

## Review Article

# Mitochondria and PGC-1 $\alpha$ in Aging and Age-Associated Diseases

**Tina Wenz**

*Institute for Genetics, Cluster of Excellence, Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Zùlpicher StraÙe 47A, 50674 Cologne, Germany*

Correspondence should be addressed to Tina Wenz, tina.wenz@uni-koeln.de

Received 15 October 2010; Revised 23 February 2011; Accepted 24 February 2011

Academic Editor: Reinald Pamplona

Copyright © 2011 Tina Wenz. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Aging is the most significant risk factor for a range of degenerative disease such as cardiovascular, neurodegenerative and metabolic disorders. While the cause of aging and its associated diseases is multifactorial, mitochondrial dysfunction has been implicated in the aging process and the onset and progression of age-associated disorders. Recent studies indicate that maintenance of mitochondrial function is beneficial in the prevention or delay of age-associated diseases. A central molecule seems to be the peroxisome proliferator-activated receptor  $\gamma$  coactivator  $\alpha$  (PGC-1 $\alpha$ ), which is the key regulator of mitochondrial biogenesis. Besides regulating mitochondrial function, PGC-1 $\alpha$  targets several other cellular processes and thereby influences cell fate on multiple levels. This paper discusses how mitochondrial function and PGC-1 $\alpha$  are affected in age-associated diseases and how modulation of PGC-1 $\alpha$  might offer a therapeutic potential for age-related pathology.

## 1. Introduction

In the last 20 years, mitochondrial dysfunction has been recognized as an important contributor to an array of human pathologies [1–3]. Mitochondrial dysfunction is particularly associated with the onset and progression of many age-related disorders such as neurodegenerative and cardiovascular diseases as well as metabolic disorders and age-related muscle wasting. In most cases it is not clear if the mitochondrial dysfunction is causative of the disease or if it is a secondary effect of the disease. Also, it is not understood if mitochondrial dysfunction is an aggravating factor in disease progression. Recent work suggests that maintenance of mitochondrial function is beneficial in at least some age-related diseases [4]. The peroxisome proliferator-activated receptor (PPAR)  $\gamma$  coactivator  $\alpha$  (PGC-1 $\alpha$ ) integrates regulation of mitochondrial function into the modulation of different, tissue-specific metabolic pathways and thereby links mitochondrial function to important cellular signaling pathways that ultimately control cell survival [5, 6]. The following review discusses how mitochondrial dysfunction is associated with age-related diseases and what impact PGC-1 $\alpha$  and its targets have in these diseases and their prevention.

## 2. Mitochondrial Function, ROS, and Aging

**2.1. Mitochondrial Function and OXPHOS.** Mitochondria play a central role in the cell metabolism: besides being key player in apoptosis, mitochondria house major cellular metabolic pathways. The fatty acid oxidation and citric acid cycle convert nutrients absorbed from ingested food to electron donors to NADH and FADH. These redox equivalents are fed into the oxidative phosphorylation system (OXPHOS), which supplies the majority of the cellular ATP supply. Here electrons are transferred from the substrates NADH and FADH via OXPHOS complex I-IV to the terminal electron acceptor oxygen. During this process, protons are transferred from across the inner membrane generating a proton gradient. This gradient is the driving force for complex V, the ATP-Synthase, to synthesize ATP [7].

**2.2. Mitochondrial ROS Production and Mitochondrial Theory of Aging.** Since OXPHOS complexes I-IV transfer electrons and consume most of the cellular oxygen, it is assumed that OXPHOS is the main cellular producer of reactive oxygen species (ROS) [8]. Leakage of electrons from the electron transfer chain can reduce oxygen to form the superoxide

anion radical. Superoxide production precedes reactions that form more reactive and potentially more dangerous ROS such as hydroxyl radical and hydrogen peroxide [9]. The superoxide anion can also oxidize cellular sulphite and nitric oxide resulting in further ROS [9].

The cells and in particular mitochondria have an antioxidant program to remove ROS. Superoxide dismutases (SODs) convert superoxide into hydrogen peroxide, which in turn is transformed into water by catalase or by peroxidases such as glutathione peroxidase (GPX). Additionally, several small molecules have ROS scavenging activity such as flavonoids, glutathione, and ascorbate [10].

Under physiological conditions, ROS production is estimated to be ~0.2% to 5% of the consumed oxygen [11]. The mitochondrial theory of aging states that since mitochondria are the major site of ROS production in the cell, the organelle is the prime target for oxidative damage leading to oxidized damaged lipids, proteins and nucleic acids resulting in dysfunctional mitochondria [12]. A vicious cycle is thought to occur, as oxidative stress leads to mitochondrial (mt) DNA mutations, which in turn can result in enzymatic abnormalities and further oxidative stress. While links between aging and oxidative stress are not new and were proposed over 50 years ago, there is much debate over whether mitochondrial changes are causes of aging or merely characteristics of aging. The relationship between ROS-induced damage, mitochondrial function and aging remains still unclear and the contribution of ROS in the aging process is poorly understood.

Dysfunctional mitochondria do not necessarily produce more ROS. There are in fact many examples of mouse model with dysfunctional OXPHOS that only have minor or no oxidative stress [13–15]. One notable study in mice with depleted proofreading function of the mitochondrial DNA polymerase  $\gamma$  (POLG) demonstrated shortened lifespan but no increase in reactive oxygen species despite increasing mtDNA mutations, suggesting that mtDNA mutations can cause lifespan shortening by other mechanisms [14]. However, it should be noted that this particular mouse models acquires a mtDNA mutation load that is much higher than observed in aged individuals. Although the POLG mice develop age-like symptoms, the questions remain, how “normal” aging is driven and what role ROS plays in the “normal” aging process.

Humans and model organisms alike accumulate oxidative damage to lipids, proteins and nucleic acids during aging supporting the mitochondrial theory of aging [16]. However, animal models with decreased antioxidant defense have increased oxidative stress, but with a normal lifespan and reproduction rate [17, 18]. Data from mice overexpressing antioxidant enzymes are conflicting: mice overexpressing superoxide dismutases have decreased ROS production, but fail to get an extended lifespan [19, 20]. In contrast, mice with mitochondrially targeted catalase (mCAT) have extended lifespan and seem to have a decreased susceptibility towards age-associated pathologies such cancer and cardiomyopathy associated with decreased oxidative damage [21–24].

The effect of ROS on lifespan regulation might be tissue specific. ROS seems to play a role in stem cell aging. SOD2

deficient hematopoietic stem cells have impaired capacity to maintain red blood cell homeostasis and an increase in ROS levels has been associated with impaired stem cell function [25]. Mitochondrial dysfunction associated with oxidative damage is suggested to play a central role in the aging process of cochlear cells and thus play an important role in age-related hearing loss [26]. Several studies have shown that ROS are generated in cochlear exposed to high-intensity noise and that cochlear hair cell loss is enhanced in mice lacking SOD1 [27], whereas mCAT mice have reduced cochlear cell damage in mice suggesting that mitochondrial ROS may play a role in age-related hearing loss [28]. In the murine aging heart, over-expression of mCAT attenuated age-related changes including decline of diastolic function, myocardial performance as well as ventricular fibrosis [22, 23]. These findings suggest that mitochondrial ROS and/or the mitochondrial antioxidant defense together with the protein degradation and protein synthesis machinery to remove and replenish oxidized protein partially might be involved in the development of the phenotype.

While increased ROS and antioxidant defense aggravate phenotypes in mouse model of several degenerative diseases such as ALS and Alzheimer’s [29–32], it is still under debate what happens during “normal” aging [33]. Short-term ROS production is apparently important in prevention of aging by induction of a process named mitohormesis and redox signaling [34]. This process seems to be particularly important for the insulin sensitizing effect of exercise [35]. Recent evidence suggests that suppression of ROS production fails to extend lifespan in worms and may even decrease lifespan in humans, presumably due to the reduction of the ROS signaling, which seems to be important for different cellular processes [36, 37]. ROS is also an important signal for induction of autophagy: starvation-induced autophagy can be suppressed by antioxidants suppressing the well-known prosurvival function of starvation-induced autophagy [38]. ROS is also involved in the regulation of the insulin/IGF-1 pathway [39].

Another factor that is discussed for playing a role in mitochondrial ROS production is the 66 kDa isoform of the growth factor adaptor shc (p66<sup>shc</sup>). p66<sup>shc</sup> is activated by stress and generates ROS within mitochondria and seems to be also required for cytochrome *c* release and opening of the permeability transition pore, which is crucial for apoptosis [40]. It remains to be clarified, what exact role p66<sup>shc</sup> plays in the aging process and how it is connected to other aging-relevant pathways.

In conclusion, the exact relationship between mitochondria, oxidative stress, and aging has not yet been settled. An important aspect to consider is that oxidative damage is the sum of actual ROS production, capacity of the cellular antioxidant defense and last the clearance of damaged molecules by repair or protein degradation. Any of these factors might contribute to increased oxidative damage, so that, for example, under normal ROS production, defective clearance of damaged molecules results in increased oxidative damage. Hence oxidative damage has to be carefully assessed in the context of ROS production, antioxidant response and damage control.

### 3. The Peroxisome Proliferator-Activated Receptor (PPAR) $\gamma$ Coactivator $\alpha$ (PGC-1 $\alpha$ ) and Mitochondrial Biogenesis

Mitochondria derive from dual genetic origin, the nuclear and mtDNA, so that biosynthesis from both genomes has to be coordinated. Mammalian mitochondria have been estimated to have up to ~1500 proteins. The vast majority of these proteins including structural genes and assembly factors for mitochondrial proteins are encoded in the nuclear DNA, are synthesized in the cytoplasm and are imported into mitochondria. mtDNA encodes only for 13 subunits of the OXPHOS enzymes CI, III, IV, and V as well as 2 rRNAs and 22 tRNAs. Expression of mtDNA-encoded proteins and RNA species is governed by the mitochondrial transcription and translation machinery, whose protein factors are encoded in the nuclear DNA [41].

It is now apparent that a relatively small number of nuclear factors serve to coordinate the transcriptional expression of nuclear and mitochondrial respiratory proteins. Among these are the nuclear respiratory factors NRF-1 and NRF-2 (GA binding protein, GABP), which are implicated in the expression of mitochondrial genes (Figure 1). In addition to the NRFs, stimulatory protein 1 (Sp1), estrogen related receptor  $\alpha$  (ERR $\alpha$ ), and yin yang 1 transcription factor (YY1) have also been linked to many genes required for respiratory chain expression and function. These factors are controlled by a common key component, namely, peroxisome proliferator-activated receptor (PPAR)  $\gamma$  coactivator  $\alpha$  (PGC-1 $\alpha$ ) [42]. PGC-1 $\alpha$  is a transcriptional coactivator and interacts with nuclear receptors and transcription factors to activate transcription of their target genes [43]. PGC-1 $\alpha$  activity is responsive to multiple stimuli including but not limited to nutrient availability, calcium, ROS, insulin, thyroid and estrogen hormone, hypoxia, ATP demand, and cytokines [43].

Besides PGC-1 $\alpha$ , other members of the PGC-1 family of coactivators, namely PGC-1 $\beta$  and PGC-related coactivator (PRC), are also implicated in modulating mitochondrial function, but their exact role is not understood [42]. Also, it is likely that other, yet unidentified factors, are involved in orchestrating mitochondrial biogenesis.

PGC-1 $\alpha$  is the first responder to stimuli and interacts with transcription factors such as NRF1, which is an intermediate transcription factor which stimulates the synthesis of TFAM (Figure 1). TFAM is crucial for mtDNA transcription and in addition plays an important role in mtDNA maintenance and mtDNA nucleoid formation [44].

PGC-1 $\alpha$  activity is regulated on both the expression and posttranslational level (Figure 1): expression is mainly regulated by the peroxisome proliferator-activated receptors (PPAR) and other tissue-specific factors such as cAMP responsive element (CREB) in skeletal muscle. PPARs respond to external stimuli and metabolic demands and by activating PGC-1 $\alpha$ , they link this changes to mitochondrial biogenesis [41]. Activation of PPARs by pharmacological agonists used in treatment for metabolic syndrome successfully induced mitochondrial biogenesis [45–47]. Recently, it has been

found that PGC-1 $\alpha$  expression is decreased by methylation of the promoter by DNA methyltransferase 3b (DNMT3B) [48]. This kind of regulation leads to long-lasting changes in PGC-1 $\alpha$  transcription and might be potentially relevant in several pathophysiologicals. PGC-1 $\alpha$  regulates its own transcription via YY1. YY1 is a common target of mammalian target of rapamycin (mTOR) and PGC-1 $\alpha$ . mTOR directly modulates the physical interaction of PGC-1 $\alpha$  with YY1 and thereby modulates mitochondrial activity. Decrease in mTOR activity likely inhibits YY1-PGC-1 $\alpha$  function resulting in decreased expression of mitochondrial genes [42, 43].

Very little is known about negative regulators of PGC-1 $\alpha$ . So far, only RIP140 and 160MYP have been identified. Both molecules suppress mitochondrial biogenesis [49, 50].

PGC-1 $\alpha$  activity can also be modulated by posttranslational modifications. AMPK, Akt and p38 MAPK target PGC-1 $\alpha$  phosphorylation sites. Important key players in this respect are the AMP-activated kinase (AMPK) and the sirtuin Sirt1 [51]. AMPK is involved in the adaptive response to energy deficit. Direct phosphorylation by AMPK not only activates PGC-1 $\alpha$ , but also promotes PGC-1 $\alpha$ -dependent induction at the PGC-1 $\alpha$  promoter [51]. Activity of PGC-1 $\alpha$  is also regulated through inhibitory acetylation by GCN5 and stimulatory deacetylation through Sirt1 [51]. Sirt1 is a member of the Sirtuin family that has been implicated in longevity in yeast, worms and flies [4]. Activation of Sirt1 through caloric restriction induces PGC-1 $\alpha$  activity and enhances mitochondrial function [52, 53]. While it is observed that resveratrol indirectly activates PGC-1 $\alpha$  and induces mitochondrial biogenesis [52, 53] it is under dispute whether this indirect mechanism involves Sirt1 or might function indirectly through AMPK [54, 55].

Since AMPK senses AMP/ATP ratios and Sirt1 is NAD<sup>+</sup> dependent, both AMPK and Sirt1 modulate PGC-1 $\alpha$  activity in response to cellular energy supply. Insulin reduces PGC-1 $\alpha$  expression, but also induces phosphorylation of PGC-1 $\alpha$  through Akt and thereby inhibits its activity [56, 57]. The p38 mitogen-activated protein kinase (p38 MAPK) phosphorylates and activates PGC-1 $\alpha$  [58]. This phosphorylation enhances PGC-1 $\alpha$  half-life, disrupts interaction with the corepressor p160MBP in myoblasts and thereby enhances PGC-1 $\alpha$  cotranscriptional activity [49]. PGC-1 $\alpha$  is also phosphorylated by glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) and thereby inhibited under oxidative stress [59]. However, Sirt1 is activated under the same conditions and activates PGC-1 $\alpha$  by deacetylation. It is so far unclear how Sirt1 and GSK3 $\beta$  act in concert to modulate PGC-1 $\alpha$  activity.

Recent work also identifies SUMOylation, ubiquitination as well as O-linked  $\beta$ -N-acetylglucosamination and methylation suggesting that PGC-1 $\alpha$  activity can be fine-tuned depending on cellular needs by various ways [60, 61].

### 4. Mitochondrial Function and PGC-1 $\alpha$ in Age-Related Pathologies of Muscle, Heart, Liver, and Brain

Aging is most likely a multifactorial process. Recent findings suggest a causal role of mitochondrial dysfunction in the

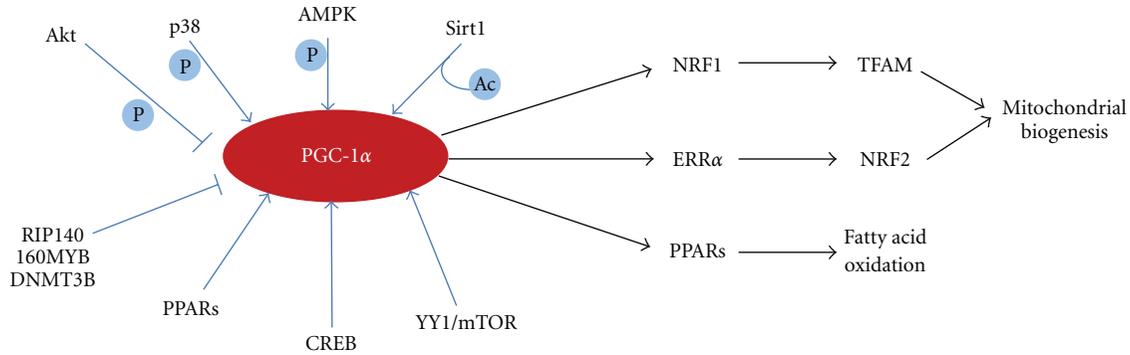


FIGURE 1: Modulation of PGC-1 $\alpha$  and its targets. Regulation of PGC-1 $\alpha$  activity on transcriptional and posttranscriptional levels as well as by interaction with inhibitory factors is summarized. The diagram shows the PGC-1 $\alpha$  targets that are involved in metabolic regulation of mitochondria. The details are discussed in the text.

aging process and a central role for mitochondrial adaptation in the mechanism of aging retardation by caloric restriction and exercise. Mitochondrial disorders often present as neurological disorders, but can manifest as myopathy, diabetes, multiple endocrinopathy, or a variety of other systemic manifestations [62]. During aging, the decline of mitochondrial function often correlated with the onset and progression of similar pathologies [63, 64].

Many other factors have been discussed to play major roles in the aging process including mTOR, Sirt1 and insulin/IGF signaling as well as stem cell aging [65]. Sirt1 is clearly connected to PGC-1 $\alpha$  function. Also, mTOR and PGC-1 $\alpha$  pathways are linked through YY1 (see above). This regulation would allow the cell to connect nutrient pathways to activate mitochondrial function and ensure energy supply for cellular activities. Very recently, also a connection between telomere dysfunction, an additional player in causing cellular senescence and age-related pathology, and the PGC-family of coactivators was established [66].

Mitochondria are the most damaged organelle during aging. Hence removal and synthesis are necessary for proper energy homeostasis. An increase in mitochondrial turnover might be beneficial for cells resulting in better maintenance of the organelle. PGC-1 $\alpha$ , poised centrally in multiple pathways affecting mitochondrial dysfunction and cellular function should play a key role in this prevention. Age-associated reductions in PGC-1 $\alpha$  itself as well as in modulating proteins such as AMPK activity may be an important contributing factor in the reduced mitochondrial function associated with aging [67, 68].

The role of mitochondrial and PGC-1 $\alpha$  likely affects different tissue. The following paragraph focuses on the effect in skeletal muscle, heart, liver, and brain, since those are the tissue, where PGC-1 $\alpha$  function is best understood (Figure 2).

**4.1. Skeletal Muscle and Sarcopenia.** PGC-1 $\alpha$  seems to be mediator of many known beneficial effects of exercise on muscle physiology. In skeletal muscle, PGC-1 $\alpha$  expression is linked to muscle contraction [69]. A major mediator is the activation of Ca<sup>2+</sup>/calmodulin-dependent protein kinase IV

(CamKIV) and calcineurin A, which are activated through the changes in calcium within the muscle in response to exercise. The heightened calcium signaling activates several important transcription factors such as CREB, which is a target of CamKIV, and myocyte enhancer factors 2 (MEF) [70]. Another factor that regulates PGC-1 $\alpha$  expression upon exercise involves p38 MAPK, which activates MEF2 and transcription factor 2 (ATF2). p38 MAPK in conjunction with ATF2 results in increased expression of PGC-1 $\alpha$  [71]. p38 MAPK also stimulates PGC-1 $\alpha$  by phosphorylation in response to cytokine stimulation in muscle cells [72]. Finally, also AMPK as an ATP gauge is activated by exercise and enhancing PGC-1 $\alpha$  transcription as well as activity (see above). The changed transcription program upon exercise induces changes in muscle plasticity such as a fiber-type switching towards more oxidative fibers and induces the mitochondrial antioxidant program [70, 73, 74].

PGC-1 $\alpha$  is also involved in regulation of muscle function and integrity: PGC-1 $\alpha$  regulates the neuromuscular junction program by being recruited to GABP-complex to stimulate a broad neuromuscular junction gene program [75]. In addition, PGC-1 $\alpha$  inhibits FoxO3 activity on transcription of atrophy-specific genes and thereby decreases muscle atrophy [76]. Transgenic PGC-1 $\alpha$  mice show smaller decrease in muscle fiber diameter and smaller induction of atrogens in denervation-induced muscle atrophy and aging muscle by suppressing FoxO3 action [68, 76].

Additionally, increased muscular PGC-1 $\alpha$  seems to be involved in the regulation of apoptosis and protein degradation during aging [68]. Loss of function studies in PGC-1 $\alpha$  knockout animals additional suggest that PGC-1 $\alpha$  modulates local or systemic inflammation and might regulate the expression of inflammatory cytokines and inflammatory markers such as TNF $\alpha$  and IL6 [77, 78], but the exact mechanism that links PGC-1 $\alpha$  and the inflammatory response is not known. PGC-1 $\alpha$  additionally controls angiogenesis in muscle by controlling VEGF expression and thus improves delivery of oxygen and substrates to muscle tissue [79].

In the aging muscle, zones of metabolically inactive tissue have been observed due to expansion of mitochondria that become damaged during aging [80]. This mitochondrial

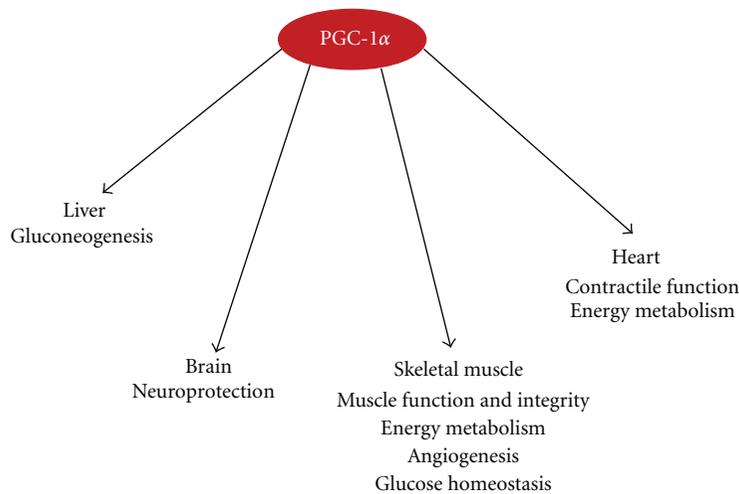


FIGURE 2: Tissue-specific function of PGC-1 $\alpha$  relevant to age-related pathologies. Different functions of PGC-1 $\alpha$  in heart, liver, brain, skeletal muscle and heart are depicted. These functions might be beneficial in age-associated pathologies as described in detail in the text.

dysfunction has been implicated in the development of sarcopenia, the age-related muscle loss [81].

Several studies have shown that elevated PGC-1 $\alpha$  levels and maintenance of mitochondrial function in muscle prevent muscle wasting in muscular disorder such as mitochondrial myopathy [46], denervation-induced muscle atrophy [76] and Duchenne muscular dystrophy [75]. Elevated PGC-1 $\alpha$  levels also have a therapeutic effect on the onset and progression of age-related loss of muscle mass (sarcopenia) [68]: here, transgenic muscle-specific expression of PGC-1 $\alpha$  significantly reduced the loss of muscle mass and maintained exercise capacity during the aging process. The elevated PGC-1 $\alpha$  levels in the aging muscle increased mitochondrial content and thereby maintained ATP supply. Additionally, transgenic PGC-1 $\alpha$  mice showed decreased markers for apoptosis and proteolysis as well as a balanced autophagy, which most likely resulted in the decreased muscle atrophy. This maintenance of muscle mass in transgenic PGC-1 $\alpha$  mice was associated with a “younger” neuromuscular junction phenotype and decreased fibrosis, which most likely also contributed to an improved muscle function. The prevention of sarcopenia in mice with elevated PGC-1 $\alpha$  and maintenance of muscle as a metabolic tissue resulted in improved insulin sensitivity and prevented hypoglycemia during aging. Additionally, muscle-specific PGC-1 $\alpha$  expression also ameliorated other pathological factors observed during aging on a systemic level: elevated muscle PGC-1 $\alpha$  levels decreased gain of fat mass and osteoporosis in mice. Additionally, the level of circulating inflammatory markers usually observed during aging and in part be caused by the muscle atrophy were markedly reduced in transgenic PGC-1 $\alpha$  animals [68].

While the precise mechanism of the observed protective effects is not entirely clear, the following possibilities could explain the effect of PGC-1 $\alpha$ : the regulation of mitochondrial mass might help to prevent the energy crisis associated with many muscular diseases [46, 68]. PGC-1 $\alpha$  also reduces the transcription of atrophy-specific genes by inhibiting FoxO3

[76]. Additionally, *de novo* protein synthesis is activated and the neuromuscular junction is stabilized [75]. Apoptosis and protein degradation, which are hallmarks of muscle wasting, are reduced [68]. These effects likely contribute to the antimuscle wasting properties of PGC-1 $\alpha$ . Maintenance of the metabolic properties of the muscle tissue as well as prevention of the muscle atrophy most likely resulted in the observed systemic effects underlining the importance of muscle function and integrity for whole-body function.

**4.2. Heart and Age-Related Cardiovascular Disorders.** In the heart, PGC-1 $\alpha$  strongly induces mitochondrial function and fatty acid oxidation [82]. Normal growth and response to exercise are controlled by PGC-1 $\alpha$  similar to skeletal muscle [83, 84]. Absence of PGC-1 $\alpha$  in the heart reduces the cardiac reserve under stress conditions and diminished the cardiac capacity under exercise conditions [85, 86]. In the failing heart, as what occurs in heart diseases and during aging, metabolism is switched from fatty acid to glucose utilization and expression of PGC-1 $\alpha$  is reduced [87]. In contrast to skeletal muscle, muscle elevated PGC-1 $\alpha$  seems to have an adverse effect in heart: elevated increased expression of PGC-1 $\alpha$  in the heart causes cardiomyopathy and heart failure in mice [88]. Also, transient activation of PGC-1 $\alpha$  diminishes cardiac contractile recovery after ischemia-reperfusion injury [89]. These findings suggest that PGC-1 $\alpha$  levels in heart need to be tightly regulated to prevent pathology. The adverse effect of PGC-1 $\alpha$  might be attributed to tissue-specific differences in the availability of transcription factor partners for PGC-1 $\alpha$ , differences in cell signaling or other heart-specific metabolic requirements.

Despite these effects of elevated PGC-1 $\alpha$  in the heart, PGC-1 $\alpha$  may nevertheless affect cardiac function. Sirt1 and PPAR $\alpha$ , two proteins that regulate PGC-1 $\alpha$  expression and activity, are major players in protecting the heart from typical age-related pathologies such as hypertrophy, metabolic dysregulation and inflammation [53]. These effects could be also

observed by administration of resveratrol, which is also an indirect activator of PGC-1 $\alpha$  implying that a PGC-1 $\alpha$  might be involved in the cardioprotective effect.

A major factor contributing to the development of heart disorders during aging is the failing vasculature. PGC-1 $\alpha$  seems to have an important role in the vasculature wall itself [90]. Endothelial dysfunction is an early feature of cardiovascular disease and is associated with increased levels of ROS. The antioxidant property of PGC-1 $\alpha$  might hence be beneficial to maintain vasculature function and thus contribute to the prevention of cardiovascular diseases. Indeed, activation of PGC-1 $\alpha$  in endothelial cells prevents oxidative damage and cellular apoptosis and prevents endothelial dysfunction in vivo [90]. It remains to be seen what effect endothelial PGC-1 $\alpha$  has on angiogenesis and atherosclerosis, two major contributing factors of cardiovascular disease.

**4.3. Brain and Age-Related Neurodegenerative Diseases.** PGC-1 $\alpha$  is expressed in all brain tissues and plays an important role in normal brain function and a major role in the oxidative stress response [91]. In mice, PGC-1 $\alpha$  deficiency causes behavioral changes including anxiety and hyperactivity as well as hind limb claspings. These behavioral changes are associated with spongiform-like vacuolization primarily in the striatum associated with gliosis and leads to reduced expression of several brain-specific genes that are all associated with normal brain function. Substantia nigra and CA1 neurons are more susceptible to neurodegeneration in response to neurotoxins suggesting an important role of PGC-1 $\alpha$  in neuronal maintenance [92]. PGC-1 $\alpha$  also seems to be involved in the control of neurite growth and neuronal synaptic function [93].

While mitochondrial dysfunction affects the whole organisms during aging its effects might be especially deleterious at the level of the CNS [94]. PGC-1 $\alpha$  might potentially relieve this defect and together with the above described brain-specific function influence age-associated neurodegeneration. In fact, PGC-1 $\alpha$  has been implicated in the onset and progression of neurodegenerative diseases. Postmortem brain samples of patients with Huntington's disease (HD) had a decreased level of PGC-1 $\alpha$  mRNA [95, 96]. Polymorphism is also associated with the onset of AD [97]. PGC-1 $\alpha$  is repressed by a mutant form of the Huntington protein which leads to mitochondrial dysfunction and neurodegeneration. Over-expression of PGC-1 $\alpha$  rescues cells from the deleterious effect of Huntington's, whereas loss of PGC-1 $\alpha$  in HD mice aggravated neurodegeneration [95]. Moreover, PGC-1 $\alpha$  KO mice show Huntington's like phenotype and neuronal lesions suggesting that PGC-1 $\alpha$  is crucial for maintenance of striatal function. Additionally, PGC-1 $\alpha$  SNPs are associated with the age of onset of HD. In a PD mouse model, PGC-1 $\alpha$  deficiency caused an increased degeneration of dopaminergic neurons in the substantia nigra associated with oxidative damage [91].

Interestingly, activators of PGC-1 $\alpha$  such as resveratrol have a neuroprotective effect in acute and chronic brain injury as well as in neurodegenerative diseases suggesting a role for PGC-1 $\alpha$  in modulating the outcome of the disease [98].

**4.4. Liver and Metabolic Disorders.** In liver, PGC-1 $\alpha$  is induced by fasting in response to glucagon and regulates most of the metabolic changes that occur during the transition from fed to fasted state [99]. The most relevant metabolic pathways in this regard are gluconeogenesis, fatty-acid-beta oxidation, ketogenesis, and heme biosynthesis [5]. Absence of PGC-1 $\alpha$  results in a blunted hepatic fasting response as well as fasting hypoglycemia and hepatic steatosis [86]. PGC-1 $\alpha$  associates in liver with several transcription factors such as HNF4- $\alpha$  and FoxO1 and thereby induces the expression of several gluconeogenic enzymes [100, 101]. Glucagon induces cAMP and CREB as well as p38 MAPK over cAMP and PKA [102]. p38 MAPK increases PGC-1 $\alpha$  transcription as in muscle and seems to be also necessary for the expression of PGC-1 $\alpha$  in response to free fatty acids to stimulate gluconeogenesis [103].

There has also been considerable interest in mitochondrial dysfunction as a contributing factor in the development of metabolic disorders. Although the involvement of mitochondrial dysfunction in insulin resistance is under dispute [104–106], several lines of evidence suggest that decreased mitochondrial function may be the underlying defect that causes insulin resistance during aging: the age-associated decline in mitochondrial function in elderly might contribute to the age-related insulin resistance [68, 107]. Increase in mitochondrial function during aging increases fuel handling, fatty acid oxidation and protects from insulin resistance [52, 68, 108, 109]. Interestingly, PGC-1 $\alpha$  promoter methylation and hence decreased PGC-1 $\alpha$  expression in skeletal muscle was found to be more prevalent in patients with diabetes compared to healthy subjects [48]. In addition, mitochondrial functional insufficiency and decreased PGC-1 $\alpha$  levels have been found in the insulin-resistant offspring of patients with T2D. The fact that this occurs in healthy individuals that are not diabetic suggests that an inherent defect in oxidative phosphorylation may be a contributing factor [110]. Severeness of steatosis is associated with impaired PGC-1 $\alpha$  expression and reduced mitochondrial gene expression [111]. Interestingly, rosiglitazone attenuates age-associated liver pathology in nonalcoholic steatohepatitis [112]. Rosiglitazone is indirectly activating PGC-1 $\alpha$  via PPAR, implying that PGC-1 $\alpha$  activating is beneficial in liver pathologies.

**4.5. Role of PGC-1 $\alpha$  Responsive Proteins in Age-Related Pathologies.** Also downstream targets of PGC-1 $\alpha$  may play a role in lifespan regulation and maintenance of tissue function. Over-expression of TFAM, for example, can reverse age-dependent memory impairment in mice, presumably through the prevention of mitochondrial dysfunction in microglia [113]. Over-expression of TFAM also protects against beta-amyloid-induced oxidative damage [114] and in addition seems to be also a target for therapeutic strategies in cardiac failure [115].

Both NRF1 and NRF2 have a broad spectrum of target genes besides mitochondrial genes. A screen for NRF1 binding sites revealed significant overlap to E2F, a transcription factor family which is involved in the regulation of cell growth. NRF1 is also involved in the regulation of the

expression fragile X mental retardation-1 gene and NRF1 promoter binding is increased in the mouse brain during aging which might be linked to the age-related deficiency in learning, memory, and cognition [116]. NRF2 is implicated in the regulation of the cell cycle, myeloid genes, T-cell development and other target genes [117, 118]. In muscle, NRF2 regulates the transcription of the nicotinic acetylcholine receptor and utrophin genes and plays a crucial role in formation and maintenance of the neuromuscular junction [119]. In conjunction with PGC-1 $\alpha$ , NRF2 (GABP) regulates the NMJ program [75] (see above).

A novel identified target of PGC-1 $\alpha$  is the mitochondrial-localized Sirtuin 3 (Sirt3) [120]. Sirt3 is a major player in mitochondrial biogenesis, regulation of metabolic enzymes and ROS suppression [121]. Recent findings show that Sirt3 also targets the mitochondrial permeability transition pore (mPTP) and prevents mPTP opening by modulating cyclophilin D [122]. mPTP opening plays a fundamental role in myocardial cell death and the development of heart disease [123].

## 5. Mitochondria and PGC-1 $\alpha$ in Antiaging Strategies

There is an abundance of studies that provide indirect and direct evidence in support of a role for PGC-1 $\alpha$  and regulation of mitochondrial function in antiaging strategies. As outline above, therapeutic modulation of PGC-1 $\alpha$  has huge potential for treatment of patients with various mitochondrial dysfunction associated with disease and age-related disorders. In the following, antiaging strategies targeting mitochondria and PGC-1 $\alpha$  in controlling age-related pathology are discussed.

**5.1. Caloric Restriction.** CR has been shown to induce longevity in many different organisms and is a common treatment for sarcopenia and insulin resistance [124–128]. Recent findings suggest a central role for mitochondrial adaptation in the mechanism of aging retardation by CR [4]. The decline in oxidative capacity in skeletal muscle during aging is prevented in CR animals [63, 129]. The slower decline of PGC-1 $\alpha$  gene expression during aging in CR animals suggests a better maintenance of mitochondrial biogenesis during aging [63].

CR has been shown to exert a positive effect on mitochondria, boosting mitochondrial activity and hence providing some of the salutary effects of CR [3, 4]. The effects of CR are thought to be mediated by the regulatory family of sirtuins, mainly SIRT1, an NAD-dependent protein deacetylase [4]. Sirt1 has many proven targets involved in protein homeostasis and metabolisms [130]. Among them is PGC-1 $\alpha$  [131]. Additionally, Sirt1 activates the endothelial nitric oxide synthase eNOS, which stimulates mitochondrial activity [132]. The resulting increase in mitochondrial activity is thought to be related to longevity effect of CR and Sirt1 upregulation. In caloric-restricted mice, Sirt1 activity is increased and protects from cancer, neurodegeneration,

inflammatory disorders, metabolic, and cardiovascular disease [133]. Intriguingly, enforced Sirt1 activity seems to result in a CR-like physiology and protection from degenerative diseases [133, 134]. Recent evidence suggests that Sirt1 is also involved in mediating the response to dietary restriction and increasing health span in humans [64].

**5.2. Exercise.** Exercise is an excellent therapeutic intervention for conditions such as obesity, T2D, neurodegeneration, osteoporosis and sarcopenia [135, 136]. PGC-1 $\alpha$  activation seems to be the mechanism that mediates those beneficial effects and increased PGC-1 $\alpha$  levels promote an exercised phenotype [74, 137, 138]. Exercise also causes a reduction in the levels of systemic inflammation after exercise, presumably through the same mechanisms [139]. Exercise also activates the AMP-activated kinase (AMPK) [140]. AMPK is considered to be a key metabolic sensor that increases translocation of Glut4 to the plasma membrane [141]. AMPK also activates PGC-1 $\alpha$  and thereby mitochondrial biogenesis in an attempt to compensate for the ATP depletion [137, 142]. This mechanism is thought to be the molecular basis for the therapeutic effect of exercise, which stimulates AMPK. Activation of PGC-1 $\alpha$  in skeletal muscle has thereby the potential to compensate for mitochondrial dysfunction and affect other pathways and thus prevent insulin resistance as shown in an animal model [68, 74, 143].

**5.3. Pharmacological Approaches.** In addition to exercise, PGC-1 $\alpha$  and hence mitochondrial biogenesis can be activated by a wide array of pharmacological substances. PGC-1 $\alpha$  activity is controlled by the PPARs, AMPK and Sirt1 (Figure 2). Thus, drugs that activate PPARs, AMPK and Sirt1 could potentially result in PGC-1 $\alpha$  activation. Such pharmaceutical activators include fibrates and rosiglitazone (PPAR), metformin and AICAR (AMPK) as well as resveratrol (Sirt1). Induction of mitochondrial biogenesis and/or PGC-1 $\alpha$  activation has been demonstrated for most of these substances both *in vitro* and *in vivo* [45–47, 52, 141, 144]. Interestingly, bezafibrate administration to a mouse model of mitochondrial myopathy mimicked the effects of transgenic PGC-1 $\alpha$  expression [46]. In mice, resveratrol prevents the decreased lifespan associated with obesity [52]. It remains to be seen what how pharmaceutical stimulated PGC-1 $\alpha$  activation affects aging and lifespan.

## 6. Conclusion

Mitochondria have been implicated in the aging process and the onset and progression of age-associated diseases since decades. While the impact of mitochondrial ROS is in question, failing ATP supply due to increasing mitochondrial dysfunction seems to be a major contributing factor to the aging process. Modulating mitochondrial function and affecting several tissue-specific pathways by PGC-1 $\alpha$  have been shown to have a beneficial effect. Notably, existing antiaging strategies as well as studies in mice suggest an important role of mitochondrial function and the PGC-1 $\alpha$  cascade in the preventing of age-associated diseases. In the same

line, control and maintenance of mitochondrial function by PGC-1 $\alpha$  activation have a huge therapeutic potential for age-related pathologies such as insulin resistance, sarcopenia and neurodegeneration. Findings on elevated PGC-1 $\alpha$  levels in the heart caution against the systemic effects of elevated PGC-1 $\alpha$  levels. Beneficial effects seem to be tissue specific, and remaining within a therapeutic window will be important.

## Acknowledgments

The author apologizes to those authors whose original work could not be cited due to space limitations. The author thanks Natalie Noe for help with the figures. The author's work is supported by the Emmy-Noether-Program of the Deutsche Forschungsgemeinschaft.

## References

- [1] D. Harman, "The biologic clock: the mitochondria?" *Journal of the American Geriatrics Society*, vol. 20, no. 4, pp. 145–147, 1972.
- [2] A. Trifunovic and N. G. Larsson, "Mitochondrial dysfunction as a cause of ageing," *Journal of Internal Medicine*, vol. 263, no. 2, pp. 167–178, 2008.
- [3] I. R. Lanza and K. S. Nair, "Mitochondrial function as a determinant of life span," *Pflugers Archiv European Journal of Physiology*, vol. 459, no. 2, pp. 277–289, 2010.
- [4] L. Guarente, "Mitochondria-A nexus for aging, calorie restriction, and sirtuins?" *Cell*, vol. 132, no. 2, pp. 171–176, 2008.
- [5] C. Handschin, "The biology of PGC-1 $\alpha$  and its therapeutic potential," *Trends in Pharmacological Sciences*, vol. 30, no. 6, pp. 322–329, 2009.
- [6] T. Wenz, "PGC-1 $\alpha$  activation as a therapeutic approach in mitochondrial disease," *IUBMB Life*, vol. 61, no. 11, pp. 1051–1062, 2009.
- [7] M. Saraste, "Oxidative phosphorylation at the fin de siecle," *Science*, vol. 283, no. 5407, pp. 1488–1493, 1999.
- [8] S. Orrenius, V. Gogvadze, and B. Zhivotovsky, "Mitochondrial oxidative stress: implications for cell death," *Annual Review of Pharmacology and Toxicology*, vol. 47, pp. 143–183, 2007.
- [9] A. Y. Andreyev, YU. E. Kushnareva, and A. A. Starkov, "Mitochondrial metabolism of reactive oxygen species," *Biochemistry*, vol. 70, no. 2, pp. 200–214, 2005.
- [10] E. Cadenas and K. J. A. Davies, "Mitochondrial free radical generation, oxidative stress, and aging," *Free Radical Biology and Medicine*, vol. 29, no. 3–4, pp. 222–230, 2000.
- [11] J. St-Pierre, J. A. Buckingham, S. J. Roebuck, and M. D. Brand, "Topology of superoxide production from different sites in the mitochondrial electron transport chain," *The Journal of Biological Chemistry*, vol. 277, no. 47, pp. 44784–44790, 2002.
- [12] J. Miquel, A. C. Economos, J. Fleming, and J. E. Johnson, "Mitochondrial role in cell aging," *Experimental Gerontology*, vol. 15, no. 6, pp. 575–591, 1980.
- [13] C. C. Kujoth, A. Hiona, T. D. Pugh et al., "Medicine: mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging," *Science*, vol. 309, no. 5733, pp. 481–484, 2005.
- [14] A. Trifunovic, A. Hansson, A. Wredenberg et al., "Somatic mtDNA mutations cause aging phenotypes without affecting reactive oxygen species production," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 50, pp. 17993–17998, 2005.
- [15] J. Wang, J. P. Silva, C. M. Gustafsson, P. Rustin, and N. G. Larsson, "Increased in vivo apoptosis in cells lacking mitochondrial DNA gene expression," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 7, pp. 4038–4043, 2001.
- [16] R. S. Balaban, S. Nemoto, and T. Finkel, "Mitochondria, oxidants, and aging," *Cell*, vol. 120, no. 4, pp. 483–495, 2005.
- [17] H. Van Remmen, Y. Ikeno, M. Hamilton et al., "Life-long reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging," *Physiological Genomics*, vol. 16, pp. 29–37, 2004.
- [18] H. Van Remmen, W. Qi, M. Sabia et al., "Multiple deficiencies in antioxidant enzymes in mice result in a compound increase in sensitivity to oxidative stress," *Free Radical Biology and Medicine*, vol. 36, no. 12, pp. 1625–1634, 2004.
- [19] T. T. Huang, E. J. Carlson, A. M. Gillespie, Y. Shi, and C. J. Epstein, "Ubiquitous overexpression of CuZn superoxide dismutase does not extend life span in mice," *Journals of Gerontology—Series A*, vol. 55, no. 1, pp. B5–B9, 2000.
- [20] S. Miwa, K. Riyahi, L. Partridge, and M. D. Brand, "Lack of correlation between mitochondrial reactive oxygen species production and life span in *Drosophila*," *Annals of the New York Academy of Sciences*, vol. 1019, pp. 388–391, 2004.
- [21] H.-Y. Lee, C. S. Choi, A. L. Birkenfeld et al., "Targeted expression of catalase to mitochondria prevents age-associated reductions in mitochondrial function and insulin resistance," *Cell Metabolism*, vol. 12, no. 6, pp. 668–674, 2010.
- [22] D. F. Dai, L. F. Santana, M. Vermulst et al., "Overexpression of catalase targeted to mitochondria attenuates murine cardiac aging," *Circulation*, vol. 119, no. 21, pp. 2789–2797, 2009.
- [23] P. M. Treuting, N. J. Linford, S. E. Knoblauch et al., "Reduction of age-associated pathology in old mice by overexpression of catalase in mitochondria," *Journals of Gerontology—Series A*, vol. 63, no. 8, pp. 813–824, 2008.
- [24] S. E. Schriener, N. J. Linford, G. M. Martin et al., "Medicine: extension of murine life span by overexpression of catalase targeted to mitochondria," *Science*, vol. 308, no. 5730, pp. 1909–1911, 2005.
- [25] A. V. Ergen and M. A. Goodell, "Mechanisms of hematopoietic stem cell aging," *Experimental Gerontology*, vol. 45, no. 4, pp. 286–290, 2010.
- [26] S. Someya and T. A. Prolla, "Mitochondrial oxidative damage and apoptosis in age-related hearing loss," *Mechanisms of Ageing and Development*, vol. 131, no. 7–8, pp. 480–486, 2010.
- [27] K. K. Ohlemiller, S. L. McFadden, DA. L. Ding et al., "Targeted deletion of the cytosolic Cu/Zn-superoxide dismutase gene (*Sod1*) increases susceptibility to noise-induced hearing loss," *Audiology and Neuro-Otology*, vol. 4, no. 5, pp. 237–246, 1999.
- [28] S. Someya, J. Xu, K. Kondo et al., "Age-related hearing loss in C57BL/6J mice is mediated by Bak-dependent mitochondrial apoptosis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 46, pp. 19432–19437, 2009.
- [29] F. Li, N. Y. Calingasan, F. Yu et al., "Increased plaque burden in brains of APP mutant MnSOD heterozygous knockout mice," *Journal of Neurochemistry*, vol. 89, no. 5, pp. 1308–1312, 2004.

- [30] S. Melov, P. A. Adlard, K. Morten et al., "Mitochondrial oxidative stress causes hyperphosphorylation of tau," *PLoS ONE*, vol. 2, no. 6, article e536, 2007.
- [31] M. Ohashi, M. S. Runge, F. M. Faraci, and D. D. Heistad, "MnSOD deficiency increases endothelial dysfunction in ApoE-deficient mice," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 26, no. 10, pp. 2331–2336, 2006.
- [32] A. M. Vincent, J. W. Russell, K. A. Sullivan et al., "SOD2 protects neurons from injury in cell culture and animal models of diabetic neuropathy," *Experimental Neurology*, vol. 208, no. 2, pp. 216–227, 2007.
- [33] D. S. Albers and M. Flint Beal, "Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease," *Journal of Neural Transmission, Supplement*, no. 59, pp. 133–154, 2000.
- [34] M. Ristow and K. Zarse, "How increased oxidative stress promotes longevity and metabolic health: the concept of mitochondrial hormesis (mitohormesis)," *Experimental Gerontology*, vol. 45, no. 6, pp. 410–418, 2010.
- [35] M. Ristow, K. Zarse, A. Oberbach et al., "Antioxidants prevent health-promoting effects of physical exercise in humans," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 21, pp. 8665–8670, 2009.
- [36] G. Bjelakovic, D. Nikolova, L. L. Gluud, R. G. Simonetti, and C. Gluud, "Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis," *Journal of the American Medical Association*, vol. 297, no. 8, pp. 842–857, 2007.
- [37] W. Yang and S. Hekimi, "A mitochondrial superoxide signal triggers increased longevity in *Caenorhabditis elegans*," *PLoS Biology*, vol. 8, no. 12, 2010.
- [38] R. Scherz-Shouval and Z. Elazar, "Regulation of autophagy by ROS: physiology and pathology," *Trends in Biochemical Sciences*, vol. 36, no. 1, pp. 30–38, 2011.
- [39] J. Papaconstantinou, "Insulin/IGF-1 and ROS signaling pathway cross-talk in aging and longevity determination," *Molecular and Cellular Endocrinology*, vol. 299, no. 1, pp. 89–100, 2009.
- [40] M. Giorgio, E. Migliaccio, F. Orsini et al., "Electron transfer between cytochrome c and p66 generates reactive oxygen species that trigger mitochondrial apoptosis," *Cell*, vol. 122, no. 2, pp. 221–233, 2005.
- [41] R. C. Scarpulla, "Transcriptional paradigms in mammalian mitochondrial biogenesis and function," *Physiological Reviews*, vol. 88, no. 2, pp. 611–638, 2008.
- [42] R. C. Scarpulla, "Nuclear control of respiratory chain expression by nuclear respiratory factors and PGC-1-related coactivator," *Annals of the New York Academy of Sciences*, vol. 1147, pp. 321–334, 2008.
- [43] P. Puigserver and B. M. Spiegelman, "Peroxisome proliferator-activated receptor- $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ): transcriptional coactivator and metabolic regulator," *Endocrine Reviews*, vol. 24, no. 1, pp. 78–90, 2003.
- [44] D. Kang and N. Hamasaki, "Mitochondrial transcription factor A in the maintenance of mitochondrial DNA: overview of its multiple roles," *Annals of the New York Academy of Sciences*, vol. 1042, pp. 101–108, 2005.
- [45] J. Bastin, F. Aubey, A. Rötig, A. Munnich, and F. Djouadi, "Activation of peroxisome proliferator-activated receptor pathway stimulates the mitochondrial respiratory chain and can correct deficiencies in patients' cells lacking its components," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 4, pp. 1433–1441, 2008.
- [46] T. Wenz, F. Diaz, B. M. Spiegelman, and C. T. Moraes, "Activation of the PPAR/PGC-1 $\alpha$  pathway prevents a bioenergetic deficit and effectively improves a mitochondrial myopathy phenotype," *Cell Metabolism*, vol. 8, no. 3, pp. 249–256, 2008.
- [47] T. Wenz et al., "A metabolic shift induced by a PPAR panagonist markedly reduces the effects of pathogenic mitochondrial tRNA mutations," *Journal of Cellular and Molecular Medicine*. In press.
- [48] R. Barrès, M. E. Osler, J. Yan et al., "Non-CpG Methylation of the PGC-1 $\alpha$  Promoter through DNMT3B Controls Mitochondrial Density," *Cell Metabolism*, vol. 10, no. 3, pp. 189–198, 2009.
- [49] M. Fan, J. Rhee, J. St-Pierre et al., "Suppression of mitochondrial respiration through recruitment of p160 myb binding protein to PGC-1 $\alpha$ : modulation by p38 MAPK," *Genes and Development*, vol. 18, no. 3, pp. 278–289, 2004.
- [50] A. M. Powelka, A. Seth, J. V. Virbasius et al., "Suppression of oxidative metabolism and mitochondrial biogenesis by the transcriptional corepressor RIP140 in mouse adipocytes," *Journal of Clinical Investigation*, vol. 116, no. 1, pp. 125–136, 2006.
- [51] C. Cantó and J. Auwerx, "PGC-1 $\alpha$ , SIRT1 and AMPK, an energy sensing network that controls energy expenditure," *Current Opinion in Lipidology*, vol. 20, no. 2, pp. 98–105, 2009.
- [52] M. Lagouge, C. Argmann, Z. Gerhart-Hines et al., "Resveratrol Improves Mitochondrial Function and Protects against Metabolic Disease by Activating SIRT1 and PGC-1 $\alpha$ ," *Cell*, vol. 127, no. 6, pp. 1109–1122, 2006.
- [53] A. Planavila et al., "Sirt1 acts in association with PPAR $\alpha$  to protect the heart from hypertrophy, metabolic dysregulation, and inflammation," *Cardiovascular Research*. In press.
- [54] D. Beher, J. Wu, S. Cumine et al., "Resveratrol is not a direct activator of sirt1 enzyme activity," *Chemical Biology and Drug Design*, vol. 74, no. 6, pp. 619–624, 2009.
- [55] H. Dai, L. Kustigian, D. Carney et al., "SIRT1 activation by small molecules: kinetic and biophysical evidence for direct interaction of enzyme and activator," *The Journal of Biological Chemistry*, vol. 285, no. 43, pp. 32695–32703, 2010.
- [56] C. Ling, P. Poulsen, E. Carlsson et al., "Multiple environmental and genetic factors influence skeletal muscle PGC-1 $\alpha$  and PGC-1 $\beta$  gene expression in twins," *Journal of Clinical Investigation*, vol. 114, no. 10, pp. 1518–1526, 2004.
- [57] R. J. Southgate, C. R. Bruce, A. L. Carey et al., "PGC-1 $\alpha$  gene expression is down-regulated by Akt-mediated phosphorylation and nuclear exclusion of FoxO1 in insulin-stimulated skeletal muscle," *FASEB Journal*, vol. 19, no. 14, pp. 2072–2074, 2005.
- [58] T. Akimoto, S. C. Pohnert, P. Li et al., "Exercise stimulates Pgc-1 $\alpha$  transcription in skeletal muscle through activation of the p38 MAPK pathway," *The Journal of Biological Chemistry*, vol. 280, no. 20, pp. 19587–19593, 2005.
- [59] R. M. Anderson, J. L. Barger, M. G. Edwards et al., "Dynamic regulation of PGC-1 $\alpha$  localization and turnover implicates mitochondrial adaptation in calorie restriction and the stress response," *Aging Cell*, vol. 7, no. 1, pp. 101–111, 2008.
- [60] M. P. Housley, N. D. Udeshi, J. T. Rodgers et al., "A PGC-1 $\alpha$ -O-GlcNAc transferase complex regulates FoxO transcription factor activity in response to glucose," *The Journal of Biological Chemistry*, vol. 284, no. 8, pp. 5148–5157, 2009.
- [61] M. M. Rytinki and J. J. Palvimö, "SUMOylation attenuates the function of PGC-1 $\alpha$ ," *The Journal of Biological Chemistry*, vol. 284, no. 38, pp. 26184–26193, 2009.

- [62] S. DiMauro and E. A. Schon, "Mitochondrial disorders in the nervous system," *Annual Review of Neuroscience*, vol. 31, pp. 91–123, 2008.
- [63] D. J. Baker, A. C. Betik, D. J. Krause, and R. T. Hepple, "No decline in skeletal muscle oxidative capacity with aging in long-term calorically restricted rats: effects are independent of mitochondrial DNA integrity," *Journals of Gerontology—Series A*, vol. 61, no. 7, pp. 675–684, 2006.
- [64] A. E. Civitarese, S. Carling, L. K. Heilbronn et al., "Calorie restriction increases muscle mitochondrial biogenesis in healthy humans," *PLoS Medicine*, vol. 4, no. 3, pp. 485–494, 2007.
- [65] G. P. Fadini, G. Ceolotto, E. Pagnin, S. De Kreutzenberg, and A. Avogaro, "At the crossroads of longevity and metabolism: the metabolic syndrome and lifespan determinant pathways," *Aging Cell*, vol. 10, no. 1, pp. 10–17, 2011.
- [66] E. Sahin, S. Colla, M. Liesa et al., "Telomere dysfunction induces metabolic and mitochondrial compromise," *Nature*, vol. 470, no. 7334, pp. 359–365, 2011.
- [67] A. A. Gonzalez, R. Kumar, J. D. Mulligan, A. J. Davis, and K. W. Saupé, "Effects of aging on cardiac and skeletal muscle AMPK activity: basal activity, allosteric activation, and response to in vivo hypoxemia in mice," *American Journal of Physiology*, vol. 287, no. 5, pp. R1270–R1275, 2004.
- [68] T. Wenz, S. G. Rossi, R. L. Rotundo, B. M. Spiegelman, and C. T. Moraes, "Increased muscle PGC-1 $\alpha$  expression protects from sarcopenia and metabolic disease during aging," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 48, pp. 20405–20410, 2010.
- [69] K. Baar, A. R. Wende, T. E. Jones et al., "Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1," *FASEB Journal*, vol. 16, no. 14, pp. 1879–1886, 2002.
- [70] C. Handschin, "Regulation of skeletal muscle cell plasticity by the peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$ ," *Journal of Receptors and Signal Transduction*, vol. 30, no. 6, pp. 376–384, 2010.
- [71] W. Cao, K. W. Daniel, J. Robidoux et al., "p38 Mitogen-activated protein kinase is the central regulator of cyclic AMP-dependent transcription of the brown fat uncoupling protein 1 gene," *Molecular and Cellular Biology*, vol. 24, no. 7, pp. 3057–3067, 2004.
- [72] P. Puigserver, J. Rhee, J. Lin et al., "Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPAR $\gamma$  coactivator-1," *Molecular Cell*, vol. 8, no. 5, pp. 971–982, 2001.
- [73] J. Lin, H. Wu, P. T. Tarr et al., "Transcriptional co-activator PGC-1 $\alpha$  drives the formation of slow-twitch muscle fibres," *Nature*, vol. 418, no. 6899, pp. 797–801, 2002.
- [74] T. Wenz, F. Diaz, D. Hernandez, and C. T. Moraes, "Endurance exercise is protective for mice with mitochondrial myopathy," *Journal of Applied Physiology*, vol. 106, no. 5, pp. 1712–1719, 2009.
- [75] C. Handschin, Y. M. Kobayashi, S. Chin, P. Seale, K. P. Campbell, and B. M. Spiegelman, "PGC-1 $\alpha$  regulates the neuromuscular junction program and ameliorates Duchenne muscular dystrophy," *Genes and Development*, vol. 21, no. 7, pp. 770–783, 2007.
- [76] M. Sandri, J. Lin, C. Handschin et al., "PGC-1 $\alpha$  protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 44, pp. 16260–16265, 2006.
- [77] A. -S. Arnold, A. Egger, and C. Handschin, "PGC-1 $\alpha$  and myokines in the aging muscle—a mini-review," *Gerontology*, vol. 57, no. 1, pp. 37–43, 2010.
- [78] C. Handschin, "Peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  in muscle links metabolism to inflammation," *Clinical and Experimental Pharmacology and Physiology*, vol. 36, no. 12, pp. 1139–1143, 2009.
- [79] J. Chinsomboon, J. Ruas, R. K. Gupta et al., "The transcriptional coactivator PGC-1 $\alpha$  mediates exercise-induced angiogenesis in skeletal muscle," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 50, pp. 21401–21406, 2009.
- [80] C. M. Lee, M. E. Lopez, R. Weindruch, and J. M. Aiken, "Association of age-related mitochondrial abnormalities with skeletal muscle fiber atrophy," *Free Radical Biology and Medicine*, vol. 25, no. 8, pp. 964–972, 1998.
- [81] E. Marzetti, H. A. Lees, S. E. Wohlgemuth, and C. Leeuwenburgh, "Sarcopenia of aging: underlying cellular mechanisms and protection by calorie restriction," *BioFactors*, vol. 35, no. 1, pp. 28–35, 2009.
- [82] J. M. Huss and D. P. Kelly, "Nuclear receptor signaling and cardiac energetics," *Circulation Research*, vol. 95, no. 6, pp. 568–578, 2004.
- [83] M. P. Czubryt et al., "Regulation of peroxisome proliferator-activated receptor gamma coactivator 1  $\alpha$  (PGC-1  $\alpha$ ) and mitochondrial function by MEF2 and HDAC5," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 4, pp. 1711–1716, 2003.
- [84] B. T. O'Neill, J. Kim, A. R. Wende et al., "A conserved role for phosphatidylinositol 3-kinase but not Akt signaling in mitochondrial adaptations that accompany physiological cardiac hypertrophy," *Cell Metabolism*, vol. 6, no. 4, pp. 294–306, 2007.
- [85] Z. Arany, H. He, J. Lin et al., "Transcriptional coactivator PGC-1 $\alpha$  controls the energy state and contractile function of cardiac muscle," *Cell Metabolism*, vol. 1, no. 4, pp. 259–271, 2005.
- [86] T. C. Leone, J. J. Lehman, B. N. Finck et al., "PGC-1 $\alpha$  deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis," *PLoS Biology*, vol. 3, no. 4, p. e101, 2005.
- [87] J. M. Huss and D. P. Kelly, "Mitochondrial energy metabolism in heart failure: a question of balance," *Journal of Clinical Investigation*, vol. 115, no. 3, pp. 547–555, 2005.
- [88] L. K. Russell, C. M. Mansfield, J. J. Lehman et al., "Cardiac-specific induction of the transcriptional coactivator peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$  promotes mitochondrial biogenesis and reversible cardiomyopathy in a developmental stage-dependent manner," *Circulation Research*, vol. 94, no. 4, pp. 525–533, 2004.
- [89] E. G. Lynn, M. V. Stevens, R. P. Wong et al., "Transient upregulation of PGC-1 $\alpha$  diminishes cardiac ischemia tolerance via upregulation of ANT1," *Journal of Molecular and Cellular Cardiology*, vol. 49, no. 4, pp. 693–698, 2010.
- [90] G. C. Rowe, A. Jiang, and Z. Arany, "PGC-1 coactivators in cardiac development and disease," *Circulation Research*, vol. 107, no. 7, pp. 825–838, 2010.
- [91] J. St-Pierre, S. Drori, M. Uldry et al., "Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators," *Cell*, vol. 127, no. 2, pp. 397–408, 2006.

- [92] J. Lin, P. H. Wu, P. T. Tarr et al., "Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1 $\alpha$  null mice," *Cell*, vol. 119, no. 1, pp. 121–135, 2004.
- [93] R. M. Cowell, P. Talati, K. R. Blake, J. H. Meador-Woodruff, and J. W. Russell, "Identification of novel targets for PGC-1 $\alpha$  and histone deacetylase inhibitors in neuroblastoma cells," *Biochemical and Biophysical Research Communications*, vol. 379, no. 2, pp. 578–582, 2009.
- [94] A. Bender, K. J. Krishnan, C. M. Morris et al., "High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease," *Nature Genetics*, vol. 38, no. 5, pp. 515–517, 2006.
- [95] L. Cui, H. Jeong, F. Borovecki, C. N. Parkhurst, N. Tanese, and D. Krainc, "Transcriptional Repression of PGC-1 $\alpha$  by Mutant Huntingtin Leads to Mitochondrial Dysfunction and Neurodegeneration," *Cell*, vol. 127, no. 1, pp. 59–69, 2006.
- [96] P. Weydt, V. V. Pineda, A. E. Torrence et al., "Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1 $\alpha$  in Huntington's disease neurodegeneration," *Cell Metabolism*, vol. 4, no. 5, pp. 349–362, 2006.
- [97] W. Qin, V. Haroutunian, P. Katsel et al., "PGC-1 $\alpha$  expression decreases in the Alzheimer disease brain as a function of dementia," *Archives of Neurology*, vol. 66, no. 3, pp. 352–361, 2009.
- [98] A. Y. Sun, Q. Wang, A. Simonyi, and G. Y. Sun, "Resveratrol as a Therapeutic Agent for Neurodegenerative Diseases," *Molecular Neurobiology*, pp. 1–9, 2010.
- [99] J. C. Yoon, P. Puigserver, G. Chen et al., "Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1," *Nature*, vol. 413, no. 6852, pp. 131–138, 2001.
- [100] P. Puigserver, J. Rhee, J. Donovan et al., "Insulin-regulated hepatic gluconeogenesis through FOXO1-PGC-1 $\alpha$  interaction," *Nature*, vol. 423, no. 6939, pp. 550–555, 2003.
- [101] J. Rhee, Y. Inoue, J. C. Yoon et al., "Regulation of hepatic fasting response by PPAR $\gamma$  coactivator-1 $\alpha$  (PGC-1): requirement for hepatocyte nuclear factor 4 $\alpha$  in gluconeogenesis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 7, pp. 4012–4017, 2003.
- [102] W. Cao, Q. F. Collins, T. C. Becker et al., "p38 mitogen-activated protein kinase plays a stimulatory role in hepatic gluconeogenesis," *The Journal of Biological Chemistry*, vol. 280, no. 52, pp. 42731–42737, 2005.
- [103] F. C. Qu, Y. Xiong, E. G. Lupo, H. Y. Liu, and W. Cao, "p38 mitogen-activated protein kinase mediates free fatty acid-induced gluconeogenesis in hepatocytes," *The Journal of Biological Chemistry*, vol. 281, no. 34, pp. 24336–24344, 2006.
- [104] C. R. Hancock, D. H. Han, M. Chen et al., "High-fat diets cause insulin resistance despite an increase in muscle mitochondria," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 22, pp. 7815–7820, 2008.
- [105] R. Boushel, E. Gnaiger, P. Schjerling, M. Skovbro, R. Kraunsøe, and F. Dela, "Patients with type 2 diabetes have normal mitochondrial function in skeletal muscle," *Diabetologia*, vol. 50, no. 4, pp. 790–796, 2007.
- [106] J. A. Pospisilik, C. Knauf, N. Joza et al., "Targeted deletion of AIF decreases mitochondrial oxidative phosphorylation and protects from obesity and diabetes," *Cell*, vol. 131, no. 3, pp. 476–491, 2007.
- [107] K. F. Petersen, D. Befroy, S. Dufour et al., "Mitochondrial dysfunction in the elderly: possible role in insulin resistance," *Science*, vol. 300, no. 5622, pp. 1140–1142, 2003.
- [108] J. F. Dumas, G. Simard, M. Flamment, P. H. Ducluzeau, and P. Ritz, "Is skeletal muscle mitochondrial dysfunction a cause or an indirect consequence of insulin resistance in humans?" *Diabetes and Metabolism*, vol. 35, no. 3, pp. 159–167, 2009.
- [109] J. A. Kim, Y. Wei, and J. R. Sowers, "Role of mitochondrial dysfunction in insulin resistance," *Circulation Research*, vol. 102, no. 4, pp. 401–414, 2008.
- [110] M. E. Patti, A. J. Butte, S. Crunkhorn et al., "Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 14, pp. 8466–8471, 2003.
- [111] S. Wang, A. Kamat, P. Pergola, A. Swamy, F. Tio, and K. Cusi, "Metabolic factors in the development of hepatic steatosis and altered mitochondrial gene expression in vivo," *Metabolism*. In press.
- [112] A. A. Gupte, J. Z. Liu, Y. Ren et al., "Rosiglitazone attenuates age- and diet-associated nonalcoholic steatohepatitis in male low-density lipoprotein receptor knockout mice," *Hepatology*, vol. 52, no. 6, pp. 2001–2011, 2010.
- [113] Y. Hayashi, M. Yoshida, M. Yamato et al., "Reverse of age-dependent memory impairment and mitochondrial DNA damage in microglia by an overexpression of human mitochondrial transcription factor A in mice," *Journal of Neuroscience*, vol. 28, no. 34, pp. 8624–8634, 2008.
- [114] S. Xu, M. Zhong, L. Zhang et al., "Overexpression of Tfam protects mitochondria against  $\beta$ -amyloid-induced oxidative damage in SH-SY5Y cells," *FEBS Journal*, vol. 276, no. 14, pp. 4224–4233, 2009.
- [115] M. Ikeuchi, H. Matsusaka, D. Kang et al., "Overexpression of mitochondrial transcription factor A ameliorates mitochondrial deficiencies and cardiac failure after myocardial infarction," *Circulation*, vol. 112, no. 5, pp. 683–690, 2005.
- [116] L. Mahishi and K. Usdin, "NF- $\kappa$ B, AP2, Nrf1 and Sp1 regulate the fragile X-related gene 2 (FXR2)," *Biochemical Journal*, vol. 400, no. 2, pp. 327–335, 2006.
- [117] A. G. Rosmarin, K. K. Resendes, Z. Yang, J. N. McMillan, and S. L. Fleming, "GA-binding protein transcription factor: a review of GABP as an integrator of intracellular signaling and protein-protein interactions," *Blood Cells, Molecules, and Diseases*, vol. 32, no. 1, pp. 143–154, 2004.
- [118] S. Yu, K. Cui, R. Jothi et al., "GABP controls a critical transcription regulatory module that is essential for maintenance and differentiation of hematopoietic stem/progenitor cells," *Blood*, vol. 117, no. 7, pp. 2166–2178, 2011.
- [119] L. M. Angus, J. V. Chakkalakal, A. Méjat et al., "Calcineurin-NFAT signaling, together with GABP and peroxisome PGC-1 $\alpha$ , drives utrophin gene expression at the neuromuscular junction," *American Journal of Physiology*, vol. 289, no. 4, pp. C908–C917, 2005.
- [120] X. Kong, R. Wang, Y. Xue et al., "Sirtuin 3, a new target of PGC-1 $\alpha$ , plays an important role in the suppression of ROS and mitochondrial biogenesis," *PLoS ONE*, vol. 5, no. 7, Article ID e11707, 2010.
- [121] E. Verdin, M. D. Hirschey, L. W.S. Finley, and M. C. Haigis, "Sirtuin regulation of mitochondria: energy production, apoptosis, and signaling," *Trends in Biochemical Sciences*, vol. 35, no. 12, pp. 669–675, 2010.
- [122] A. V. Hafner, J. Dai, A. P. Gomes et al., "Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy," *Aging*, vol. 2, no. 12, pp. 914–923, 2010.
- [123] J. Sadoshima, "Sirt3 targets mPTP and prevents aging in the heart," *Aging*, vol. 3, no. 1, pp. 12–13, 2011.

- [124] A. Bartke, M. Masternak, K. Al-Regaiey, and M. Bonkowski, "Effects of dietary restriction on the expression of insulin-signaling-related genes in long-lived mutant mice," *Interdisciplinary Topics in Gerontology*, vol. 35, pp. 69–82, 2007.
- [125] L. Bordone and L. Guarente, "Calorie restriction, SIRT1 and metabolism: understanding longevity," *Nature Reviews Molecular Cell Biology*, vol. 6, no. 4, pp. 298–305, 2005.
- [126] S. J. Lin and L. Guarente, "Increased life span due to calorie restriction in respiratory-deficient yeast," *PLoS Genetics*, vol. 2, no. 3, p. e33, 2006.
- [127] J. J. Ramsey, R. J. Colman, N. C. Binkley et al., "Dietary restriction and aging in rhesus monkeys: the University of Wisconsin study," *Experimental Gerontology*, vol. 35, no. 9-10, pp. 1131–1149, 2000.
- [128] R. Weindruch, R. L. Walford, S. Fligiel, and D. Guthrie, "The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake," *Journal of Nutrition*, vol. 116, no. 4, pp. 641–654, 1986.
- [129] A. E. Civitarese, S. R. Smith, and E. Ravussin, "Diet, energy metabolism and mitochondrial biogenesis," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 10, no. 6, pp. 679–687, 2007.
- [130] J. T. Rodgers, C. Lerin, Z. Gerhart-Hines, and P. Puigserver, "Metabolic adaptations through the PGC-1 $\alpha$  and SIRT1 pathways," *FEBS Letters*, vol. 582, no. 1, pp. 46–53, 2008.
- [131] S. Nemoto, M. M. Fergusson, and T. Finkel, "SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1 $\alpha$ ," *The Journal of Biological Chemistry*, vol. 280, no. 16, pp. 16456–16460, 2005.
- [132] G. Arunachalam, H. Yao, I. K. Sundar, S. Caito, and I. Rahman, "SIRT1 regulates oxidant- and cigarette smoke-induced eNOS acetylation in endothelial cells: role of resveratrol," *Biochemical and Biophysical Research Communications*, vol. 393, no. 1, pp. 66–72, 2010.
- [133] M. C. Haigis and D. A. Sinclair, "Mammalian sirtuins: biological insights and disease relevance," *Annual Review of Pathology*, vol. 5, pp. 253–295, 2010.
- [134] J. A. Baur, D. Chen, E. N. Chini et al., "Dietary restriction: standing up for sirtuins," *Science*, vol. 329, no. 5995, pp. 1012–1013, 2010.
- [135] F. Dela and M. Kjaer, "Resistance training, insulin sensitivity and muscle function in the elderly," *Essays in Biochemistry*, vol. 42, pp. 75–88, 2006.
- [136] R. A. Winett and R. N. Carpinelli, "Potential health-related benefits of resistance training," *Preventive Medicine*, vol. 33, no. 5, pp. 503–513, 2001.
- [137] V. A. Lira, C. R. Benton, Z. Yan, and A. Bonen, "PGC-1 $\alpha$  regulation by exercise training and its influences on muscle function and insulin sensitivity," *American Journal of Physiology*, vol. 299, no. 2, pp. E145–E161, 2010.
- [138] Z. Yan, "Exercise, PGC-1 $\alpha$ , and metabolic adaptation in skeletal muscle," *Applied Physiology, Nutrition and Metabolism*, vol. 34, no. 3, pp. 424–427, 2009.
- [139] A. M. W. Petersen and B. K. Pedersen, "The anti-inflammatory effect of exercise," *Journal of Applied Physiology*, vol. 98, no. 4, pp. 1154–1162, 2005.
- [140] S. B. Jorgensen and A. J. Rose, "How is AMPK activity regulated in skeletal muscles during exercise?" *Frontiers in Bioscience*, vol. 13, pp. 5589–5604, 2008.
- [141] J. O. Lee, S. K. Lee, J. H. Jung et al., "Metformin induces Rab4 through AMPK and modulates GLUT4 translocation in skeletal muscle cells," *Journal of Cellular Physiology*, vol. 226, no. 4, pp. 974–981, 2011.
- [142] W. J. Lee, M. Kim, H. S. Park et al., "AMPK activation increases fatty acid oxidation in skeletal muscle by activating PPAR $\alpha$  and PGC-1," *Biochemical and Biophysical Research Communications*, vol. 340, no. 1, pp. 291–295, 2006.
- [143] L. F. Michael, Z. Wu, R. B. Cheatham et al., "Restoration of insulin-sensitive glucose transporter (GLUT4) gene expression in muscle cells by the transcriptional coactivator PGC-1," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 7, pp. 3820–3825, 2001.
- [144] R. A. Quintanilla, Y. N. Jin, K. Fuenzalida, M. Bronfman, and G. V. W. Johnson, "Rosiglitazone treatment prevents mitochondrial dysfunction in mutant huntingtin-expressing cells: possible role of peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) in the pathogenesis of huntington disease," *The Journal of Biological Chemistry*, vol. 283, no. 37, pp. 25628–25637, 2008.



**Hindawi**  
Submit your manuscripts at  
<http://www.hindawi.com>

