). Also, $p16^{Ink4a}$ (p16, encoded by the Ink4a gene) deletion in fibroblasts rescued the expression of the SIRT1-PGC-1α pathway, which could lead to the anti-aging effects (Zhang et al., 2021).

Protein posttranslational modifications perform a critical role in PGC-1α translocation and activation. Elegantly, evidence suggests that acetylation or phosphorylation of upstream signaling can modulate PGC-1α transcription or translation. Some investigations elucidated a reduction in AMPK phosphorylation and p38 MAPK in aged skeletal muscle (Qiang et al., 2007; Williamson et al., 2003). Likewise, the phospho-CREB to CREB ratio was drastically decreased in the same tissue, accompanied by considerably reduced DNA binding (Kang et al., 2013). Moreover, a recent investigation observed PGC-1α acetylation was increased by aging, which negatively impacts PGC-1α function, such as mitochondrial mechanisms and metabolism. From a mechanistic

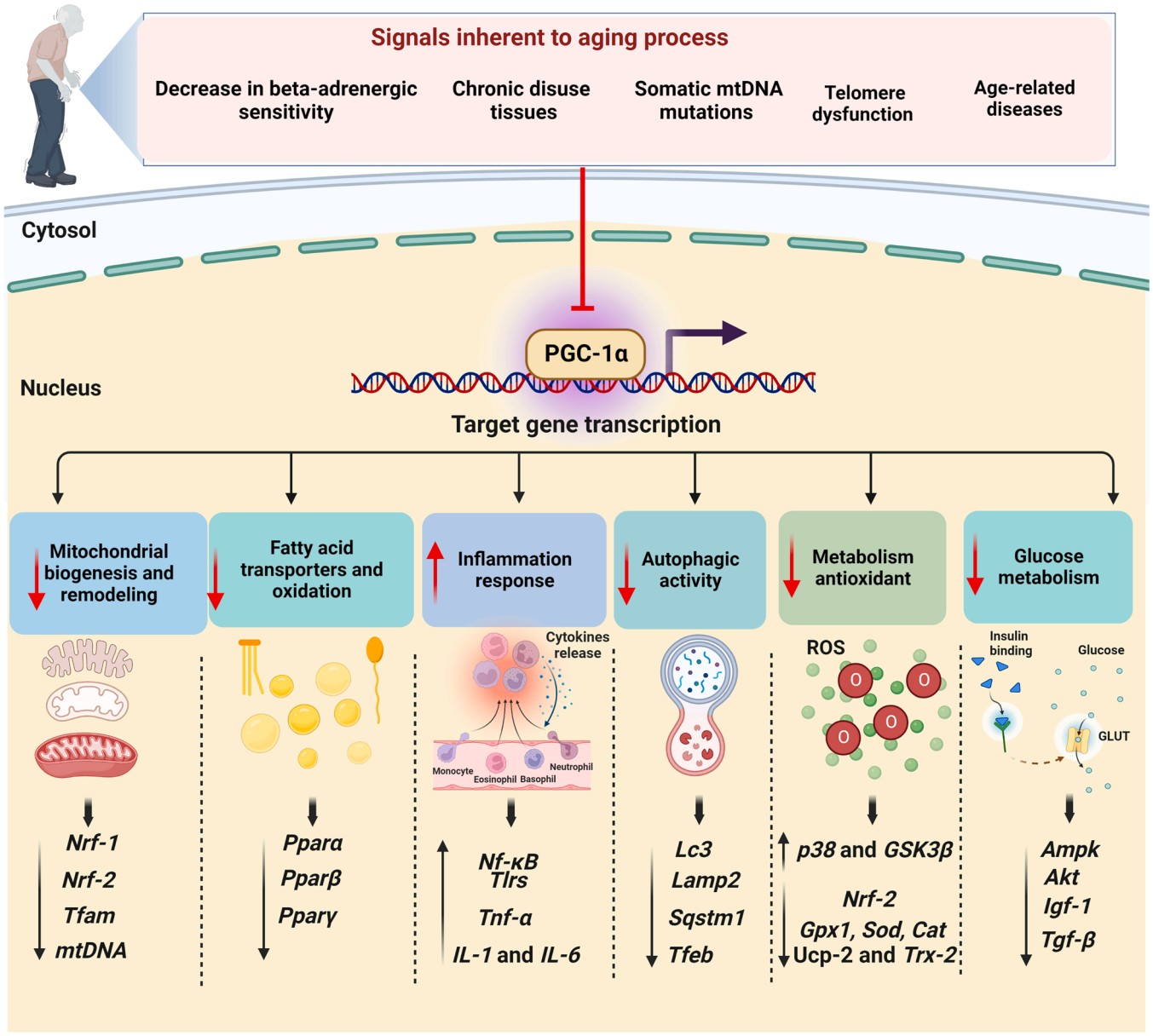

Fig. 2. Hypothetical causes leading to PGC-1α decline during aging. Outline of the main molecules modulated by PGC-1α during the mitochondrial biogenesis (↓ Nrf-1, Nrf-2, Tfam, and mtDNA), fatty acid transporters, and oxidation (↓ Pparα, Pparβ/δ, and Pparγ), inflammatory responses (↑ NF-κB, Tnf-α, IL-1, and IL-6), antioxidant metabolism (↑GSK3β and p38; ↓Nrf2, GPx, Cat, Ucp-2, and TrxR), and glucose metabolic regulation (↓Ampk, Akt, Igf-1, and Tgf-β). Biorender webbased software was used to create the figure (License Number FC24O7DE3Q).

perspective, the depletion of histone deacetylase 1 (HDAC1) reduced SIRT1 levels in aged brain endothelial cells, thereby promoting PGC-1α acetylation (Kim et al., 2019). Subsequently, lower PGC-1α transcriptional activity reduced downstream mitochondrial genes (Kim et al., 2019). Furthermore, aging diminished SIRT1 deacetylates, decreasing mRNA levels of hepatic *Ppargc1a* (Kwon et al., 2017).

Aging is deeply related to epigenetic changes such as DNA methylation (Su et al., 2015). Older adults with Parkinson's disease display promoter-proximal non-canonical cytosine methylation of the *PPARGC1A* gene and reduced mRNA levels in the brain, which is probably associated with the endoplasmic reticulum (ER) stress and inflammatory signaling cascade (Su et al., 2015). Furthermore, evidence indicates PGC- α hypermethylation occurs concomitantly with reduced mitochondrial levels in type 2 diabetic older adults (Barres et al., 2009). Therefore, the aging process can induce nucleosome repositioning in the PGC-1α locus (Fig. 3).

4. Exercise training coordinates PGC-1α signaling pathways in the distinct aged cells, tissues, and physiological systems

4.1. Musculoskeletal system

4.1.1. Animal models

One of the major physiological systems affected during aging is the musculoskeletal system, which is fundamental for movement and mobility, as well as energy balance and metabolism (McCormick and Vasilaki, 2018). Aging induces a progressive reduction in skeletal muscle function and mass, a situation established as sarcopenia, and some studies indicate mitochondrial involvement in this degenerative condition (McCormick and Vasilaki, 2018). However, the scientific literature suggests physical training similarly regulates the PGC-1α in the skeletal muscle of young and old conditions (Ribeiro et al., 2017; Lanza et al., 2008), reinforcing the positive effects of PGC-1α on mitochondrial

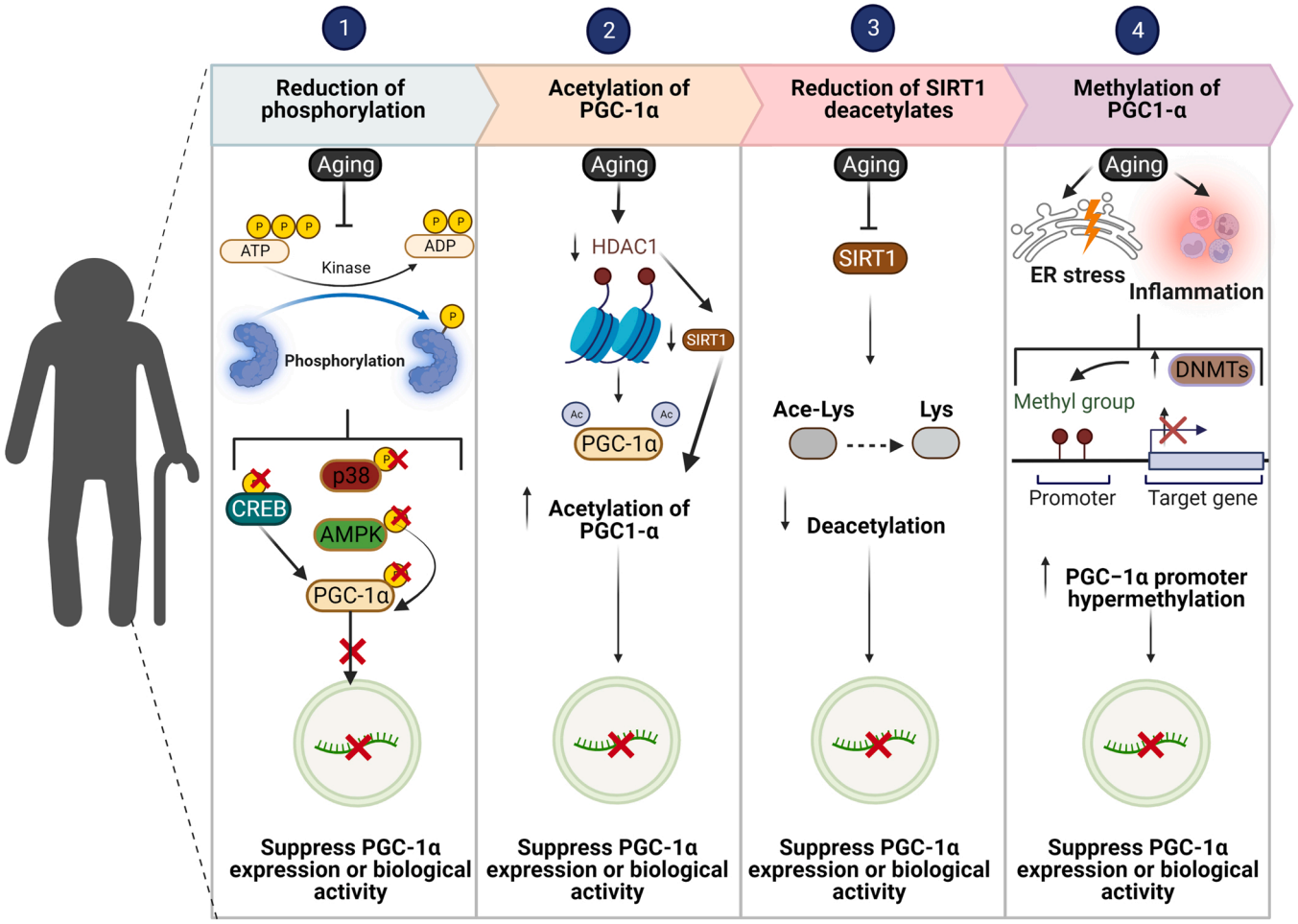

Fig. 3. Summary of posttranslational modification that mediates PGC-1α expression during aging. (1) Reduction in phosphorylation in the upstream proteins. (2) Increase in PGC-1α acetylation by decrease in HDAC1 and SIRT1. (3) Reduction in SIRT1 deacetylases. (4) Involvement of ER stress and inflammation on PGC-1α promoter hypermethylation. Biorender webbased software was used to create the figure (License Number WQ24O7IOTN).

health. Furthermore, several reports underline the action of PGC-1α in atrophy (Sandri et al., 2006), fiber type switching (Handschin et al., 2007), biogenic pathway (Baar et al., 2002), cellular oxidant-antioxidant homeostasis, and mitophagy (Anderson and Prolla, 2009; Dillon et al., 2012; Gill et al., 2018).

Koltai et al. (2012) showed aerobic exercise training (6 weeks, 5 times per week at 60% of maximal oxygen uptake/VO_2max) increased the protein content of many factors in the PGC-1α pathway (i.e., PGC-1α, SIRT1 activity, AMPK, and pAMPK) in the gastrocnemius muscle of aged rats, as well as several indicators of mitochondrial biogenesis (i.e., succinate dehydrogenase, citrate synthase, cytochrome-c oxidase-4, mtDNA). Furthermore, this exercise protocol reduced the difference between young and aged animals for other relevant molecules involved in mitochondrial health, such as NRF-1, fission-1, and mitofusin-1, which critically modulate the renewal of the mitochondrial network via fission and fusion. (Koltai et al., 2012).

In agreement with these findings, Kang et al. (2013) demonstrated that treadmill running (12 weeks, 5 days/week for 45 min/day at 17.5 m/min) increased PGC-1α, TFAM, cytochrome C, and mtDNA content, besides upregulating pAMPK, MAPK, and SIRT1 in the soleus muscle. In addition, endurance training prevents muscle apoptosis through a reduced *Bax/Bcl2* mRNA ratio and *Caspase-3* mRNA levels in aged rats, suggesting that PGC-1α can promote antiapoptotic responses. Similarly, in response to aerobic training, the gastrocnemius and soleus muscles of 3, 12, and 18-month-old rats presented higher protein contents of AMPK, PGC-1α, and SIRT1 compared to aged sedentary animals (Huang et al., 2016), suggesting PGC-1α possibly has a central role in regulating metabolic adaptations during aging.

The relevance of preserving PGC-1α levels on muscle function was highlighted by Derbré et al., 2012. The global deficiency in PGC-1α resulted in delayed mitochondrial responses to treadmill training (4 weeks, 5 times per week, at 75% of VO_{2max}). The authors found similar results in exercised-aged rats, which displayed lower protein content of PGC-1α, NRF-1, and cytochrome C in the soleus muscle. Therefore, these data suggest the aging process is similar to PGC-1α deletion. Moreover, young animals showed up-regulation of PGC-1α protein in response to physical training, which was not observed during aging. Thus, the age-associated worsening mitochondrial function may be justified by an absence of normal PGC-1α levels.

Regarding the underlying molecular mechanisms, Halling et al. (2019) showed that decreased aerobic capacity in aged mice was related to mitochondrial fragmentation and impaired cellular respiration in skeletal muscle, which were normalized by physical training (7 weeks, 5 times per week, at 60% of the velocity max). Furthermore, mitochondrial ADP-stimulated respiration in the muscle-specific PGC-1α knockout aged mice was enhanced by exercise training. This result was further associated with decreased mitochondrial ROS emission (Halling et al., 2019). Thus, PGC-1α via exercise is essential to counterbalance oxidative stress and organelle fragmentation.

Certainly, transgenic rodents with targets in the genome can elucidate intricate mechanisms in skeletal muscle submitted to physical exercise. PGC-1α muscle-specific knockout and overexpression impaired

and improved aging-related muscle function in aged mice, respectively (Gill et al., 2018). However, the positive effects of treadmill exercise (12 weeks, 3 times per week, for 30 min) on oxidative phosphorylation proteins were blunted by skeletal muscle PGC-1α deletion. In contrast, PGC-1α overexpression enhanced the exercise properties on mitochondrial morphology and the proportion of the oxidative fiber, besides leading to beneficial responses in motor skills and balance (Gill et al., 2018), suggesting a therapeutic relevance in muscle biology.

Strong evidence revealed organelle turnover is the balance between mitochondrial biogenesis and autophagy, and the combination of these activities aid in energetic homeostasis maintenance (Seo et al., 2010; Halling et al., 2017). Aging has been shown to induce an accelerated imbalance of these two opposing processes, leading to disturbances in the skeletal muscle of mice (Yeo et al., 2019). However, the overexpression of PGC-1α effectively alleviated the mitophagy pathway in aged skeletal muscle and can fine-tune autophagy in a manner specific to the cellular metabolic state (Yeo et al., 2019). Furthermore, aerobic exercise (15 months of running 6.0 km/week on a wheel) can induce PGC-1α-mediated crosstalk between these two opposing processes, rescuing the aging-induced increase in the LC3II/I ratio (Halling et al., 2017).

More recently, compared to control mice, Christensen et al. (2023) described the upregulation of Parkin protein levels in liver mitochondria of aged mice with specific deletion of PGC-1α in skeletal muscles. Thus, the status of metabolic muscle capacity can control mitophagy in the liver during aging, and PGC-1α can mediate this inter-organ signaling. Consequently, the improved knowledge about these inter-organ networks can help us to redefine specific exercise strategies.

Paradoxically, the overexpression of PGC-1α in the skeletal muscle of sedentary mice can exacerbate fat-induced insulin resistance, although positive effects on mitochondrial density and activity were observed (Choi et al., 2008; Summermatter et al., 2013). On the other hand, elevated PGC-1α in conjunction with aerobic exercise preferentially improved glucose homeostasis and increased Krebs cycle activity, besides changing lipid metabolism for insulin sensitivity improvement (Summermatter et al., 2013). Thus, the overexpression of PGC-1α must be accompanied by exercise to prevent the development of some harmful consequences.

Although distinctive studies have demonstrated aerobic exercise protocols can modulate PGC-1α signaling pathways, resistance training (RT) elicited positive benefits to muscle hypertrophy (Ribeiro et al., 2017), enhancing muscle strength through multiple intracellular pathways, especially in aging populations. Ribeiro et al. (2017) showed that RT [12 weeks, 3 times/week with progressive overload during 4 climbs (65%, 85%, 95%, and 100% of the maximum load)] elevated *Ppargc1α* mRNA levels in gastrocnemius and soleus muscles of young and aged rats. This adaptation was associated with significant increases in skeletal muscle fiber cross-sectional area while decreasing intramyocellular lipid accumulation. Hence, PGC-1α is crucial to lipogenesis, oxidative metabolism, and lipid catabolism in skeletal muscle, indicating this molecule can be related to the protective mechanisms preventing muscle wasting.

To explore the role of aerobic (1 week of swimming training, 7 days per week, 20 min at 2.3% of anaerobic threshold) or resistance exercise training (1 week, 7 days per week, 3 sets of 10 jumps with vest at 60% of the one repetition maximum test) during aging, Vechetti-Junior et al. (2016) suggested a novel mechanistic insight by which exercise training improved muscle recovery after disuse in aged rats. After an atrophic stimulus (7 days of immobilization), the authors observed that only the trained rodents showed upregulation of PGC-1α protein levels, besides total recovery of muscle size after 3 days of recovery, which was linked to the suppression of the ubiquitin-proteasome system (FoxO pathway). The findings support the hypothesis that PGC-1α pathway activation may also be necessary for muscle restoration. Also, it is feasible to suppose that the minimal anabolic impact of PGC-1α is induced by aerobic training.

On the other hand, dynamic RT can be difficult for fragile older subjects with impaired motion range. From this perspective, Liu et al. (2021) determined the advantages of static resistance training (8 weeks of upper limb suspension for 15 min with the rats grasping the metal rod) on muscle function and PGC-1α signaling as a critical mechanism to attenuate muscle atrophy in aged rats. Interestingly, the authors observed that this training type effectively increased the protein content of PGC-1α, UCP1, and FNDC5 in the biceps brachii muscle after static RT. Furthermore, static RT revealed an advantage by decreasing fat and weight gain while increasing muscle fiber size (Liu et al., 2021). Therefore, PGC-1α is essential in adjusting mitochondrial dysfunction and fat metabolism, preventing sarcopenia in an animal model.

Despite substantial progress in understanding the role of PGC-1α in the skeletal muscle of rodents following different exercise protocols, future studies are necessary to elucidate the function of this transcription coactivator in the bone, tendon, and myotendinous junction in aged animals, since these other tissues are also responsive to mitochondrial metabolism and exercise. Further experiments could measure the specified molecular characterization in these tissues. For advanced molecular approaches, a blend of proteomics, metabolomics, transcriptomics, and lipidomics post-exercise could be indispensable for discovering additional mechanisms mediating PGC-1α activation. New biomarkers implicated in the relationship between PGC-1α could implement innovative ideas in the health context and the interaction between organs and different physiological systems.

4.1.2. Human trials

The biopsy technique is a valuable tool utilized in exercise and applied physiology to study human skeletal muscle morphology, regeneration, and overall regeneration (Roth et al., 2000). In addition, tissue biopsy is necessary to clarify the human skeletal muscle shape and molecular conjectures responsible for modifications in skeletal muscle fiber (Roth et al., 2000). Interestingly, the findings observed in human trials agree with animal studies, indicating the successful translation of PGC-1α as a potential therapeutic in aging research. Exercise acts as mitochondrial medicine for disused human skeletal muscle, improving the poor oxidative status and metabolic inflexibility.

The initial evidence regarding the exercise effects on human skeletal muscle PGC-1α expression was presented twenty years ago. In a classic study, Short et al. (2003) discovered aerobic exercise training (16 weeks on a stationary bicycle; 20–40 min, 3 sessions/week, at 70–80% of maximal heart rate) induced an increase of 55% in the vastus lateralis muscle *PPARGC1A* mRNA levels of young and elderly. Moreover, in a cross-sectional study, the protein content of PGC-1α, NRF-1, and TFAM in the vastus lateralis muscle was higher in young and older trained adults (1 h of cycling or running, 6 days per week, over the past 4 years) compared to sedentary age-matched counterparts. (exercised less than 30 min per day, twice per week) (Lanza et al., 2008). Also, the proteomic analysis revealed that endurance-trained older people displayed a higher abundance of oxidative ATP production proteins than sedentary subjects (Lanza et al., 2008), indicating endurance training may normalize age-related mitochondrial dysfunction through pathways linked to mitochondrial health.

Regarding controlled exercise, aerobic training (12 weeks on a cycle ergometer; 20–45 min, 3–4 sessions/week, at 60–80% of heart rate reserve) increased protein contents related to mitochondrial biogenesis (PGC-1α, citrate synthase/CS, succinate dehydrogenase/SDH, and cytochrome C) and markers of mitochondrial fusion (MFN1 and MFN2) and fission (FIS1), as well as vastus lateralis muscle hypertrophy, independent of age (Konopka et al., 2014). Additionally, exercise training (16 weeks, 30–60 min of walking and biking, at 75% of the maximum heart rate) increased the protein contents related to electron transport chain complexes (I, IV, V). These adaptations occurred concomitantly with elevated *PPARGC1A* and *TFAM* mRNA levels in the vastus lateralis biopsies of older individuals (Broskey et al., 2014). These data provide practical effects for ameliorating metabolic health after regular exercise.

Similarly to aerobic exercise training, Mesquita et al. (2020)

demonstrated 10 weeks of RT (whole body workout performed twice weekly, 10–12 repetitions, with intensity controlled by individual scale perception) increased markers of mitochondrial biogenesis (PGC-1α, NRF1, and TFAM), fusion (mitofusin 1/MFN1, mitofusin 2/MFN2, and optic atrophy 1/OPA 1), and fission (dynamin-related protein 1/DRP1). However, no differences were detected in these targets following the first bout. Moreover, the molecules involved in mitophagy (Pink1 and Parkin) were not significantly modified in response to the exercise protocol. The researchers caution that acute mitochondrial adaptation may not illustrate the chronic state and that repetitive sessions are needed for a positive outcome.

Additional studies showed that other isoforms of PGC-1α can be important for resistance exercise adaptations. Ruas et al. (2012) verified PGC-1α4 is highly expressed in exercised skeletal muscle of humans after RT, and these changes had a high correlation with performance in the leg press exercise. Furthermore, PGC-1α4 represses myostatin mRNA levels, modulating hypertrophy. Elegantly, Koh et al. (2022) demonstrated in human and cell line experiments that RT provokes metabolic benefits governed by the upregulation of PGC-1α4. In human skeletal muscles, PGC-1α4 promotes glycolysis and proper ATP production for muscle contractions during exercise. Moreover, the authors discovered PGC-1α4 overexpression in the myotubes induced fat oxidation and anaerobic glycolysis in a PPARβ-dependent manner. Thus, considering the importance of RT to old individuals, detecting these molecular players may lead to imminent translational investigations to prevent aging-related diseases.

Wohlgemuth et al. (2011) evaluated the impact of a 6-month weight loss strategy conjugated with moderate-intensity exercise (3 times per week of aerobic walking at 13 on the Borg Scale), strength training (whole-body exercise with 2 sets of 10 repetitions at 13 on the Borg Scale), and flexibility exercises on cellular quality control mechanisms, such as autophagy, apoptosis, and mitochondrial function, in the skeletal muscle of older obese women. The authors observed increased mRNA levels of the autophagy regulators *MAP1LC3B*, autophagy protein 7 (*ATG7*), and lysosome-associated membrane protein-2 (*LAMP-2*). Furthermore, the intervention increased *PPARGC1A* and *TFAM* mRNA levels, but no meaningful adjustments in mitochondrial complex activity were observed to accompany these mentioned responses. In summary, this investigation suggests the intervention improved mitochondrial turnover, biogenesis, and autophagic process, but the effects on electron transport chain complexes were limited.

Chronic kidney disease is a complex comorbid, which is additionally intensified by the aging process. Older individuals with chronic kidney disease (stage 3) reduced skeletal muscle mitochondrial mass compared to healthy individuals, coupled with a decrease in the gene expression of transcription factors related to mitochondrial biogenesis (i.e., *PPARGC1A*, *NRF-1*, *NRF2*, *TFAM*, and *MFN2*) (Watson et al., 2020). However, 12 weeks of exercise training (12 weeks, 3 times per week, consisting of a combination of treadmill, cycling, and rowing exercises for 30 min, at 70–80% of maximum heart rate, as well as leg press with 3 sets of 12–15 repetitions at 70% of repetition maximum/RM)) do not change this deficit, although this training model increased *PPARGC1A* mRNA levels in the vastus lateralis (Watson et al., 2020). Despite increasing transcript levels, the exercise program did not trigger the AMPK, P38 MAPK, and SIRT1 axis, suppressing nuclear translocation of PGC-1α and successive downstream target expressions. Thus, future investigations are necessary to evaluate the appropriate exercise dose to improve mitochondrial response.

Further studies instigating different exercise intensities, frequencies, and times must elucidate the possible mechanisms involved in mitochondrial function. Relevantly, comparisons between aerobic training versus RT and concurrent exercise training are needed to distinguish how each modality can precisely modulate PGC-1α signaling pathways. Finally, the intrinsic and extrinsic factors affecting PGC-1α expression in significantly older adults (those over 80) have not yet been thoroughly investigated. These reports may aid health professionals in designing interventions targeted at muscle health. Addressing the critical predictors of PGC-1α has significant implications for clinical management and could help health professionals create optimal rehabilitative programs. In addition, to the best of our knowledge, the connection between PGC-1α content in different aged fiber types after an exercise program has never been investigated. Since type I fibers have the highest PGC-1α content (Lin et al., 2002) and age advanced induces an adaptation from fast to slow fibers (de Sousa Neto et al., 2020), the distinction of PGC-1α expression in type I and II fibers must be addressed in the future.

Additionally, it is essential to highlight skeletal muscle can undergo the direct influence of PGC-1α. In contrast, indirect responses can affect other tissues, including exercise-associated metabolism changes or circulating hormones (Bostrom et al., 2012). Skeletal muscle is a critical systemic effector of physical exercise, acting as an endocrine tissue that releases myokines, inferring an intricate interplay between tissues and different physiological systems (Bostrom et al., 2012). Based on this statement, future studies should aim to obtain a holistic picture of the interaction between tissues playing an essential role in exercise-induced PGC-1α.

4.2. Metabolic system

4.2.1. Liver

4.2.1.1. Animal models. One hallmark of liver diseases inherent to the aging process is the occurrence of modifications in mitochondrial structure and overall activity that are attended by a blocked flow of electrons in the respiratory chain, which enhances mitochondrial reactive oxygen species formation in a self-perpetuating vicious cycle (Kristensen et al., 2017). In this context, mitochondrial oxidative stress is modulated by PGC-1α signaling pathways through organelle turnover, unfolded protein response, mitophagy, and mitochondrial biogenesis, which, in turn, maintain hepatic energy homeostasis (Leveille et al., 2020).

Mitochondrial dysfunction has been related to ER stress triggered by misfolded protein accumulation due to decreased ER-linked degradation. Elegantly, Kristensen et al. (2017) analyzed the impact of PGC-1α in aging, and lifelong exercise training-induced hepatic unfolded protein response in aged mice. Lifelong exercise training (6 months on running wheels, approximately 6 km per week) prevented the age-associated alteration in binding immunoglobulin protein (BIP), inositol-requiring protein 1α (IRE1α), and protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), but not cleaved activating transcription factor 6 (ATF6) protein in aged wild-type mice. However, the authors observed that the global deletion of PGC-1α did not modulate the hepatic unfolded protein content after exercise training, except for the lower IRE1α levels. These findings indicate PGC-1α controls the ability of the liver to induce UPR in a particular manner. As these experiments were conducted in mice with global deletion, it was impossible to differentiate between the systemic and local functions of PGC-1α in hepatic physiology.

Moderate aerobic exercise (3 months of treadmill training, 3 times per week, for 20-min at 20 cm/s) increased hepatic NAD^+ levels, SIRT activity, and NF-kB deacetylation while decreasing overall PGC-1α acetylation in the liver of aged mice (Bianchi et al., 2021). In addition, this exercise protocol increased *Ppargc1a* gene expression (i.e., Phosphoenolpyruvate Carboxykinase 1 and Glucose-6-phosphatase, catalytic subunit), confirming the broad downstream consequences of SIRT activity. Consequently, exercise effectively reduced tissue inflammation and oxidative damage, reversing hepatic steatosis and preventing tumor development (Bianchi et al., 2021). In addition, other authors found that long-term aerobic exercise (36 weeks, 4–5 days per week, at 12 m/min) can protect the aged liver through an enhancement in PGC-1α and SIRT1 protein levels, as well as p53 acetylation, besides increasing vascular endothelial growth factor (VEGF) levels and reducing carbonylated

proteins (Bayod et al., 2012). These results show aerobic exercise may be a non-drug approach to modify hepatotoxicity through its beneficial influence on mitochondrial and oxidant biomarkers.

Interestingly, lifestyle interventions can exert anti-fibrotic action by upregulating PGC-1α in the liver. Indeed, aging reduced the *Ppargc1a* and *Mfn1* gene expressions in the rat liver while increasing collagen deposition (Khodabandeh et al., 2021). However, RT (20 min on ladders with weights, performed for 8 weeks, three days a week, 20 min per day) significantly increased *Ppargc1a* mRNA levels and reduced collagen deposition (Khodabandeh et al., 2021). Future studies must develop new therapeutic interventions to understand the complex interplay between hepatic unfolded protein, mitochondrial biogenesis, extracellular matrix, and lipophagy.

4.2.2. Adipose tissue

4.2.2.1. Animal models. Numerous age-related alterations ensue at the cellular level in adipose tissue, such as impaired mitochondrial function (Boudina and Graham, 2014; Moon et al., 2013). Mitochondrial damage in the adipocytes induces whole-body deleterious effects and participates in metabolism and adipocyte differentiation since they control oxidative phosphorylation, fatty acid metabolism, and balance redox (Ejarque et al., 2019; Macedo et al., 2021; Meng et al., 2018; Woo et al., 2019). Beige and brown adipocytes have high PGC-1α expression, which is responsible for enhancing thermogenesis-related gene expression (Sutherland et al., 2009). Consequently, these adipose tissue types are distinguished by high mitochondrial numbers and play a central role in uncoupled respiration (Vernochet et al., 2014).

In an elegant study, Ziegler et al. (2019) examined the inflammatory status, oxidative capacity, and visceral adipose tissue integrity in different exercise training models of lean adult and aged mice. The authors showed that RT wheels (5 g in week 1, 6 g in week 2, followed by an increase of 1 g every second week ending at 10 g in weeks 9–10) and endurance training (10 weeks of voluntary wheel running with 1.5 g throughout the intervention) reduced epididymal fat mass and adipocyte size accompanied by enhanced anti-inflammatory phenotype. In both adult and old mice, exercise training upregulated the *Ppargc1a* mRNA levels in the white adipose tissue, with a more pronounced effect of endurance training than RT. These alterations raised the concept that adipocyte size changes might be related to browning adipose tissue, reinforcing that exercise can favor metabolic response on adipose tissue and rejuvenate adipocytes.

Likewise, Thirupathi et al. (2019) observed plausible mechanisms through exercise training controlling the activity of mitochondria on adipose tissue to decrease aging-related body adiposity. Interestingly, both RT (8 weeks, 4 times per week, at 50% of the maximal load in weeks 1 and 2; 50% in weeks 3 and 4; 75% in weeks 5 and 6; and 100% in weeks 7 and 8) and aerobic exercise (8 weeks, 4 times per week at 50–70% of the maximal running speed) increased mitochondrial regulatory protein contents (i.e., PGC-1α, SIRT1, and pAMPK) and respiratory chain activities (complexes I, II/III, III, and IV) of brown adipose tissue, while body fat and adiposity decreased in aged rats. This investigation reinforced that different exercise types partially normalize mitochondria function decline of adipose tissue due to aging.

More recently, Sun et al. (2021) analyzed the effects of lifelong treadmill exercise (18 months, 5 times per week, for 45 min, at 75–80% of VO_{2max}) and long-term detraining (8 months) on age-linked modifications in mitochondrial function, and lipolysis in the perirenal fat of aged rats. The authors found that lifelong exercise upregulated PGC-1α, UCP1, and COX IV protein levels in the perirenal adipose tissue, indicating that this practice effectively reinforces mitochondrial biogenesis and respiratory activity in aged rats. These outcomes were accompanied by higher levels of hormone-sensitive lipase (HSL) in the perirenal fat and elevated free fatty acids in blood circulation, improving lipolysis in natural aging. On the other hand, discontinued training resulted in the loss of the beneficial adaptive effect, demonstrating the importance of regular exercise.

Nevertheless, the growing volume of experimental evidence indicates varied adipokine in distinct adipose types and depots after exercise training, which probably modulates PGC-1α signaling pathways (de Sousa Neto et al., 2022; Lehnig et al., 2019). Therefore, further studies could assess the specific PGC-1α signatures in each fat depot. These data may offer clinically valuable evidence and support successful interventions.

4.2.2.2. Human trials. The impact of chronic exercise on PGC-1α signaling of adipose tissue in human aging is scarce and controversial compared to animal studies. For example, HIIT (High-Intensity Interval Training; 12 weeks, 3 times per week during 20 min of multiple 30 s sprints at a high intensity/80–85% maximal heart rate) alternating with 90 s at moderate intensity (65% maximal heart rate) does not impact gene expressions related to browning of adipocytes (*UCP1*, *PDRM16*), lipid oxidation (*CPT1B*), and mitochondrial biogenesis (*PPARGC1A*) in abdominal subcutaneous adipose tissue of obese older adults (Marcangeli et al., 2022). Furthermore, after 12 weeks of combined training (two endurance bicycle sessions for 60 min at 70% of VO_{2max} and two whole-body strength training sessions for 60 min per week), the *PPARGC1A* and *FNDC5* mRNAs levels were not significantly enhanced in the subcutaneous adipose tissue of older subjects (Norheim et al., 2014). However, these outcomes should be interpreted cautiously since the researchers only explored transcriptional levels, limiting molecular understanding. In our viewpoint, morphological, molecular, and cellular responses should be investigated concurrently to clarify the complete adaptation of the adipose tissue.

In addition, the culture of adipose cells may reveal the sequential processes relate to the development of adipocytes (proliferation or differentiation) (Skurk and Hauner, 2012). *In vitro* analysis, with primary cell culture, may be closer to human physiology, preserving phenotypical states (body weight, sex, and age) (Skurk and Hauner, 2012). Acquiring adipocyte heterogeneity at the single cell within a fat depot is critical to understanding the diversities in cardiometabolic factors among young and older individuals. Additionally, there is a necessity for further experiments to comprehend the possible sex divergences in response to unlike exercise, as well as the impact of interrupting the regular practice of physical exercise, in addition to the potential effects of training throughout life.

4.3. Cardiovascular system

4.3.1. Animal models

Cardiovascular aging leads to a progressive decline in heart structure and function, making older organisms more susceptible to cardiovascular diseases, morbidity, and mortality. Maladaptive cardiac remodeling involves a range of modifications, such as decreased mitochondrial function via the decline in PGC-1α expression, which is considered a key manager of mitochondrial biogenesis and metabolic adaptation in the myocardium (Di et al., 2018; Schilling and Kelly, 2011; Whitehead et al., 2018). Low levels of PGC-1α in the heart impair energy metabolism, excitation-contraction, and calcium signaling homeostasis (Chen et al., 2010). Although the drastic reduction in PGC-1α in the cardiovascular system is unsatisfactory to initiate an aging phenotype, an increase in this molecule potentially reduces the pathological heart remodeling of old mice (Whitehead et al., 2018).

Swimming exercise training (8 weeks, 5 days/week, for 60 min per session) induced improvements in cardiac histology, attenuating cardiomyocyte disarrangements in aged rat hearts (Chen et al., 2018). Exercise training enhanced the protein contents of SIRT1, PGC-1α, and AMPKα1 in the left ventricle and suppressed the aging-associated inflammatory signaling pathways (i.e., TNF-α, NFκB, and inducible nitric oxide synthase/iNOS) (Chen et al., 2018). Bayod et al. (2012) displayed

that suitable long-term exercise training (36 weeks, 4–5 days per week, at 12 m/min) could protect the aged heart through upregulation of PGC-1α and SIRT1 activation, besides increasing VEGF levels and catalase activity, supporting the use of moderate physical exercise to preventing age-related disorders. Of note, PGC-1α activation in the Drosophila heart via exercise (climbing training for 5 weeks, 5 times per week for 1.5 h/day) improved mobility and lifespan (Wen et al., 2021).

However, short moderate-intensity exercise (motorized wheel system, 3 weeks, 5 times per week, at 5.2 m/min) augmented PGC-1α content and mitochondrial DNA density in type 2 diabetic hearts at an advanced age without changing body weight or glycemic blood levels (Botta et al., 2013). Furthermore, this exercise lowered cardiac (macrophage infiltration and TNF-α) and systemic inflammation (Botta et al., 2013). Alternatively, the authors found increased hydrogen peroxide (H_2O_2) concentrations in H9c2 cardiomyocytes in vitro (Botta et al., 2013). However, the exercise dose failed to increase respiratory enzymes and transcriptional activators (i.e., NRF-1 and NRF-2, and TFAM). Therefore, more intense training for a more extended period could be necessary to promote complete cardiac adaptations in the diabetes condition.

Yeo and Lim (2022) recently evaluated PGC-1α modulation in the left ventricle in response to exercise modality (combined, resistance, or aerobic) in aged rats. The authors observed that all types of exercise training enhanced the amount of PGC-1α in old myocardial tissue. However, only the aerobic training group displayed higher VEGF protein levels than sedentary animals, indicating that this modality stimulates the PGC-1α-induced VEGF pathway. Furthermore, Hypoxia-inducible factor and Angiotensin II proteins increased in this group compared to the other modalities, suggesting that angiogenesis-related proteins differed according to the exercise type in aging.

Mitochondrial dysregulation can impact central upstream mechanisms mediating vascular function. With advancing age, vessel arterial stiffening and endothelial malfunction are determining cardiovascular risk factors. However, chronic aerobic exercise (treadmill daily for 12 weeks for 60 min per day, at 8–20 m/min) preserved aortic mitochondrial integrity, swelling and DNA content while reducing ROS production in aged rats. Also, it restored complex I/III activities and electron-coupling capacity (Gu et al., 2014). In addition, aerobic exercise training enhanced the protein contents of PGC-1α, UCP-2, SOD, aldehyde dehydrogenase 2 (ALDH-2), and AMPK phosphorylation in old aortas. These molecular effects possibly contributed to attenuated pulse wave velocity and aortic stiffening by reducing collagen concentration while increasing elastin content. Moreover, exercise attenuated endothelial dysfunction by enhancing endothelium-mediated vascular relaxation (Gu et al., 2014). Thus, exercise induces extensive physiological effects, promoting beneficial adaptations in aorta structure and cellular function, as well as maintaining homeostasis.

Similarly, 10 weeks of voluntary aerobic exercise (3.13 km/day) enhanced arterial resilience in an *ex-vivo* mimicked western diet. Moreover, exercise training controlled age-related arterial health adjustments (PGC-1α, SIRT-3, and FIS1 expression) and augmented arterial antioxidant defense markers (Catalase) and cellular stress response (Heat shock protein 90) of aged mice (Gioscia-Ryan et al., 2016), suggesting arterial mitochondrial health can be essential to vascular homeostasis. More lately, Mahdavi et al. (2022) reported that blood flow restriction combined with moderate-intensity endurance exercise reduced left ventricular diastolic pressure, and improved cardiac contractility of aging rats by increasing PGC1-α and Klotho expression.

4.4. Human

4.4.1. Blood circulation

Due to ethical considerations of using human heart samples, the mitochondrial biomarkers in blood circulation have been documented as a non-invasive and reliable assessment to examine possible cardiovascular system responses. From this perspective, Hooshmand-Moghadam et al. (2020) described that a 12-week RT program (3 sessions/week, 15 repetitions, at ~60% of 1RM involved in different muscle groups) increases the protein levels linked to the aging process, such as SIRT1, SIRT3, SIRT6, PGC-1α, and telomerase enzyme in older men. Thus, RT can modulate crucial molecules involved in human mitochondrial function and chromosome integrity, potentially enhancing healthspan.

Additionally, peripheral blood mononuclear cells (PBMCs) are utilized as representative compartments offering a valuable alternative for protein or gene expression evaluations in the skeletal muscle or myocardium, which are not readily available in human biopsies. Hence, Estébanez et al. (2019) showed that an 8-week RT protocol (2 times per week, 8–12 repetitions, at 40%−80% of 1RM) increased the PGC-1α and MFN1 protein levels, besides upregulating protein phosphorylations involved in the unfolded protein response (PERK, IRE1, ATF4, and XBP1). However, this protocol did not modify proteins related to mitophagy (BCL2 protein-interacting protein 3/BNIP3), Pten-induced kinase 1/PINK1, and Parkin) in PBMCs of older adults. This study suggests a possible interplay between UPR and mitochondria in the older population after an 8-week RT program. Thus, PGC-1α could be an "exerkine" since it encompasses critical molecule signaling and exerts its effects through endocrine pathways. Table 1 demonstrates the detailed results of different exercise modalities on PGC-1α content in human physiological systems. Moreover, the synthesis of PGC-1α outcomes observed in the exercised older adults is reported in Fig. 4.

4.5. Neural system

4.5.1. Animal models

The mitochondria are particularly crucial in the neural system because neurons need a significant quantity of functional mitochondria to supply their high energy prerequisite for synaptic activities (McMeekin et al., 2021; Picard and McEwen, 2014). A decline in the quality or activity of the brain mitochondria, mainly in the hippocampus structure, is linked with aging progress, neurodegenerative disorders, and dementia, compromising neurological performance (McMeekin et al., 2021). Despite synaptic and cognitive dysfunction being a multifactorial process, mitochondria perform a vital role in these processes, suggesting that proper organelle function could counteract age-related changes (Lin et al., 2020). In this sense, many studies propose PGC-1α can contribute to dendritic spines and synapses, improving synaptogenesis and neurogenesis (Cheng et al., 2012; Katsouri et al., 2016; Kuczynska et al., 2021).

A pioneering investigation showed treadmill exercise above the lactate threshold (8 weeks, 5 days per week, 2 sessions per day, at 21–26 m/min) affects bioenergetics-relevant targets (E et al., 2014). The PGC-1α, mTOR, phospho-mTOR protein levels and mtDNA copy number were increased in aged mice brains, indicating that physical exercise can improve neurogenesis and mitochondrial dysfunction associated with the aging process (E et al., 2014). These data suggest that high-intensity training can activate partial brain mitochondrial biogenesis, which is relevant for tissue health maintenance.

In another study, Lin et al. (2020) reported that swimming exercise training (12 weeks, 5 times per week, with a 20 min duration in the first and second weeks, 30 min duration in the third week, and 60 min duration in the fourth week onwards) enhanced hippocampus cell density, accompanied by upregulation of the IGF1R/PI3K/Akt axis and AMPK/SIRT1/PGC-1α pathways in the of D-galactose-induced aged rat hippocampus. Moreover, exercise reversed the adverse effects of aging on apoptotic (FAS receptor and caspases) and inflammatory pathways (TNFα, p-NFκB, iNOS, and ciclo-oxigenase-2), which is essential for cell survival maintenance and cellular longevity.

Gusdon et al. (2017) showed that coupled complex I to III enzymatic activity and dynamin-related protein 1 expression enhanced in trained aged mice. However, mitochondrial protein content and mitochondrial biogenesis markers (PGC-1α, TFAM, and SIRT3) were not altered by

Table 1
Effects of different exercise modes on PGC1-α levels in the physiological systems of aged animals.

Reference	Study model	Gender	Age	Exercise modality and intensity	Exercise duration	Exercise frequency	Tissue	PGC1-α detection assay and findings
Musculoskeletal system								
Koltai et al. (2012)	Rat	Male	26 months old	Treadmill training at 60% of the VO_{2max}	60 min per day	6 weeks, 5 times per week	Gastrocnemius muscle	↑ PGC1-α protein content compared with 26- month-old sedentary rat.
Kang et al. (2013)	Rat	Male	22 months old	Treadmill training at 60% of the 17.5 m/min	45 min per day	12 weeks, 5 times per week	Soleus muscle	↑ *Ppargc1a* mRNA levels and protein content compared with 22- month-old sedentary rat.
Huang et al. (2016)	Rat	Male	18 months old	Swimming training (2–5% of the animal's BW)	40 min per day	12 weeks, 5 times per week	Soleus muscle	↑ PGC1-α protein content compared with 18- month-old sedentary rat.
Derbré et al. (2012)	Rat	Male	24 months old	Treadmill training at 75% of the VO_{2max}	45–60 min per day	3 weeks, 5 times per week	Soleus muscle	↑ PGC1-α protein content compared with 24- month-old sedentary rat.
Halling et al. (2019)	Mice (PGC-1α iMKO)	Male	15 months old	Treadmill training at 60% of the Vmax	60 min per day	7 weeks, 5 times per week	Quadriceps muscle	↑submaximal ADP-stimulated respiration. ↓ mitochondrial ROS emission and oxidative stress compared with aged untrained PGC-1α iMKO.
Gill et al. (2018)	Mice (WT) PGC-1α mKO PGC-1α mTg	Male	24 months old	Treadmill training at 50–80% of the Vmax	30 min per day	12 weeks, 3 times per week	Tibialis anterior muscles	↑ *Ppargc1a* mRNA levels in the trained mice compared with 24- month-old sedentary rats. ↓ Lean mass, strength motor coordination in the aged mice PGC-1α iMKO and mTg compared with respective young control mice.
Halling et al. (2017)	Mice (WT) Whole-body PGC1-α KO	Male	15 months old	Lifelong Running wheel	Average distance 5.9 ± 1.9 (WT), 6.0 ± 2.4 (KO) km/week	15 months, Voluntary times per week	Triceps brachii muscle	↓ Fragmentation mitochondrial networks and FIS1, DRP1 LC3II/I ratio protein content in the trained mice compared with 15- month-old sedentary mice No effects of exercise in the Whole-body PGC1-α KO trained
Ribeiro et al. (2017)	Rat	Male	20 months old	Resistance training (4 climbs of 65%, 85%, 95%, and 100% of the max load)	20 min per day	12 weeks, 5 times per week	Gastrocnemius and soleus muscle	↑ *Ppargc1a* mRNA levels compared with 22- month-old sedentary rats
Vechetti-Junio et al. (2016)	Rat submitted to short-term immobilization	Male	18 months old	Swimming training (2–7% of the animal's BW)	20 min per day	7 days	Gastrocnemius muscle	↑ PGC1-α protein content compared with the control group
Liu et al. (2021)	Rat	Male	24 months old	Static resistance training (BW)	15 min per day	8 weeks	Biceps brachii muscle	↑ PGC1-α protein content, ATP production, and muscle hypertrophic compared with the control group
Endocrine system								
Kristensen et al. (2017)	Mice (Whole-body PGC1-α KO)	Male	15 months old	Lifelong Running wheel	Voluntary min per day	Voluntary times per week	Liver	↓ IRE1α protein content in the trained whole-body PGC1-α KO compared with untrained whole-body PGC1-α KO
Bianchi et al. (2021)	Mice	Male	16–19 months old	Treadmill training at 20 cm/s	20 min per day	12 weeks, 3 times per week	Liver	↓ PGC1-α acetylation compared with 16- month-old sedentary mice.
Bayod et al. (2012)	Rat	Male	10-months-old	Lifelong Running wheel (12 m/min)	Voluntary min per day	36 weeks, 4–5 times per week (152 sessions per animal)	Liver	↑ PGC1-α protein content compared with 10- month-old sedentary rat.
Khodabandeh et al., 2021	Rat	Male	13-months-old	Resistance training	20 min per day	8 weeks, 3 times per week	Liver	↑ *Ppargc1a* mRNA levels compared with 10- month-old sedentary rat.

(*continued on next page*)

Table 1 (*continued*)

Reference	Study model	Gender	Age	Exercise modality and intensity	Exercise duration	Exercise frequency	Tissue	PGC1-α detection assay and findings
Ziegler et al. (2019)	Mice	Male	23 months old	Voluntary wheel running with resistance (5–10 g) Voluntary wheel running (1.5 g)	Voluntary times per week	10 weeks	Epididymal adipose tissue	↑ *Ppargc1a* mRNA levels compared with 23- month-old sedentary rats after bots both training modalities. ↑ *Ppargc1a* mRNA levels in the voluntary wheel running compared with resistance.
Thirupathi et al. (2019)	Mice	Male	18 months old	Resistance training (climbs of 50–100% of the max load) Aerobic training Treadmill training (50–70% of the Vmax)	50 min per day	8 weeks, 4 times per week	Brown adipose tissue	↑ PGC1-α protein content compared with 18- month-old sedentary rats after both training modalities.
Sun et al. (2021)	Rat	Male	26 months old	Lifelong treadmill exercise (75–80% of VO2max)	50 min per day	18 months, 5 times per week	Perirenal adipose tissue	↑ PGC1-α protein content compared with 26- month-old sedentary rat
Cardiovascular system								
Chen et al. (2018)	Rat received D-galactose during eight weeks.	Male	3 months old	Swimming exercise (Weight-bearing exercise)	20–60 min per day	8 weeks, 5 times per week	Left ventricle	↑ PGC1-α protein content compared with rats without D-galactose
Bayod et al. (2012)	Rat	Male	10-months-old (Middle age)	Lifelong Running wheel (12 m/min)	Voluntary min per day	36 weeks, 4–5 times per week (152 sessions per animal)	Heart	↑ PGC1-α protein content compared with 10- month-old sedentary rat.
Botta et al. (2013)	db/db mice	Male	32 weeks	Motorized wheel system at 5.2 m/min		3 weeks, 5 times per week	Heart	↑ PGC1-α protein content compared with db/db sedentary mice
Yeo and Lim (2022)	Rat	Male	23 months old	Treadmill training (60% of VO_{2max}) Resistance training (50–130% of BW) Combined (30 min of each modality with the same intensity)	60 min per day	8 weeks, 5 times per week	Left ventricle	↑ PGC1-α protein content compared with 23- month-old sedentary rats after all training modalities.
Gu et al. (2014)	Rat	Male	23 months old	Treadmill training at 8–20 m/min	60 min per day	12 weeks, 5 times per week	Aorta	↑ PGC1-α protein content compared with 23- month-old sedentary rat.
Gioscia-Ryan et al. (2016)	Mice	Male	23 months old	Running wheel (3.13 km/day)	Voluntary min per week	Voluntary times per week	Carotid arteries	↑ PGC1-α protein content compared with 23- month-old sedentary mice.
Mahdavi et al. (2022)	Mice	Male	23 months old	Blood flow restriction plus treadmill exercise (15 m/min)	60 min per day	8 weeks, 5 times per week	Left ventricle	↑ PGC1-α protein content compared with 23- month-old sedentary mice.
Neural system								
E et al. (2014)	Mice	Male	18 months old	Treadmill training (2 sessions per day at 21–26 m/min)	60 min per day	8 weeks, 5 times per week	Hippocampus	↑ PGC1-α protein content compared with 18- month-old sedentary mice.
Lin et al. (2020)	Rat received D-galactose during eight weeks.	Male	3 months old	Swimming exercise (Weight-bearing exercise)	20–60 min per day	12 weeks, 5 times per week	Hippocampus	↑ PGC1-α protein content compared with rats without D-galactose
Gusdon et al. (2017)	Mice	Male	24 months old	Treadmill training at 15–19 m/min)	60 min per day	3 weeks, 5 times per week	Cortex and striatum	No effects of exercise in the PGC1-α protein content of 24- month-old mice.
Karlsson et al. (2021)	Mice (MCK-PGC-1α)	Male and Female	11 months old	voluntary wheel running	Voluntary min per week	4 weeks	Hippocampus	No effects of exercise in the PGC1-α protein content of 11- month-old mice.
Sexual system								
Joseph et al. (2014)	Rat	Male	24 months old	Treadmill training at 15 m/min	60 min per day	10 weeks, 5 times per week	Testes	No effects of exercise in the PGC1-α protein content of 24- month-old mice.

Note: iMKO = inducible muscle-specific KO, mKO = conventional muscle KO, KO = knockout, ROS = reactive oxidative species, Mtg = overexpression, BW= body weight, MCK = muscle creatine kinase.

aerobic training (3 weeks, 5 times per week, at 15–19 m/min on a treadmill) in the brain (cortex and striatum), suggesting alternative pathways can affect brain mitochondria function. Indeed, the brain-derived neurotrophic factor, which was not altered in this study, stimulates PGC-1α expression (Gusdon et al., 2017). Thus, it is possible to consider that physical exercise stimulates complex outcomes through diverse mechanisms. Also, the sustainable exercise-mimicking responses to neuroprotection will likely need to target more than one molecular pathway.

From another perspective, Karlsson et al. (2021) evaluated whether skeletal muscle PGC-1α overexpression could increase neurogenesis. The authors also investigated whether endurance exercise (28 days of

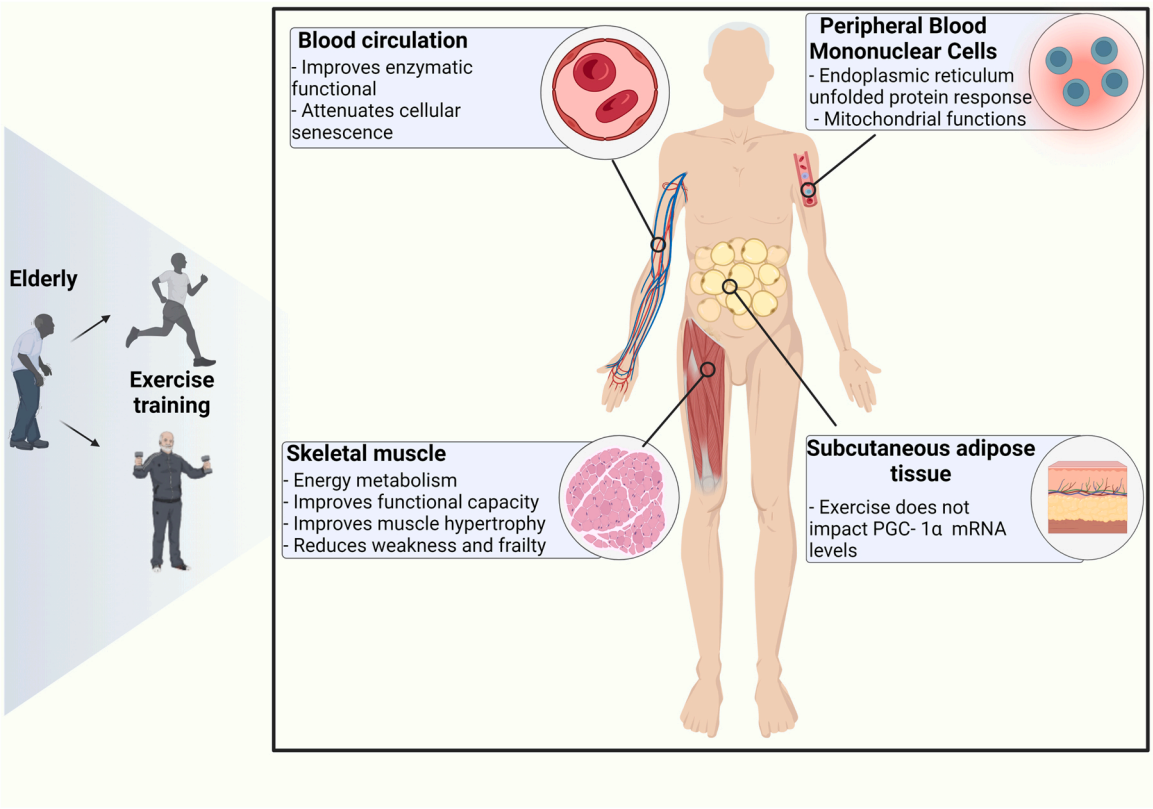

Fig. 4. Primary outcomes of PGC-1α induced by exercise training in the physiological systems of older adults. There is upregulation of the PGC-1α content in skeletal muscle (process: energy metabolism, functional capacity, hypertrophy), blood circulation (process: enzymatic function in plasma and serum, cellular senescence), and peripheral blood mononuclear cells (process: mitochondrial function and unfolded protein response). Biorender webbased software was used to create the figure (License Number LH24O7JW4H).

voluntary wheel running) could further add to these impacts during aging. In summary, no other positive effects of skeletal muscle PGC-1α overexpression or exercise-induced improvement in age-dependent neuronal decline were observed in aged mice. However, the intensity and volume of voluntary exercise cannot be precisely measured, which may mitigate the beneficial effects. On the other hand, a plausible explanation is that β-oxidation is not preferred in the brain because neurons show a greater need for glucose metabolism than peripheral tissues (Schonfeld and Reiser, 2013). Hence, the brain mitochondria exercise impact may be different in other organs. Additional investigations are required to determine other signals from skeletal muscles and organs that could be critical players in exercise-inducing changes in the neural system.

Despite the exciting results of PGC-1α in the neural system, some limitations must be mentioned. First, previous studies did not evaluate the relationship between the increase in PGC-1α with functional tests and morphology modifications. Thus, it is essential to apply a good and reliable battery of tests to determine behavioral abilities, cognition, memory, and brain function in animals to clarify the PGC-1α role as a brain performance marker. Considering the brain is a multifaceted organ, we suggest analyzing the PGC-1α role in activating different structures, connectivity, and complex networks (Mustafa et al., 2012). The application of functional magnetic resonance imaging could introduce advantages to revealing the interactions of several brain structures in response to exercise training (Vieira de Sousa Neto et al., 2021).

Fig. 5 summarizes the molecular landscape contributing to the negative regulation of PGC-1α during aging. Furthermore, it reports part of the mechanisms inherent to physical training reversing this process through upregulating diverse molecules and pathways. Consequently, increasing PGC-1α leads to mitochondrial biogenesis and respiration, antioxidant responses, and autophagy process while reducing ER stress and inflammation in the different physiological systems.

4.6. Renal system

The age-associated decline of kidney integrity has been liked to mitochondrial dysfunction, and some fascinating investigations have addressed the possible key role of PGC-1α in protecting against renal injury (Lim et al., 2012; Mohammad et al., 2022). For instance, a specific mutation of the *PPARGC1A* gene upregulated PGC-1α protein levels and oxidative metabolism, protecting against kidney disease (Dumesic et al., 2019). However, aged mice with nephron PGC-1α deactivation showed higher urinary sodium excretion and aggravated metabolic stress-induced renal steatosis (Svensson et al., 2016).

Other authors showed that inducible tubular transgenic mice (iNephPGC-1α) display more local NAD precursor niacinamide and less fat accumulation than control animals, improving renal function after ischemia (Tran et al., 2016). Furthermore, PGC-1α can ameliorate mitochondrial dysfunction via transcription factor EB (TFEB)-mediated autophagy in cisplatin-induced kidney injury (Yuan et al., 2021), besides alleviating kidney fibrosis, a characteristic of aging (Han et al., 2017).

Cellular senescence is also characterized by diabetic nephropathy-associated secretory phenotype. However, physical exercise can improve renal function and treat diabetic complications. For example, Liu et al. (2019) demonstrated that moderate aerobic exercise protocol (5.2 m/min, 1 h/day, 5 days/week for a total of 8 weeks) increased PGC-1α protein content, citrate synthase and mitochondrial complex I, II, and V activity in the kidney of db/db mice. Moreover, exercise training (12 m/min, 1 h/day, and 6 days/week for 7 weeks) avoids the SIRT1 downregulation, possibly by reducing renal NF-κB acetylation. Interestingly, SIRT1 silencing abrogated the beneficial impact of aerobic

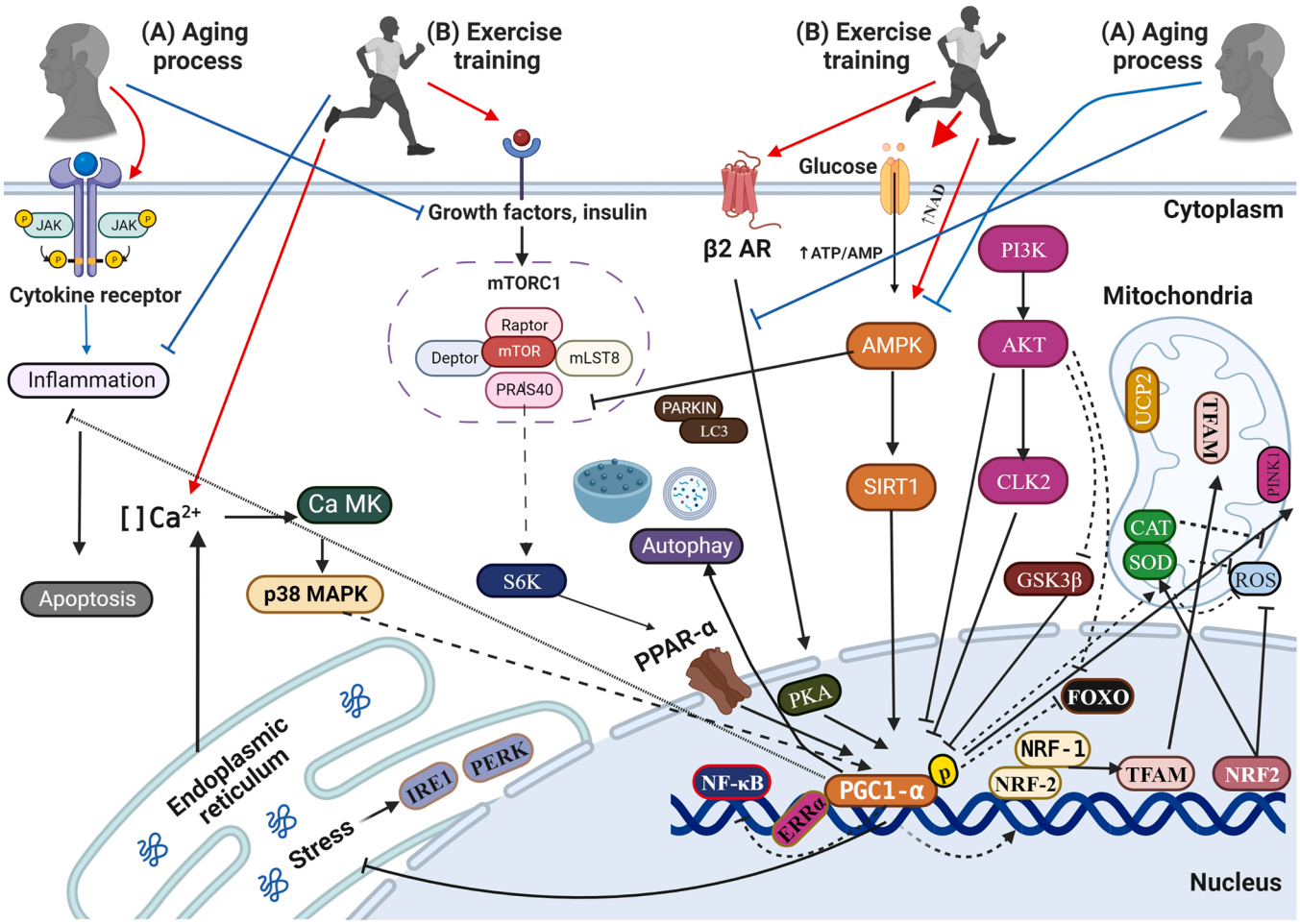

Fig. 5. Overview of molecular pathways that mediate PGC-1α signaling during the aging process and exercise training. (A) represents pathways that contribute to age-related negative regulation of PGC-1α (decrease of beta-adrenergic sensitivity (↓β2-AR and PKA), inflammatory responses (↑ NF-κB, Tnf-α, IL-1, and IL-6), and insulin/IGF-1 pathway suppression (↓ mTORC1). (B) represents molecular mechanisms behind exercise-induced PGC-1α upregulation [increase of metabolic sensors (↑Ampk, Sirt1, and glucose uptake)], improvement of lipid metabolism (↑ PPARA), and calcium signaling activation (Ca mK and p38 MAPK). As a result of the PGC-1α upregulation, exercise induces mitochondrial biogenesis and respiration (↑ NRF-1, NRF-2, TFAM), antioxidant responses (↓GSK3β and p38; ↑ GPX, CAT, UCP-2, AND TRXR), ER stress reduction (↓ PERK and IRE1) and autophagy process improvement (↑ PARKIN and LC3). Blue arrows (age-related negative regulation), red arrows (exercise-induced upregulation), and black arrows (intracellular pathways and interplay). Biorender webbased software was used to create the figure (License Number YC24O7H1UU).

training against diabetes-induced renal damage (fibrosis density and the level of urinary protein/creatine), besides reducing the PGC-1α content and mitochondrial ATP production in the kidney of diabetic mice (Tang et al., 2018). For progress in the aging field, it is essential to understand how changes across the lifespan can modulate PGC-1α signaling pathways in human kidneys and mice with 3, 6, 12, 18, and 24 months.

4.7. Sexual system

4.7.1. Testes

Testicular atrophy in response to aging led to defects in sperm and testosterone release in diverse mammalian species, which may be linked to mitochondrial changes (Joseph et al., 2014). Pre-diabetes increases with age and potentially impairs testicular mitochondrial integrity by suppressing PGC-1α/Sirt3 axis and respiratory function while increasing mtDNA damage and oxidative stress in mice (Rato et al., 2014). Similarly, mtDNA mutator mice display a mitochondrial aberration of spermatocytes and abnormal testes morphology (Jiang et al., 2017). Relevantly, the overexpression of PGC-1α enhanced the ATP levels and SDH activity, mitigating the mitochondria damage in mouse testicular Sertoli cells submitted to toxicity (Li et al., 2016). Thus, understanding the basic molecular mechanisms controlling metabolic changes at the testicular level is a highly pertinent health concern.

In an intriguing investigation, Joseph et al. (2014) reported aging caused considerable testicular atrophy in mice; nevertheless, this result was not related to the downregulation of mitochondrial content (Cytochrome C) and biogenesis regulators (PGC-1α, NRF-1, or TFAM). On the other hand, endurance training increased mtDNA, Mfn-2, and SOD protein content, while reducing DNA damage and testes atrophy in older animals. Additionally, in divergence from other organs, the mitochondrial changes imposed by physical exercise were not connected with increased PGC-1α protein content.

Similarly, Silva et al. (2022) observed that exercise did not avoid the aging process-induced mitochondrial dysfunction in the testes. Although the authors showed lifelong moderate-intensity physical training upregulated antioxidative enzymes (SOD1 and GPx4) and molecular chaperones (HSP27) in the testes of aged mice, there was a decrease in the *Sirt1*, *Ppargc1a*, and *Nrf2* mRNA levels in the exercised groups compared to non-exercised. Concomitantly, these effects were accompanied by reduced levels of complexes III and V. The underlying mechanisms of PGC-1α in the health of male and female sexual organs are mainly unknown, requiring more attention in the coming years.

Fig. 6 summarizes the physiological and molecular processes mediated by PGC-1α upregulation in various animal tissues following

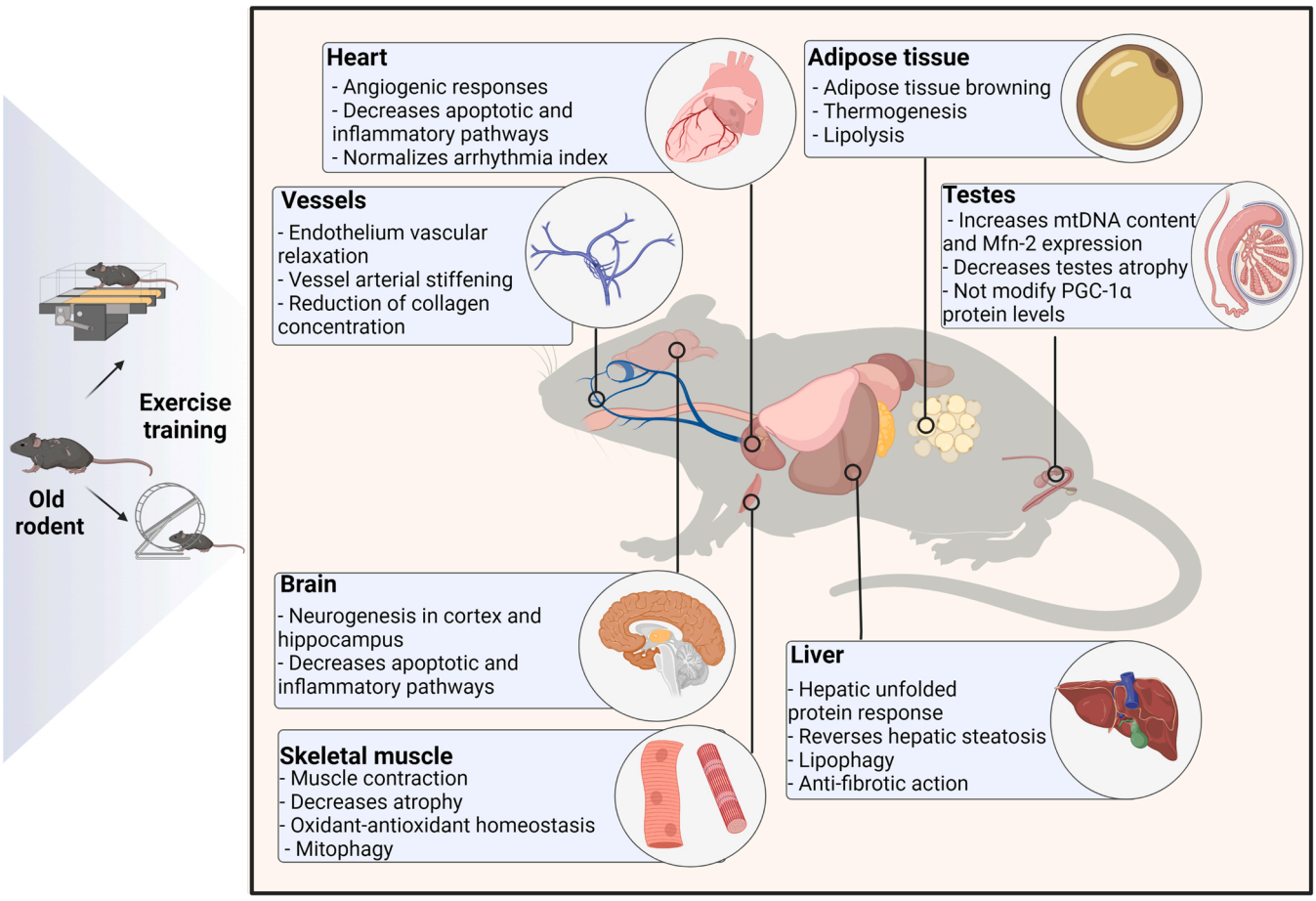

Fig. 6. Main effects of PGC-1α induced by exercise training in the animal's physiological systems. There is an increase in PGC-1α content in skeletal muscle (process: tissue contraction, decreases atrophy, balance redox, and mitophagy), heart (process: angiogenesis, and inflammatory status), vessel (endothelium relaxation, stiffness, and collagen deposition), brain (neurogenesis, and inflammatory status), liver (hepatic steatosis, lipophagy, and fibrosis), and adipose tissue (browning, thermogenesis, and lipolysis). Biorender webbased software was used to create the figure (License Number BW24O7EDSG).

exercise training (Fig. 6). Also, Table 2 shows the detailed impacts of different exercise models on PGC-1α levels in the physiological systems of aged animals.

5. Current challenges and perspectives for all physiological systems

In animal models, aging impacts the PGC-1α expression in the stem cell intestine (Zhou et al., 2011), lung (Summer et al., 2019), and pancreas (Sczelecki et al., 2014), but the effects of exercise on these tissues are unknown. In addition, whether PGC-1α signaling activation during aging depends on other pathways remains a provocative hypothesis for further investigation. These aspects could illustrate whether PGC-1α is indispensable or dispensable and elucidate the pleiotropic effects of exercise on the different physiological systems that are not mediated by a singular pathway. Functional crosstalk is essential for understanding the multi-regulatory network of PGC-1α. Animal models of Alzheimer's disease and Down syndrome have received attention recently due to their potential to clarify premature aging (Herault et al., 2017; McKean et al., 2021). They may offer future opportunities for therapeutic approaches based on PGC-1α action.

The mice with PGC-1α-deficient aortas had reduced expression and activity of telomerase reverse transcriptase, decreasing telomere function (Xiong et al., 2015). As chromosome shortening occurs during aging cell replication, future studies should investigate the promising role of exercise on the crosstalk of PGC-1α with telomere signaling pathways in different physiological systems. Understanding how PGC-1α impacts the telomere structure in each tissue or shelterin complex is relevant for clarifying non-communicable disease risks inherent to the senescence process.

In human trials, some investigations have been conducted in small single-center studies whose core findings should be validated in larger samples. The relationship between the dose-response for individual PGC-1α expression and clinical outcomes remains to be determined. The phenomenon of responsiveness ("high" and "low responders") based on minor differences clinically significant can account for valuable training adaptations.

Additionally, the high expression of PGC-1α is linked to better prognosis in cancer patients, besides tumor-suppressive features (Bost and Kaminski, 2019). Considering aging is a significant risk factor for cancer, understanding the PGC-1α behavior inherent to exercise could provide important information concerning patient prognosis. Finally, minimal dose strategies with reduced intensity and volumes rather than standard exercise guidelines modulating PGC-1α may encourage individuals to initiate physical training, in addition to having beneficial implications for the viability and engagement of the older population.

The effects of aging combined with physical exercise on mitochondrial morphology are mainly focused on skeletal muscle, neglecting the responses in other metabolic tissues. Thus, the transmission electron microscope with high resolution is a robust tool for morphological examination (Sasaki, 2010), and it is expected that further investigations can explore how PGC-1α affects specific mitochondrial structures. In parallel, it is crucial to interpret energetic flux and mitochondrial structures together with other organelles, which could deliver

Table 2
Effects of different exercise modes on PGC1-α levels in the physiological systems of elderly.

Reference	Study model	Gender	Age	Exercise modality and intensity	Exercise duration	Exercise frequency	Tissue	PGC1-α detection assay and findings
Musculoskeletal system								
Short et al. (2003)	Human	Male, female	59–70 years old	Aerobic training at 70–80% of maximal heart rate	20–40 min of cycling	16 weeks, 3 times per week	Vastus lateralis muscle	↑ *PPARGC1A* mRNA levels compared with elderly sedentary
Lanza et al. (2008)	Human	Male, female	59–76 years old	Aerobic training	60 min of cycling or running	6 days per week over the past 4 years	Vastus lateralis muscle	↑ PGC1-α protein content and abundance of proteins involved in oxidative ATP production compared with elderly sedentary
Konopka et al. (2014)	Human	Male, female	74 ± 3 years old	Aerobic training at 60–80% of heart rate reserve	20–45 min of cycling	12 weeks, 3–4 times per week	Vastus lateralis muscle	↑ PGC1-α protein content compared with elderly sedentary
Broskey et al. (2014)	Human	Male, female	60–80 years old	Aerobic training at 75% of heart rate reserve	30–60 min of cycling, rowing, walking or running	16 weeks, 3 times per week	Vastus lateralis muscle	↑ *PPARGC1A* mRNA levels compared with elderly sedentary
Mesquita et al. (2020)	Human	Male, female	59 ± 4 years old	Resistance training (3 sets of 10–12 repetitions at 7 on the RPE	~60 min of session	10 weeks, 2 times per week	Vastus lateralis muscle	↑ *PPARGC1A* mRNA levels compared with elderly sedentary
Wohlgemuth et al. (2011)	Human	Male, female	55–79 years old	Combined training at moderate-intensity exercise (Aerobic at 13 on the Borg Scale), Resistance training (whole-body exercise with 2 sets of 10 repetitions at 13 on the Borg Scale)	~150 min per week	6 months, 3 times per week	Vastus lateralis muscle	↑ *PPARGC1A* mRNA levels compared with elderly sedentary
Watson et al. (2020)	Human (with chronic kidney disease)	Male, female	61.3 ± 13.9 years old	Combined training at moderate-intensity exercise (treadmill, cycling, and rowing for 30 min, at 70–80% of maximum heart rate), Resistance training (lower upper exercise with 3 sets of 12–15 repetitions at 70% of 1RM	~30 min per week	12 weeks, 3 times per week	Vastus lateralis muscle	↑ *PPARGC1A* mRNA levels compared with elderly sedentary
Endocrine system								
Marcangeli et al. (2022)	Human (Obese)	Male, female	67.2 ± 4.9 years old	Aerobic training (HIIT in elliptical trainer at 80–85% maximal heart rate or Borg's scale > 17)	20 min of multiple 30 s sprints alternating with 90 s at a moderate intensity (65% maximal heart rate)	12 weeks, 3 times per week	Abdominal adipose tissue	No effects of exercise in the *PPARGC1A* mRNA levels.
Norheim et al. (2014)	Human	Male	40–65 years old	Combined training (Aerobic and Resistance training at 70% of VO_{2max}).	2 endurance bicycles and whole-body strength sessions per week (120 min)	12 weeks, 4 times per week	Subcutaneous adipose tissue	No effects of exercise in the *PPARGC1A* mRNA levels.
Blood circulation								
Hooshmand-Moghadam et al. (2020)	Human	Male	66.23 ± 0.57 years old	Resistance training (whole-body exercise with 4 sets of 15 repetitions at ~60% of 1RM	~60 min of session	12 weeks, 3 times per week	Serum	↑ PGC1-α protein levels compared with elderly sedentary
Estebanéz et al., 2019	Human	Male, female	73.7 ± 2.2 years old	Resistance training (whole-body exercise with 8–12 repetitions at 40%−80% of 1RM	~60 min of session	8 weeks, 2 times per week	peripheral blood mononuclear cells	↑ PGC1-α protein content compared with elderly sedentary

Note: RPE= Rating of Perceived Exertion, HIIT= High-Intensity Interval Training, 1RM= one repetition maximum.

innovative insights into the intra- and inter-organelle networks.

It is valuable to underscore that PGC-1α activity is mediated by posttranslational processes (Carter et al., 2018). Therefore, without these cellular processes, the extent of PGC-1α involvement in the physiological system cannot be entirely understood. Moreover, several splice PGC-1α sites produce multiple isoforms (Jannig et al., 2022); however, the different functions of these isoforms during aging and exercise are still unexplored. In addition, some authors have highlighted those epigenetic factors can modulate PGC-1α through RNA interference and non-coding RNAs (Aguilo et al., 2016; Lemecha et al., 2018). These modifications may alter transcription process steps and represent the potential molecular basis that explains the adaptive exercise

mechanisms at the organismal, tissue, cellular, and subcellular levels.

6. Conclusions

The PGC-1α signaling pathways mediate the positive impact of exercise on mitochondria health in young and aging conditions. Distinct exercise protocols (short and long-term) and modalities (aerobic and resistance training) increase the transcriptional and translational levels of PGC-1α in various organs (adipose tissue, brain, heart, liver, and skeletal muscle) of aged animals, suggesting that PGC-1α is a versatile molecule inducing pleiotropic responses. However, the PGC-1α function in some human tissues of the elderly (adipose tissue, heart, and brain) remains a challenge for further investigations. The PGC-1α is a common transcriptional coactivator and supports a biochemical environment in mitochondrial dynamics, modulating many physiological processes (cell cycle, primary metabolism, tissue plasticity/remodeling, autophagy, inflammation, redox balance). Acting as an adaptive mechanism, the long-term effects of PGC-1α following exercise may reflect the energy demand to coordinate multiple organ systems.

Identifying a tissue-particular PGC-1α signature can provide new points of view regarding mitochondrial response complexity and pharmacological and non-pharmacological targets, clarifying the positive impact of physical exercise on lifespan extension and cellular longevity. PGC-1α might exclusively affect developing diseases related to the aging course. Thus, PGC-1α modulation by physical training is a non-pharmacological intervention to reducing frailty, weakness, and other age-related comorbidities.

CRediT authorship contribution statement

Ivo V. S. Neto and A. S. R. Silva conceived the paper, Ivo V. S. Neto, Ana P. Pinto, Vitor. R. Muñoz, Rita. C. Marqueti and A. S. R. Silva wrote the original manuscript, Ivo V. S. Neto drew all the figures, Ivo V. S. Neto collected the data in the table, José R, Pauli, Eduardo. R Ropelle revised the manuscript and checked all the references and manuscript. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Data Availability

Data will be made available on request.

Acknowledgments

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References

Aguilo, F., Li, S., Balasubramaniyan, N., Sancho, A., Benko, S., Zhang, F., Vashisht, A., Rengasamy, M., Andino, B., Chen, C.H., Zhou, F., Qian, C., Zhou, M.M., Wohlschlegel, J.A., Zhang, W., Suchy, F.J., Walsh, M.J., 2016. Deposition of 5-Methylcytosine on Enhancer RNAs Enables the Coactivator Function of PGC-1alpha. Cell Rep. 14, 479–492.

Amartuvshin, O., Lin, C.H., Hsu, S.C., Kao, S.H., Chen, A., Tang, W.C., Chou, H.L., Chang, D.L., Hsu, Y.Y., Hsiao, B.S., Rastegari, E., Lin, K.Y., Wang, Y.T., Yao, C.K., Chen, G.C., Chen, B.C., Hsu, H.J., 2020. Aging shifts mitochondrial dynamics toward fission to promote germline stem cell loss. Aging Cell 19, e13191.

Anderson, R., Prolla, T., 2009. PGC-1alpha in aging and anti-aging interventions. Biochim. Biophys. Acta 1790, 1059–1066.

Aquilano, K., Baldelli, S., Pagliei, B., Cannata, S.M., Rotilio, G., Ciriolo, M.R., 2013. p53 orchestrates the PGC-1alpha-mediated antioxidant response upon mild redox and metabolic imbalance. Antioxid. Redox Signal. 18, 386–399.

Baar, K., Wende, A.R., Jones, T.E., Marison, M., Nolte, L.A., Chen, M., Kelly, D.P., Holloszy, J.O., 2002. Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1. FASEB J. 16, 1879–1886.

Barres, R., Osler, M.E., Yan, J., Rune, A., Fritz, T., Caidahl, K., Krook, A., Zierath, J.R., 2009. Non-CpG methylation of the PGC-1alpha promoter through DNMT3B controls mitochondrial density. Cell Metab. 10, 189–198.

Bayod, S., Del Valle, J., Lalanza, J.F., Sanchez-Roige, S., de Luxan-Delgado, B., Coto-Montes, A., Canudas, A.M., Camins, A., Escorihuela, R.M., Pallas, M., 2012. Long-term physical exercise induces changes in sirtuin 1 pathway and oxidative parameters in adult rat tissues. Exp. Gerontol. 47, 925–935.

Berlowska, J., Kregiel, D., Klimek, L., Orzeszyna, B., Ambroziak, W., 2006. Novel yeast cell dehydrogenase activity assay in situ. Pol. J. Microbiol 55, 127–131.

Besse-Patin, A., Jeromson, S., Levesque-Damphousse, P., Secco, B., Laplante, M., Estall, J. L., 2019. PGC1A regulates the IRS1:IRS2 ratio during fasting to influence hepatic metabolism downstream of insulin. Proc. Natl. Acad. Sci. USA 116, 4285–4290.

Bianchi, A., Marchetti, L., Hall, Z., Lemos, H., Vacca, M., Paish, H., Green, K., Elliott, B., Tiniakos, D., Passos, J.F., Jurk, D., Mann, D.A., Wilson, C.L., 2021. Moderate exercise inhibits age-related inflammation, liver steatosis, senescence, and tumorigenesis. J. Immunol. 206, 904–916.

Bost, F., Kaminski, L., 2019. The metabolic modulator PGC-1alpha in cancer. Am. J. Cancer Res. 9, 198–211.

Bostrom, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Bostrom, E.A., Choi, J.H., Long, J.Z., Kajimura, S., Zingaretti, M.C., Vind, B.F., Tu, H., Cinti, S., Hojlund, K., Gygi, S.P., Spiegelman, B.M., 2012. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481, 463–468.

Botta, A., Laher, I., Beam, J., Decoffe, D., Brown, K., Halder, S., Devlin, A., Gibson, D.L., Ghosh, S., 2013. Short term exercise induces PGC-1alpha, ameliorates inflammation and increases mitochondrial membrane proteins but fails to increase respiratory enzymes in aging diabetic hearts. PLoS One 8, e70248.

Boudina, S., Graham, T.E., 2014. Mitochondrial function/dysfunction in white adipose tissue. Exp. Physiol. 99, 1168–1178.

Broskey, N.T., Greggio, C., Boss, A., Boutant, M., Dwyer, A., Schlueter, L., Hans, D., Gremion, G., Kreis, R., Boesch, C., Canto, C., Amati, F., 2014. Skeletal muscle mitochondria in the elderly: effects of physical fitness and exercise training. J. Clin. Endocrinol. Metab. 99, 1852–1861.

Carter, H.N., Pauly, M., Tryon, L.D., Hood, D.A., 2018. Effect of contractile activity on PGC-1alpha transcription in young and aged skeletal muscle. J. Appl. Physiol. 1985 (124), 1605–1615.

Chen, M., Wang, Y., Qu, A., 2010. PGC-1 alpha accelerates cytosolic Ca2+ clearance without disturbing Ca2+ homeostasis in cardiac myocytes. Biochem. Biophys. Res. Commun. 396, 894–900.

Chen, W.K., Tsai, Y.L., Shibu, M.A., Shen, C.Y., Chang-Lee, S.N., Chen, R.J., Yao, C.H., Ban, B., Kuo, W.W., Huang, C.Y., 2018. Exercise training augments Sirt1-signaling and attenuates cardiac inflammation in D-galactose induced-aging rats. Aging 10, 4166–4174.

Cheng, A., Wan, R., Yang, J.L., Kamimura, N., Son, T.G., Ouyang, X., Luo, Y., Okun, E., Mattson, M.P., 2012. Involvement of PGC-1alpha in the formation and maintenance of neuronal dendritic spines. Nat. Commun. 3, 1250.

Cheng, C.F., Ku, H.C., Lin, H., 2018. PGC-1alpha as a pivotal factor in lipid and metabolic regulation. Int. J. Mol. Sci. 19.

Chevalier, B., Mansier, P., Teiger, E., Callen-el Amrani, F., Swynghedauw, B., 1991. Alterations in beta adrenergic and muscarinic receptors in aged rat heart. Effects of chronic administration of propranolol and atropine. Mech. Ageing Dev. 60, 215–224.

Chistiakov, D.A., Sobenin, I.A., Revin, V.V., Orekhov, A.N., Bobryshev, Y.V., 2014. Mitochondrial aging and age-related dysfunction of mitochondria. Biomed. Res. Int. 2014, 238463.

Choi, C.S., Befroy, D.E., Codella, R., Kim, S., Reznick, R.M., Hwang, Y.J., Liu, Z.X., Lee, H.Y., Distefano, A., Samuel, V.T., Zhang, D., Cline, G.W., Handschin, C., Lin, J., Petersen, K.F., Spiegelman, B.M., Shulman, G.I., 2008. Paradoxical effects of increased expression of PGC-1alpha on muscle mitochondrial function and insulin-stimulated muscle glucose metabolism. Proc. Natl. Acad. Sci. USA 105, 19926–19931.

Choi, H.I., Kim, H.J., Park, J.S., Kim, I.J., Bae, E.H., Ma, S.K., Kim, S.W., 2017. PGC-1alpha attenuates hydrogen peroxide-induced apoptotic cell death by upregulating Nrf-2 via GSK3beta inactivation mediated by activated p38 in HK-2 Cells. Sci. Rep. 7, 4319.

Choksi, K.B., Nuss, J.E., DeFord, J.H., Papaconstantinou, J., 2011. Mitochondrial electron transport chain functions in long-lived Ames dwarf mice. Aging 3, 754–767.

Christensen, N.M., Ringholm, S., Buch, B.T., Gudiksen, A., Halling, J.F., Pilegaard, H., 2023. Muscle PGC-1alpha modulates hepatic mitophagy regulation during aging. Exp. Gerontol. 172, 112046.

Delrio-Lorenzo, A., Rojo-Ruiz, J., Alonso, M.T., Garcia-Sancho, J., 2020. Sarcoplasmic reticulum Ca(2+) decreases with age and correlates with the decline in muscle function in Drosophila. J. Cell Sci. 133.

Derbré, F., Gomez-Cabrera, M.C., Nascimento, A.L., Sanchis-Gomar, F., Martinez-Bello, V.E., Tresguerres, J.A., Fuentes, T., Gratas-Delamarche, A., Monsalve, M., Vina, J., 2012. Age associated low mitochondrial biogenesis may be explained by lack of response of PGC-1alpha to exercise training. Age 34, 669–679.

Di, W., Lv, J., Jiang, S., Lu, C., Yang, Z., Ma, Z., Hu, W., Yang, Y., Xu, B., 2018. PGC-1: the energetic regulator in cardiac metabolism. Curr. Issues Mol. Biol. 28, 29–46.

Dillon, L.M., Rebelo, A.P., Moraes, C.T., 2012. The role of PGC-1 coactivators in aging skeletal muscle and heart. IUBMB Life 64, 231–241.

Dillon, L.M., Williams, S.L., Hida, A., Peacock, J.D., Prolla, T.A., Lincoln, J., Moraes, C.T., 2012. Increased mitochondrial biogenesis in muscle improves aging phenotypes in the mtDNA mutator mouse. Hum. Mol. Genet 21, 2288–2297.

Dogra, S., Dunstan, D.W., Sugiyama, T., Stathi, A., Gardiner, P.A., Owen, N., 2022. Active aging and public health: evidence, implications, and opportunities. Annu. Rev. Public Health 43, 439–459.
Dumesic, P.A., Egan, D.F., Gut, P., Tran, M.T., Parisi, A., Chatterjee, N., Jedrychowski, M., Paschini, M., Kazak, L., Wilensky, S.E., Dou, F., Bogoslavski, D., Cartier, J.A., Perrimon, N., Kajimura, S., Parikh, S.M., Spiegelman, B.M., 2019. An evolutionarily conserved uORF regulates PGC1alpha and oxidative metabolism in mice, flies, and bluefin tuna. Cell Metab. 30 (190–200), e196.
E, L., Burns, J.M., Swerdlow, R.H., 2014. Effect of high-intensity exercise on aged mouse brain mitochondria, neurogenesis, and inflammation. Neurobiol. Aging 35, 2574–2583.
Edifizi, D., Schumacher, B., 2015. Genome instability in development and aging: insights from nucleotide excision repair in humans, mice, and worms. Biomolecules 5, 1855–1869.
Ejarque, M., Ceperuelo-Mallafre, V., Serena, C., Maymo-Masip, E., Duran, X., Diaz-Ramos, A., Millan-Scheiding, M., Nunez-Alvarez, Y., Nunez-Roa, C., Gama, P., Garcia-Roves, P.M., Peinado, M.A., Gimble, J.M., Zorzano, A., Vendrell, J., Fernandez-Veledo, S., 2019. Adipose tissue mitochondrial dysfunction in human obesity is linked to a specific DNA methylation signature in adipose-derived stem cells. Int. J. Obes. 43, 1256–1268.
Emelyanova, L., Preston, C., Gupta, A., Viqar, M., Negmadjanov, U., Edwards, S., Kraft, K., Devana, K., Holmuhamedov, E., O'Hair, D., Tajik, A.J., Jahangir, A., 2018. Effect of aging on mitochondrial energetics in the human atria. J. Gerontol. A Biol. Sci. Med. Sci. 73, 608–616.
Estebanéz, B., Moreira, O.C., Almar, M., de Paz, J.A., Gonzalez-Gallego, J., Cuevas, M.J., 2019. Effects of a resistance-training programme on endoplasmic reticulum unfolded protein response and mitochondrial functions in PBMCs from elderly subjects. Eur. J. Sport Sci. 19, 931–940.
Feingold, K., Kim, M.S., Shigenaga, J., Moser, A., Grunfeld, C., 2004. Altered expression of nuclear hormone receptors and coactivators in mouse heart during the acute-phase response. Am. J. Physiol. Endocrinol. Metab. 286, E201–E207.
Feng, Z., Hanson, R.W., Berger, N.A., Trubitsyn, A., 2016. Reprogramming of energy metabolism as a driver of aging. Oncotarget 7, 15410–15420.
Fernandez-Marcos, P.J., Auwerx, J., 2011. Regulation of PGC-1alpha, a nodal regulator of mitochondrial biogenesis. Am. J. Clin. Nutr. 93, 884S–890S.
Fogarty, M.J., Marin Mathieu, N., Mantilla, C.B., Sieck, G.C., 2020. Aging reduces succinate dehydrogenase activity in rat type IIx/IIb diaphragm muscle fibers. J. Appl. Physiol. 128 (1985), 70–77.
Garcia, S., Nissanka, N., Mareco, E.A., Rossi, S., Peralta, S., Diaz, F., Rotundo, R.L., Carvalho, R.F., Moraes, C.T., 2018. Overexpression of PGC-1alpha in aging muscle enhances a subset of young-like molecular patterns. Aging Cell 17.
Gill, J.F., Santos, G., Schnyder, S., Handschin, C., 2018. PGC-1alpha affects aging-related changes in muscle and motor function by modulating specific exercise-mediated changes in old mice. Aging Cell 17.
Gioscia-Ryan, R.A., Battson, M.L., Cuevas, L.M., Zigler, M.C., Sindler, A.L., Seals, D.R., 2016. Voluntary aerobic exercise increases arterial resilience and mitochondrial health with aging in mice. Aging 8, 2897–2914.
Greenberg, L.H., Weiss, B., 1978. beta-Adrenergic receptors in aged rat brain: reduced number and capacity of pineal gland to develop supersensitivity. Science 201, 61–63.
Gu, Q., Wang, B., Zhang, X.F., Ma, Y.P., Liu, J.D., Wang, X.Z., 2014. Chronic aerobic exercise training attenuates aortic stiffening and endothelial dysfunction through preserving aortic mitochondrial function in aged rats. Exp. Gerontol. 56, 37–44.
Gusdon, A.M., Callio, J., Distefano, G., O'Doherty, R.M., Goodpaster, B.H., Coen, P.M., Chu, C.T., 2017. Exercise increases mitochondrial complex I activity and DRP1 expression in the brains of aged mice. Exp. Gerontol. 90, 1–13.
Halling, J.F., Ringholm, S., Olesen, J., Prats, C., Pilegaard, H., 2017. Exercise training protects against aging-induced mitochondrial fragmentation in mouse skeletal muscle in a PGC-1alpha dependent manner. Exp. Gerontol. 96, 1–6.
Halling, J.F., Jessen, H., Nohr-Meldgaard, J., Buch, B.T., Christensen, N.M., Gudiksen, A., Ringholm, S., Neufer, P.D., Prats, C., Pilegaard, H., 2019. PGC-1alpha regulates mitochondrial properties beyond biogenesis with aging and exercise training. Am. J. Physiol. Endocrinol. Metab. 317, E513–E525.
Han, S.H., Wu, M.Y., Nam, B.Y., Park, J.T., Yoo, T.H., Kang, S.W., Park, J., Chinga, F., Li, S.Y., Susztak, K., 2017. PGC-1alpha protects from notch-induced kidney fibrosis development. J. Am. Soc. Nephrol. 28, 3312–3322.
Handschin, C., Chin, S., Li, P., Liu, F., Maratos-Flier, E., Lebrasseur, N.K., Yan, Z., Spiegelman, B.M., 2007. Skeletal muscle fiber-type switching, exercise intolerance, and myopathy in PGC-1alpha muscle-specific knock-out animals. J. Biol. Chem. 282, 30014–30021.
Herault, Y., Delabar, J.M., Fisher, E.M.C., Tybulewicz, V.L.J., Yu, E., Brault, V., 2017. Rodent models in Down syndrome research: impact and future opportunities. Dis. Model Mech. 10, 1165–1186.
Hooshmand-Moghadam, B., Eskandari, M., Golestani, F., Rezae, S., Mahmoudi, N., Gaeini, A.A., 2020. The effect of 12-week resistance exercise training on serum levels of cellular aging process parameters in elderly men. Exp. Gerontol. 141, 111090.
Huang, C.C., Wang, T., Tung, Y.T., Lin, W.T., 2016. Effect of exercise training on skeletal muscle SIRT1 and PGC-1alpha expression levels in rats of different age. Int. J. Med. Sci. 13, 260–270.
Huang, D.D., Fan, S.D., Chen, X.Y., Yan, X.L., Zhang, X.Z., Ma, B.W., Yu, D.Y., Xiao, W.Y., Zhuang, C.L., Yu, Z., 2019. Nrf2 deficiency exacerbates frailty and sarcopenia by impairing skeletal muscle mitochondrial biogenesis and dynamics in an age-dependent manner. Exp. Gerontol. 119, 61–73.
Janikiewicz, J., Szymanski, J., Malinska, D., Patalas-Krawczyk, P., Michalska, B., Duszynski, J., Giorgi, C., Bonora, M., Dobrzyn, A., Wieckowski, M.R., 2018. Mitochondria-associated membranes in aging and senescence: structure, function, and dynamics. Cell Death Dis. 9, 332.
Jannig, P.R., Dumesic, P.A., Spiegelman, B.M., Ruas, J.L., 2022. SnapShot: regulation and biology of PGC-1alpha. Cell 185 (1444–1444), e1441.
Jiang, M., Kauppila, T.E.S., Motori, E., Li, X., Atanassov, I., Folz-Donahue, K., Bonekamp, N.A., Albarran-Gutierrez, S., Stewart, J.B., Larsson, N.G., 2017. Increased total mtDNA copy number cures male infertility despite unaltered mtDNA mutation load. Cell Metab. 26 (429–436), e424.
Joseph, A.M., Nguyen, L.M., Welter, A.E., Dominguez 2nd, J.M., Behnke, B.J., Adhihetty, P.J., 2014. Mitochondrial adaptations evoked with exercise are associated with a reduction in age-induced testicular atrophy in Fischer-344 rats. Biogerontology 15, 517–534.
Kadoglou, N.P., Perrea, D., Iliadis, F., Angelopoulou, N., Liapis, C., Alevizos, M., 2007. Exercise reduces resistin and inflammatory cytokines in patients with type 2 diabetes. Diabetes Care 30, 719–721.
Kang, C., Chung, E., Diffee, G., Ji, L.L., 2013. Exercise training attenuates aging-associated mitochondrial dysfunction in rat skeletal muscle: role of PGC-1alpha. Exp. Gerontol. 48, 1343–1350.
Karlsson, L., Gonzalez-Alvarado, M.N., Motalleb, R., Wang, Y., Wang, Y., Borjesson, M., Zhu, C., Kuhn, H.G., 2021. Constitutive PGC-1alpha overexpression in skeletal muscle does not contribute to exercise-induced neurogenesis. Mol. Neurobiol. 58, 1465–1481.
Katsouri, L., Lim, Y.M., Blondrath, K., Eleftheriadou, I., Lombardero, L., Birch, A.M., Mirzaei, N., Irvine, E.E., Mazarakis, N.D., Sastre, M., 2016. PPARgamma-coactivator-1alpha gene transfer reduces neuronal loss and amyloid-beta generation by reducing beta-secretase in an Alzheimer's disease model. Proc. Natl. Acad. Sci. USA 113, 12292–12297.
Khodabandeh, M., Peeri, M., Azarbayjani, M.A., Matinhomaee, M., 2021. Effect of resistance exercise and liposomal vitamin C on some factors of mitochondrial dynamics and biogenesis. Complement. Med. J. 11, 82–97.
Kim, S.B., Heo, J.I., Kim, H., Kim, K.S., 2019. Acetylation of PGC1alpha by histone deacetylase 1 downregulation is implicated in radiation-induced senescence of brain endothelial cells. J. Gerontol. A Biol. Sci. Med Sci. 74, 787–793.
Koh, J.H., Pataky, M.W., Dasari, S., Klaus, K.A., Vuckovic, I., Ruegsegger, G.N., Kumar, A.P., Robinson, M.M., Nair, K.S., 2022. Enhancement of anaerobic glycolysis - a role of PGC-1alpha4 in resistance exercise. Nat. Commun. 13, 2324.
Koltai, E., Hart, N., Taylor, A.W., Goto, S., Ngo, J.K., Davies, K.J., Radak, Z., 2012. Age-associated declines in mitochondrial biogenesis and protein quality control factors are minimized by exercise training. Am. J. Physiol. Regul. Integr. Comp. Physiol. 303, R127–R134.
Konopka, A.R., Suer, M.K., Wolff, C.A., Harber, M.P., 2014. Markers of human skeletal muscle mitochondrial biogenesis and quality control: effects of age and aerobic exercise training. J. Gerontol. A Biol. Sci. Med. Sci. 69, 371–378.
Koves, T.R., Li, P., An, J., Akimoto, T., Slentz, D., Ilkayeva, O., Dohm, G.L., Yan, Z., Newgard, C.B., Muoio, D.M., 2005. Peroxisome proliferator-activated receptor-gamma co-activator 1alpha-mediated metabolic remodeling of skeletal myocytes mimics exercise training and reverses lipid-induced mitochondrial inefficiency. J. Biol. Chem. 280, 33588–33598.
Kristensen, C.M., Brandt, C.T., Ringholm, S., Pilegaard, H., 2017. PGC-1alpha in aging and lifelong exercise training-mediated regulation of UPR in mouse liver. Exp. Gerontol. 98, 124–133.
Kuczynska, Z., Metin, E., Liput, M., Buzanska, L., 2021. Covering the role of PGC-1alpha in the nervous system. Cells 11.
Kumaran, S., Subathra, M., Balu, M., Panneerselvam, C., 2004. Age-associated decreased activities of mitochondrial electron transport chain complexes in heart and skeletal muscle: role of L-carnitine. Chem. Biol. Interact. 148, 11–18.
Kwon, S., Seok, S., Yau, P., Li, X., Kemper, B., Kemper, J.K., 2017. Obesity and aging diminish sirtuin 1 (SIRT1)-mediated deacetylation of SIRT3, leading to hyperacetylation and decreased activity and stability of SIRT3. J. Biol. Chem. 292, 17312–17323.
Lanza, I.R., Short, D.K., Short, K.R., Raghavakaimal, S., Basu, R., Joyner, M.J., McConnell, J.P., Nair, K.S., 2008. Endurance exercise as a countermeasure for aging. Diabetes 57, 2933–2942.
Lehnig, A.C., Dewal, R.S., Baer, L.A., Kitching, K.M., Munoz, V.R., Arts, P.J., Sindeldecker, D.A., May, F.J., Lauritzen, H., Goodyear, L.J., Stanford, K.I., 2019. Exercise training induces depot-specific adaptations to white and brown adipose tissue. iScience 11, 425–439.
Lemecha, M., Morino, K., Imamura, T., Iwasaki, H., Ohashi, N., Ida, S., Sato, D., Sekine, O., Ugi, S., Maegawa, H., 2018. MiR-494-3p regulates mitochondrial biogenesis and thermogenesis through PGC1-alpha signalling in beige adipocytes. Sci. Rep. 8, 15096.
Leveille, M., Besse-Patin, A., Jouvet, N., Gunes, A., Sczelecki, S., Jeromson, S., Khan, N. P., Baldwin, C., Dumouchel, A., Correia, J.C., Jannig, P.R., Boulais, J., Ruas, J.L., Estall, J.L., 2020. PGC-1alpha isoforms coordinate to balance hepatic metabolism and apoptosis in inflammatory environments. Mol. Metab. 34, 72–84.
Li, Z., Liu, X., Wang, L., Wang, Y., Du, C., Xu, S., Zhang, Y., Wang, C., Yang, C., 2016. The role of PGC-1alpha and MRP1 in lead-induced mitochondrial toxicity in testicular Sertoli cells. Toxicology 355–356, 39–48.
Liang, H., Ward, W.F., 2006. PGC-1alpha: a key regulator of energy metabolism. Adv. Physiol. Educ. 30, 145–151.
Lim, J.H., Kim, E.N., Kim, M.Y., Chung, S., Shin, S.J., Kim, H.W., Yang, C.W., Kim, Y.S., Chang, Y.S., Park, C.W., Choi, B.S., 2012. Age-associated molecular changes in the kidney in aged mice. Oxid. Med. Cell. Longev. 2012, 171383.
Lima, T., Li, T.Y., Mottis, A., Auwerx, J., 2022. Pleiotropic effects of mitochondria in aging. Nat. Aging 2, 199–213.

Lin, J., Wu, H., Tarr, P.T., Zhang, C.Y., Wu, Z., Boss, O., Michael, L.F., Puigserver, P., Isotani, E., Olson, E.N., Lowell, B.B., Bassel-Duby, R., Spiegelman, B.M., 2002. Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. Nature 418, 797–801.

Lin, J., Wu, P.H., Tarr, P.T., Lindenberg, K.S., St-Pierre, J., Zhang, C.Y., Mootha, V.K., Jager, S., Vianna, C.R., Reznick, R.M., Cui, L., Manieri, M., Donovan, M.X., Wu, Z., Cooper, M.P., Fan, M.C., Rohas, L.M., Zavacki, A.M., Cinti, S., Shulman, G.I., Lowell, B.B., Krainc, D., Spiegelman, B.M., 2004. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. Cell 119, 121–135.

Lin, J.Y., Kuo, W.W., Baskaran, R., Kuo, C.H., Chen, Y.A., Chen, W.S., Ho, T.J., Day, C.H., Mahalakshmi, B., Huang, C.Y., 2020. Swimming exercise stimulates IGF1/ PI3K/Akt and AMPK/SIRT1/PGC1alpha survival signaling to suppress apoptosis and inflammation in aging hippocampus. Aging 12, 6852–6864.

Liu, H.W., Kao, H.H., Wu, C.H., 2019. Exercise training upregulates SIRT1 to attenuate inflammation and metabolic dysfunction in kidney and liver of diabetic db/db mice. Nutr. Metab. 16, 22.

Liu, Y., Guo, C., Liu, S., Zhang, S., Mao, Y., Fang, L., 2021. Eight weeks of high-intensity interval static strength training improves skeletal muscle atrophy and motor function in aged rats via the PGC-1alpha/FNDC5/UCP1 pathway. Clin. Inter. Aging 16, 811–821.

Liu, Y.J., McIntyre, R.L., Janssens, G.E., Houtkooper, R.H., 2020. Mitochondrial fission and fusion: A dynamic role in aging and potential target for age-related disease. Mech. Ageing Dev. 186, 111212.

Macedo, A.P.A., da Silva, A.S.R., Munoz, V.R., Ropelle, E.R., Pauli, J.R., 2021. Mitochondrial dysfunction plays an essential role in remodeling aging adipose tissue. Mech. Ageing Dev. 200, 111598.

Mahdavi, N., Joukar, S., Najafipour, H., Naderi-Boldaji, V., 2022. Promotion of aging heart function and its redox balance following hind-limb blood flow restriction plus endurance exercise training in rats: klotho and PGC1-alpha as involving candidate molecules. Pflug. Arch. 474, 699–708.

Maitra, U., Singh, N., Gan, L., Ringwood, L., Li, L., 2009. IRAK-1 contributes to lipopolysaccharide-induced reactive oxygen species generation in macrophages by inducing NOX-1 transcription and Rac1 activation and suppressing the expression of antioxidative enzymes. J. Biol. Chem. 284, 35403–35411.

Marcangeli, V., Youssef, L., Dulac, M., Carvalho, L.P., Hajj-Boutros, G., Reynaud, O., Guegan, B., Buckinx, F., Gaudreau, P., Morais, J.A., Mauriege, P., Noirez, P., Aubertin-Leheudre, M., Gouspillou, G., 2022. Impact of high-intensity interval training with or without l-citrulline on physical performance, skeletal muscle, and adipose tissue in obese older adults. J. Cachexia Sarcopenia Muscle 13, 1526–1540.

Mc Auley, M.T., Guimera, A.M., Hodgson, D., McDonald, N., Mooney, K.M., Morgan, A. E., Proctor, C.J., 2017. Modelling the molecular mechanisms of aging. Biosci. Rep. 37.

McCormick, R., Vasilaki, A., 2018. Age-related changes in skeletal muscle: changes to life-style as a therapy. Biogerontology 19, 519–536.

McKean, N.E., Handley, R.R., Snell, R.G., 2021. A review of the current mammalian models of alzheimer's disease and challenges that need to be overcome. Int. J. Mol. Sci. 22.

McMeekin, L.J., Fox, S.N., Boas, S.M., Cowell, R.M., 2021. Dysregulation of PGC-1alpha-dependent transcriptional programs in neurological and developmental disorders: therapeutic challenges and opportunities. Cells 10.

Meng, Y., Eirin, A., Zhu, X.Y., Tang, H., Chanana, P., Lerman, A., van Wijnen, A.J., Lerman, L.O., 2018. Obesity-induced mitochondrial dysfunction in porcine adipose tissue-derived mesenchymal stem cells. J. Cell. Physiol. 233, 5926–5936.

Mesquita, P.H.C., Lamb, D.A., Parry, H.A., Moore, J.H., Smith, M.A., Vann, C.G., Osburn, S.C., Fox, C.D., Ruple, B.A., Huggins, K.W., Fruge, A.D., Young, K.C., Kavazis, A.N., Roberts, M.D., 2020. Acute and chronic effects of resistance training on skeletal muscle markers of mitochondrial remodeling in older adults. Physiol. Rep. 8, e14526.

Mohammad, R.S., Lokhandwala, M.F., Banday, A.A., 2022. Age-related mitochondrial impairment and renal injury is ameliorated by sulforaphane via activation of transcription factor NRF2. Antioxidants 11.

Molenaars, M., Janssens, G.E., Williams, E.G., Jongejan, A., Lan, J., Rabot, S., Joly, F., Moerland, P.D., Schomakers, B.V., Lezzerini, M., Liu, Y.J., McCormick, M.A., Kennedy, B.K., van Weeghel, M., van Kampen, A.H.C., Aebersold, R., MacInnes, A. W., Houtkooper, R.H., 2020. A conserved mito-cytosolic translational balance links two longevity pathways. Cell Metab. 31 (549–563), e547.

Moon, H.E., Yoon, S.H., Hur, Y.S., Park, H.W., Ha, J.Y., Kim, K.H., Shim, J.H., Yoo, S.H., Son, J.H., Paek, S.L., Kim, I.K., Hwang, J.H., Kim, D.G., Kim, H.J., Jeon, B.S., Park, S. S., Paek, S.H., 2013. Mitochondrial dysfunction of immortalized human adipose tissue-derived mesenchymal stromal cells from patients with Parkinson's disease. Exp. Neurobiol. 22, 283–300.

Mustafa, N., Ahearn, T.S., Waiter, G.D., Murray, A.D., Whalley, L.J., Staff, R.T., 2012. Brain structural complexity and life course cognitive change. Neuroimage 61, 694–701.

Norheim, F., Langleite, T.M., Hjorth, M., Holen, T., Kielland, A., Stadheim, H.K., Gulseth, H.L., Birkeland, K.I., Jensen, J., Drevon, C.A., 2014. The effects of acute and chronic exercise on PGC-1alpha, irisin and browning of subcutaneous adipose tissue in humans. FEBS J. 281, 739–749.

Palomer, X., Alvarez-Guardia, D., Rodriguez-Calvo, R., Coll, T., Laguna, J.C., Davidson, M.M., Chan, T.O., Feldman, A.M., Vazquez-Carrera, M., 2009. TNF-alpha reduces PGC-1alpha expression through NF-kappaB and p38 MAPK leading to increased glucose oxidation in a human cardiac cell model. Cardiovasc. Res. 81, 703–712.

Papaconstantinou, J., 2009. Insulin/IGF-1 and ROS signaling pathway cross-talk in aging and longevity determination. Mol. Cell. Endocrinol. 299, 89–100.

Picard, M., McEwen, B.S., 2014. Mitochondria impact brain function and cognition. Proc. Natl. Acad. Sci. USA 111, 7–8.

Picca, A., Fracasso, F., Pesce, V., Cantatore, P., Joseph, A.M., Leeuwenburgh, C., Gadaleta, M.N., Lezza, A.M., 2013a. Age- and calorie restriction-related changes in rat brain mitochondrial DNA and TFAM binding. DAge Disord. 35, 1607–1620.

Picca, A., Pesce, V., Fracasso, F., Joseph, A.M., Leeuwenburgh, C., Lezza, A.M., 2013b. Aging and calorie restriction oppositely affect mitochondrial biogenesis through TFAM binding at both origins of mitochondrial DNA replication in rat liver. PLoS One 8, e74644.

Planavila, A., Sanchez, R.M., Merlos, M., Laguna, J.C., Vazquez-Carrera, M., 2005. Atorvastatin prevents peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) downregulation in lipopolysaccharide-stimulated H9c2 cells. Biochim. Biophys. Acta 1736, 120–127.

Puigserver, P., Wu, Z., Park, C.W., Graves, R., Wright, M., Spiegelman, B.M., 1998. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell 92, 829–839.

Qiang, W., Weiqiang, K., Qing, Z., Pengju, Z., Yi, L., 2007. Aging impairs insulin-stimulated glucose uptake in rat skeletal muscle via suppressing AMPKalpha. Exp. Mol. Med. 39, 535–543.

Radak, Z., Torma, F., Berkes, I., Goto, S., Mimura, T., Posa, A., Balogh, L., Boldogh, I., Suzuki, K., Higuchi, M., Koltai, E., 2019. Exercise effects on physiological function during aging. Free Radic. Biol. Med. 132, 33–41.

Rato, L., Duarte, A.I., Tomas, G.D., Santos, M.S., Moreira, P.I., Socorro, S., Cavaco, J.E., Alves, M.G., Oliveira, P.F., 2014. Pre-diabetes alters testicular PGC1-alpha/SIRT3 axis modulating mitochondrial bioenergetics and oxidative stress. Biochim. Biophys. Acta 1837, 335–344.

Rera, M., Bahadorani, S., Cho, J., Koehler, C.L., Ulgherait, M., Hur, J.H., Ansari, W.S., Lo Jr., T., Jones, D.L., Walker, D.W., 2011. Modulation of longevity and tissue homeostasis by the Drosophila PGC-1 homolog. Cell Metab. 14, 623–634.

Ribeiro, M.B.T., Guzzoni, V., Hord, J.M., Lopes, G.N., Marqueti, R.C., de Andrade, R.V., Selistre-de-Araujo, H.S., Durigan, J.L.Q., 2017. Resistance training regulates gene expression of molecules associated with intramyocellular lipids, glucose signaling and fiber size in old rats. Sci. Rep. 7, 8593.

Rius-Perez, S., Torres-Cuevas, I., Millan, I., Ortega, A.L., Perez, S., 2020. PGC-1alpha, Inflammation, and Oxidative Stress: An Integrative View in Metabolism. Oxid. Med. Cell. Longev. 2020, 1452696.

Roth, S.M., Martel, G.F., Rogers, M.A., 2000. Muscle biopsy and muscle fiber hypercontraction: a brief review. Eur. J. Appl. Physiol. 83, 239–245.

Rowe, G.C., Arany, Z., 2014. Genetic models of PGC-1 and glucose metabolism and homeostasis. Rev. Endocr. Metab. Disord. 15, 21–29.

Ruas, J.L., White, J.P., Rao, R.R., Kleiner, S., Brannan, K.T., Harrison, B.C., Greene, N.P., Wu, J., Estall, J.L., Irving, B.A., Lanza, I.R., Rasbach, K.A., Okutsu, M., Nair, K.S., Yan, Z., Leinwand, L.A., Spiegelman, B.M., 2012. A PGC-1alpha isoform induced by resistance training regulates skeletal muscle hypertrophy. Cell 151, 1319–1331.

Rubinsztein, D.C., Marino, G., Kroemer, G., 2011. Autophagy and aging. Cell 146, 682–695.

Ryall, J.G., Plant, D.R., Gregorevic, P., Sillence, M.N., Lynch, G.S., 2004. Beta 2-agonist administration reverses muscle wasting and improves muscle function in aged rats. J. Physiol. 555, 175–188.

Sahin, E., Colla, S., Liesa, M., Moslehi, J., Muller, F.L., Guo, M., Cooper, M., Kotton, D., Fabian, A.J., Walkey, C., Maser, R.S., Tonon, G., Foerster, F., Xiong, R., Wang, Y.A., Shukla, S.A., Jaskelioff, M., Martin, E.S., Heffernan, T.P., Protopopov, A., Ivanova, E., Mahoney, J.E., Kost-Alimova, M., Perry, S.R., Bronson, R., Liao, R., Mulligan, R., Shirihai, O.S., Chin, L., DePinho, R.A., 2011. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 470, 359–365.

Salazar, G., Cullen, A., Huang, J., Zhao, Y., Serino, A., Hilenski, L., Patrushev, N., Forouzandeh, F., Hwang, H.S., 2020. SQSTM1/p62 and PPARGC1A/PGC-1alpha at the interface of autophagy and vascular senescence. Autophagy 16, 1092–1110.

Sandri, M., Lin, J., Handschin, C., Yang, W., Arany, Z.P., Lecker, S.H., Goldberg, A.L., Spiegelman, B.M., 2006. PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. Proc. Natl. Acad. Sci. USA 103, 16260–16265.

Sasaki, S., 2010. Determination of altered mitochondria ultrastructure by electron microscopy. Methods Mol. Biol. 648, 279–290.

Schilling, J., Kelly, D.P., 2011. The PGC-1 cascade as a therapeutic target for heart failure. J. Mol. Cell. Cardiol. 51, 578–583.

Schonfeld, P., Reiser, G., 2013. Why does brain metabolism not favor burning of fatty acids to provide energy? Reflections on disadvantages of the use of free fatty acids as fuel for brain. J. Cereb. Blood Flow Metab. 33, 1493–1499.

Sczelecki, S., Besse-Patin, A., Abboud, A., Kleiner, S., Laznik-Bogoslavski, D., Wrann, C. D., Ruas, J.L., Haibe-Kains, B., Estall, J.L., 2014. Loss of Pgc-1alpha expression in aging mouse muscle potentiates glucose intolerance and systemic inflammation. Am. J. Physiol. Endocrinol. Metab. 306, E157–E167.

Seo, A.Y., Joseph, A.M., Dutta, D., Hwang, J.C., Aris, J.P., Leeuwenburgh, C., 2010. New insights into the role of mitochondria in aging: mitochondrial dynamics and more. J. Cell Sci. 123, 2533–2542.

Sharma, A., Smith, H.J., Yao, P., Mair, W.B., 2019. Causal roles of mitochondrial dynamics in longevity and healthy aging. EMBO Rep. 20, e48395.

Shi, Y., Shu, Z.J., Wang, H., Barnes, J.L., Yeh, C.K., Ghosh, P.M., Katz, M.S., Kamat, A., 2018. Altered expression of hepatic beta-adrenergic receptors in aging rats: implications for age-related metabolic dysfunction in liver. Am. J. Physiol. Regul. Integr. Comp. Physiol. 314, R574–R583.

Short, K.R., Vittone, J.L., Bigelow, M.L., Proctor, D.N., Rizza, R.A., Coenen-Schimke, J. M., Nair, K.S., 2003. Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. Diabetes 52, 1888–1896.

Silva, J.V., Santiago, J., Matos, B., Henriques, M.C., Patricio, D., Martins, A.D., Duarte, J. A., Ferreira, R., Alves, M.G., Oliveira, P., Oliveira, P.F., Fardilha, M., 2022. Effects of age and lifelong moderate-intensity exercise training on rats' testicular function. Int. J. Mol. Sci. 23.
Skurk, T., Hauner, H., 2012. Primary culture of human adipocyte precursor cells: expansion and differentiation. Methods Mol. Biol. 806, 215–226.
Soesanto, Y., Luo, B., Parker, G., Jones, D., Cooksey, R.C., McClain, D.A., 2011. Pleiotropic and age-dependent effects of decreased protein modification by O-linked N-acetylglucosamine on pancreatic beta-cell function and vascularization. J. Biol. Chem. 286, 26118–26126.
de Sousa Neto, I.V., Carvalho, M.M., Marqueti, R.C., Almeida, J.A., Oliveira, K.S., Barin, F.R., Petriz, B., de Araujo, H.S.S., Franco, O.L., Durigan, J.L.Q., 2020. Proteomic changes in skeletal muscle of aged rats in response to resistance training. Cell Biochem. Funct. 38, 500–509.
de Sousa Neto, I.V., Durigan, J.L.Q., da Silva, A.S.R., de Cassia Marqueti, R., 2022. Adipose tissue extracellular matrix remodeling in response to dietary patterns and exercise: molecular landscape, mechanistic insights, and therapeutic approaches. Biology 11.
Soyal, S., Krempler, F., Oberkofler, H., Patsch, W., 2006. PGC-1alpha: a potent transcriptional cofactor involved in the pathogenesis of type 2 diabetes. Diabetologia 49, 1477–1488.
Su, X., Chu, Y., Kordower, J.H., Li, B., Cao, H., Huang, L., Nishida, M., Song, L., Wang, D., Federoff, H.J., 2015. PGC-1alpha promoter methylation in Parkinson's disease. PLoS One 10, e0134087.
Summer, R., Shaghaghi, H., Schriner, D., Roque, W., Sales, D., Cuevas-Mora, K., Desai, V., Bhushan, A., Ramirez, M.I., Romero, F., 2019. Activation of the mTORC1/PGC-1 axis promotes mitochondrial biogenesis and induces cellular senescence in the lung epithelium. Am. J. Physiol. Lung Cell. Mol. Physiol. 316, L1049–L1060.
Summermatter, S., Shui, G., Maag, D., Santos, G., Wenk, M.R., Handschin, C., 2013. PGC-1alpha improves glucose homeostasis in skeletal muscle in an activity-dependent manner. Diabetes 62, 85–95.
Sun, L., Li, F.H., Han, C., Wang, Z.Z., Gao, K.K., Qiao, Y.B., Ma, S., Xie, T., Wang, J., 2021. Alterations in mitochondrial biogenesis and respiratory activity, inflammation of the senescence-associated secretory phenotype, and lipolysis in the perirenal fat and liver of rats following lifelong exercise and detraining. FASEB J. 35, e21890.
Sutherland, L.N., Bomhof, M.R., Capozzi, L.C., Basaraba, S.A., Wright, D.C., 2009. Exercise and adrenaline increase PGC-1{alpha} mRNA expression in rat adipose tissue. J. Physiol. 587, 1607–1617.
Svensson, K., Schnyder, S., Cardel, B., Handschin, C., 2016. Loss of renal tubular PGC-1alpha exacerbates diet-induced renal steatosis and age-related urinary sodium excretion in mice. PLoS One 11, e0158716.
Tang, L.X., Wang, B., Wu, Z.K., 2018. Aerobic exercise training alleviates renal injury by interfering with mitochondrial function in type-1 diabetic mice. Med. Sci. Monit. 24, 9081–9089.
Tatarkova, Z., Kuka, S., Racay, P., Lehotsky, J., Dobrota, D., Mistuna, D., Kaplan, P., 2011. Effects of aging on activities of mitochondrial electron transport chain complexes and oxidative damage in rat heart. Physiol. Res. 60, 281–289.
Thirupathi, A., da Silva Pieri, B.L., Queiroz, J., Rodrigues, M.S., de Bem Silveira, G., de Souza, D.R., Luciano, T.F., Silveira, P.C.L., De Souza, C.T., 2019. Strength training and aerobic exercise alter mitochondrial parameters in brown adipose tissue and equally reduce body adiposity in aged rats. J. Physiol. Biochem. 75, 101–108.
Tinkerhess, M.J., Healy, L., Morgan, M., Sujkowski, A., Matthys, E., Zheng, L., Wessells, R.J., 2012. The Drosophila PGC-1alpha homolog spargel modulates the physiological effects of endurance exercise. PLoS One 7, e31633.
Tran, M.T., Zsengeller, Z.K., Berg, A.H., Khankin, E.V., Bhasin, M.K., Kim, W., Clish, C.B., Stillman, I.E., Karumanchi, S.A., Rhee, E.P., Parikh, S.M., 2016. PGC1alpha drives NAD biosynthesis linking oxidative metabolism to renal protection. Nature 531, 528–532.
Uldry, M., Yang, W., St-Pierre, J., Lin, J., Seale, P., Spiegelman, B.M., 2006. Complementary action of the PGC-1 coactivators in mitochondrial biogenesis and brown fat differentiation. Cell Metab. 3, 333–341.
Vainshtein, A., Desjardins, E.M., Armani, A., Sandri, M., Hood, D.A., 2015. PGC-1alpha modulates denervation-induced mitophagy in skeletal muscle. Skelet. Muscle.
Valle, I., Alvarez-Barrientos, A., Arza, E., Lamas, S., Monsalve, M., 2005. PGC-1alpha regulates the mitochondrial antioxidant defense system in vascular endothelial cells. Cardiovasc. Res. 66, 562–573.
Vechetti-Junior, I.J., Bertaglia, R.S., Fernandez, G.J., de Paula, T.G., de Souza, R.W., Moraes, L.N., Mareco, E.A., de Freitas, C.E., Aguiar, A.F., Carvalho, R.F., Dal-Pai-Silva, M., 2016. Aerobic exercise recovers disuse-induced atrophy through the stimulus of the LRP130/PGC-1alpha complex in aged rats. J. Gerontol. A Biol. Sci. Med. Sci. 71, 601–609.
Vernochet, C., Damilano, F., Mourier, A., Bezy, O., Mori, M.A., Smyth, G., Rosenzweig, A., Larsson, N.G., Kahn, C.R., 2014. Adipose tissue mitochondrial dysfunction triggers a lipodystrophic syndrome with insulin resistance, hepatosteatosis, and cardiovascular complications. FASEB J. 28, 4408–4419.
Vezza, T., Diaz-Pozo, P., Canet, F., de Maranon, A.M., Abad-Jimenez, Z., Garcia-Gargallo, C., Roldan, I., Sola, E., Banuls, C., Lopez-Domenech, S., Rocha, M., Victor, V.M., 2022. The role of mitochondrial dynamic dysfunction in age-associated type 2 diabetes. World J. Mens. Health.
Vieira de Sousa Neto, I., Fontes, W., Prestes, J., de Cassia Marqueti, R., 2021. Impact of paternal exercise on physiological systems in the offspring. Acta Physiol. 231, e13620.
Watson, E.L., Baker, L.A., Wilkinson, T.J., Gould, D.W., Graham-Brown, M.P.M., Major, R.W., Ashford, R.U., Philp, A., Smith, A.C., 2020. Reductions in skeletal muscle mitochondrial mass are not restored following exercise training in patients with chronic kidney disease. FASEB J. 34, 1755–1767.
Wen, D.T., Zheng, L., Lu, K., Hou, W.Q., 2021. Physical exercise prevents age-related heart dysfunction induced by high-salt intake and heart salt-specific overexpression in Drosophila. Aging 13, 19542–19560.
Whitehead, N., Gill, J.F., Brink, M., Handschin, C., 2018. Moderate modulation of cardiac PGC-1alpha expression partially affects age-associated transcriptional remodeling of the heart. Front. Physiol. 9, 242.
Williamson, D., Gallagher, P., Harber, M., Hollon, C., Trappe, S., 2003. Mitogen-activated protein kinase (MAPK) pathway activation: effects of age and acute exercise on human skeletal muscle. J. Physiol. 547, 977–987.
Wohlgemuth, S.E., Lees, H.A., Marzetti, E., Manini, T.M., Aranda, J.M., Daniels, M.J., Pahor, M., Perri, M.G., Leeuwenburgh, C., Anton, S.D., 2011. An exploratory analysis of the effects of a weight loss plus exercise program on cellular quality control mechanisms in older overweight women. Rejuvenation Res. 14, 315–324.
Woo, C.Y., Jang, J.E., Lee, S.E., Koh, E.H., Lee, K.U., 2019. Mitochondrial dysfunction in adipocytes as a primary cause of adipose tissue inflammation. Diabetes Metab. J. 43, 247–256.
Wu, J.J., Quijano, C., Chen, E., Liu, H., Cao, L., Fergusson, M.M., Rovira, I.I., Gutkind, S., Daniels, M.P., Komatsu, M., Finkel, T., 2009. Mitochondrial dysfunction and oxidative stress mediate the physiological impairment induced by the disruption of autophagy. Aging 1, 425–437.
Xiong, S., Patrushev, N., Forouzandeh, F., Hilenski, L., Alexander, R.W., 2015. PGC-1alpha modulates telomere function and DNA damage in protecting against aging-related chronic diseases. Cell Rep. 12, 1391–1399.
Xu, A., Narayanan, N., 1998. Effects of aging on sarcoplasmic reticulum Ca2+-cycling proteins and their phosphorylation in rat myocardium. Am. J. Physiol. 275, H2087–H2094.
Xu, H., Du, X., Xu, J., Zhang, Y., Tian, Y., Liu, G., Wang, X., Ma, M., Du, W., Liu, Y., Dai, L., Huang, W., Tong, N., Wei, Y., Fu, X., 2020. Pancreatic beta cell microRNA-26a alleviates type 2 diabetes by improving peripheral insulin sensitivity and preserving beta cell function. PLoS Biol. 18, e3000603.
Yeo, D., Kang, C., Gomez-Cabrera, M.C., Vina, J., Ji, L.L., 2019. Intensified mitophagy in skeletal muscle with aging is downregulated by PGC-1alpha overexpression in vivo. Free Radic. Biol. Med. 130, 361–368.
Yeo, H.S., Lim, J.Y., 2022. Effects of different types of exercise training on angiogenic responses in the left ventricular muscle of aged rats. Exp. Gerontol. 158, 111650.
Yuan, L., Yuan, Y., Liu, F., Li, L., Liu, J., Chen, Y., Cheng, J., Lu, Y., 2021. PGC-1alpha alleviates mitochondrial dysfunction via TFEB-mediated autophagy in cisplatin-induced acute kidney injury. Aging 13, 8421–8439.
Yuan, Y., Hakimi, P., Kao, C., Kao, A., Liu, R., Janocha, A., Boyd-Tressler, A., Hang, X., Alhoraibi, H., Slater, E., Xia, K., Cao, P., Shue, Q., Ching, T.T., Hsu, A.L., Erzurum, S. C., Dubyak, G.R., Berger, N.A., Hanson, R.W., Feng, Z., 2016. Reciprocal changes in phosphoenolpyruvate carboxykinase and pyruvate kinase with age are a determinant of aging in caenorhabditis elegans. J. Biol. Chem. 291, 1307–1319.
Zhang, Y., Shao, C., Li, H., Wu, K., Gong, L., Zheng, Q., Dan, J., Jia, S., Tang, X., Wu, X., Luo, Y., 2021. The Distinct Function of p21(Waf1/Cip1) With p16(Ink4a) in Modulating Aging Phenotypes of Werner Syndrome by Affecting Tissue Homeostasis. Front Genet 12, 597566.
Zhou, Y., Lu, T., Xie, T., 2011. A PGC-1 tale: healthier intestinal stem cells, longer life. Cell Metab. 14, 571–572.
Ziegler, A.K., Damgaard, A., Mackey, A.L., Schjerling, P., Magnusson, P., Olesen, A.T., Kjaer, M., Scheele, C., 2019. An anti-inflammatory phenotype in visceral adipose tissue of old lean mice, augmented by exercise. Sci. Rep. 9, 12069.