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Review Article

Mitochondria and PGC-1α in Aging and Age-Associated Diseases

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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 γ coactivator α (PGC-1α), which is the key regulator of mitochondrial biogenesis. Besides regulating mitochondrial function, PGC-1α targets several other cellular processes and thereby influences cell fate on multiple levels. This paper discusses how mitochondrial function and PGC-1α are affected in age-associated diseases and how modulation of PGC-1α 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) γ coactivator α (PGC-1α) 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-1α 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 γ (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 particulary 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 ($p66^{shc}$). $p66^{shc}$ 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 $p66^{shc}$ 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 import 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) γ Coactivator α (PGC-1α) 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 α (ERRα), 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) γ coactivator α (PGC-1α) [42]. PGC-1α is a transcriptional coactivator and interacts with nuclear receptors and transcription factors to activate transcription of their target genes [43]. PGC-1α 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-1α, other members of the PGC-1 family of coactivators, namely PGC-1β 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-1α 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-1α 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-1α, 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-1α 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-1α transcription and might be potentially relevant in several pathophysiologies. PGC-1α regulates its own transcription via YY1. YY1 is a common target of mammalian target of rapamycin (mTOR) and PGC-1α. mTOR directly modulates the physical interaction of PGC-1α with YY1 and thereby modulates mitochondrial activity. Decrease in mTOR activity likely inhibits YY1-PGC-1α function resulting in decreased expression of mitochondrial genes [42, 43].

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

PGC-1α activity can also be modulated by posttranslational modifications. AMPK, Akt and p38 MAPK target PGC-1α 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-1α, but also promotes PGC-1α-dependent induction at the PGC-1α promoter [51]. Activity of PGC-1α 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-1α activity and enhances mitochondrial function [52, 53]. While it is observed that resveratrol indirectly activates PGC-1α 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+ dependent, both AMPK and Sirt1 modulate PGC-1α activity in response to cellular energy supply. Insulin reduces PGC-1α expression, but also induces phosphorylation of PGC-1α through Akt and thereby inhibits its activity [56, 57]. The p38 mitogen-activated protein kinase (p38 MAPK) phosphorylates and activates PGC-1α [58]. This phosphorylation enhances PGC-1α half-life, disrupts interaction with the corepressor p160MBP in myoblasts and thereby enhances PGC-1α cotranscriptional activity [49]. PGC-1α is also phosphorylated by glycogen synthase kinase 3β (GSK3β) and thereby inhibited under oxidative stress [59]. However, Sirt1 is activated under the same conditions and activates PGC-1α by deacetylation. It is so far unclear how Sirt1 and GSK3b act in concert to modulate PGC-1α activity.

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

4. Mitochondrial Function and PGC-1α 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

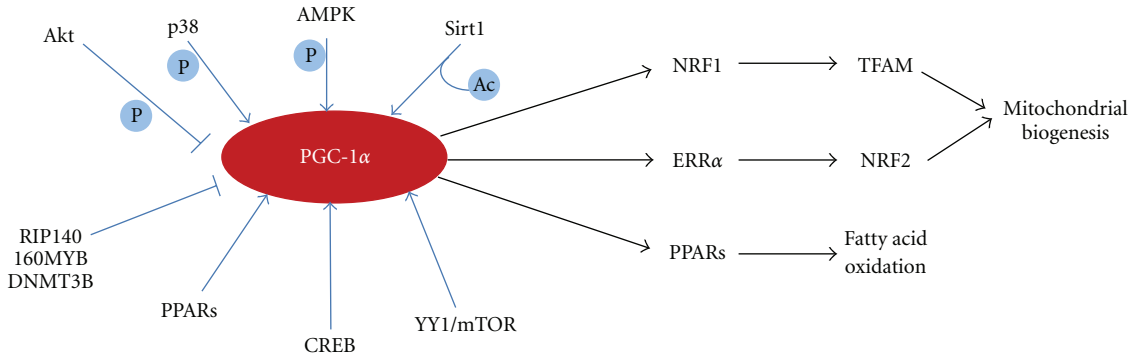

Figure 1: Modulation of PGC-1α and its targets. Regulation of PGC-1α activity on transcriptional and posttranscriptional levels as well as by interaction with inhibitory factors is summarized. The diagram shows the PGC-1α targets that are involved in metabolic regulation of mitochondria. The details 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-1α function. Also, mTOR and PGC-1α 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-1α, poised centrally in multiple pathways affecting mitochondrial dysfunction and cellular function should play a key role in this prevention. Age-associated reductions in PGC-1α 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-1α 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-1α function is best understood (Figure 2).

4.1. Skeletal Muscle and Sarcopenia. PGC-1α seems to be mediator of many known beneficial effects of exercise on muscle physiology. In skeletal muscle, PGC-1α expression is linked to muscle contraction [69]. A major mediator is the activation of Ca2+/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-1α 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-1α [71]. p38 MAPK also stimulates PGC-1α 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-1a 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-1α is also involved in regulation of muscle function and integrity: PGC-1α regulates the neuromuscular junction program by being recruited to GABP-complex to stimulate a broad neuromuscular junction gene program [75]. In addition, PGC-1α inhibits FoxO3 activity on transcription of atrophy-specific genes and thereby decreases muscle atrophy [76]. Transgenic PGC-1α mice show smaller decrease in muscle fiber diameter and smaller induction of atrogenes in denervation-induced muscle atrophy and aging muscle by suppressing FoxO3 action [68, 76].

Additionally, increased muscular PGC-1α seems to be involved in the regulation of apoptosis and protein degradation during aging [68]. Loss of function studies in PGC-1α knockout animals additional suggest that PGC-1α modulates local or systemic inflammation and might regulate the expression of inflammatory cytokines and inflammatory markers such as TNFα and IL6 [77, 78], but the exact mechanism that links PGC-1α and the inflammatory response is not known. PGC-1α 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

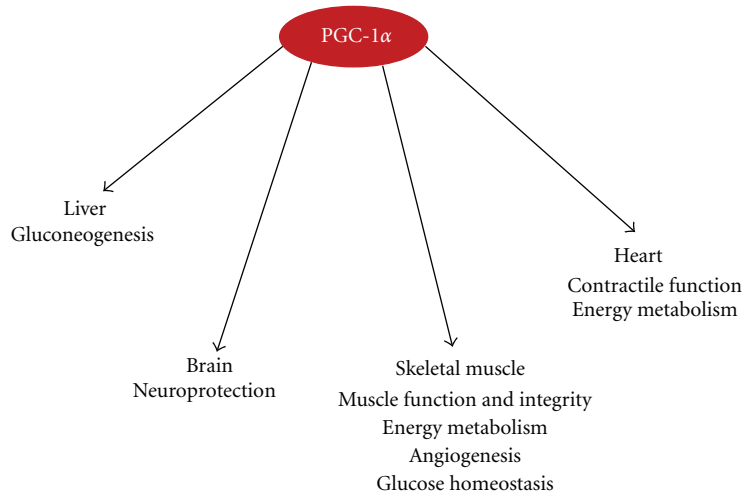

Figure 2: Tissue-specific function of PGC-1α relevant to age-related pathologies. Different functions of PGC-1α in heart, liver, brain, skeletal muscle and heart are depicted. These functions might be beneficial in age-associated pathologies as described in detail in the text.

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

Several studies have shown that elevated PGC-1α 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-1α 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-1α significantly reduced the loss of muscle mass and maintained exercise capacity during the aging process. The elevated PGC-1α levels in the aging muscle increased mitochondrial content and thereby maintained ATP supply. Additionally, transgenic PGC-1α 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-1α 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-1α and maintenance of muscle as a metabolic tissue resulted in improved insulin sensitivity and prevented hypoglycemia during aging. Additionally, muscle-specific PGC-1α expression also ameliorated other pathological factors observed during aging on a systemic level: elevated muscle PGC-1α 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-1α animals [68].

While the precise mechanism of the observed protective effects is not entirely clear, the following possibilities could explain the effect of PGC-1α: the regulation of mitochondrial mass might help to prevent the energy crisis associated with many muscular diseases [46, 68]. PGC-1α 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-1α. 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-1α strongly induces mitochondrial function and fatty acid oxidation [82]. Normal growth and response to exercise are controlled by PGC-1α similar to skeletal muscle [83, 84]. Absence of PGC-1α 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-1α is reduced [87]. In contrast to skeletal muscle, muscle elevated PGC-1α seems to have an adverse effect in heart: elevated increased expression of PGC-1α in the heart causes cardiomyopathy and heart failure in mice [88]. Also, transient activation of PGC-1α diminishes cardiac contractile recovery after ischemia-reperfusion injury [89]. These findings suggest that PGC-1α levels in heart need to be tightly regulated to prevent pathology. The adverse effect of PGC-1α might be attributed to tissue-specific differences in the availability of transcription factor partners for PGC-1α, differences in cell signaling or other heart-specific metabolic requirements.

Despite these effects of elevated PGC-1α in the heart, PGC-1α may nevertheless affect cardiac function. Sirt1 and PPARα, two proteins that regulate PGC-1α 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-1α implying that a PGC-1α might be involved in the cardioprotective effect.

A major factor contributing to the development of heart disorders during aging is the failing vasculature. PGC-1α 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-1α might hence be beneficial to maintain vasculature function and thus contribute to the prevention of cardiovascular diseases. Indeed, activation of PGC-1α 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-1α has on angiogenesis and atherosclerosis, two major contributing factors of cardiovascular disease.

4.3. Brain and Age-Related Neurodegenerative Diseases. PGC-1α 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-1α deficiency causes behavioral changes including anxiety and hyperactivity as well as hind limb clasping. 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-1α in neuronal maintenance [92]. PGC-1α 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-1α might potentially relieve this defect and together with the above described brain-specific function influence age-associated neurodegeneration. In fact, PGC-1α 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-1α mRNA [95, 96]. Polymorphism is also associated with the onset of AD [97]. PGC-1α is repressed by a mutant form of the Huntington protein which leads to mitochondrial dysfunction and neurodegeneration. Over-expression of PGC-1α rescues cells from the deleterious effect of Huntington's, whereas loss of PGC-1α in HD mice aggravated neurodegeneration [95]. Moreover, PGC-1α KO mice show Huntington's like phenotype and neuronal lesions suggesting that PGC-1α is crucial for maintenance of striatal function. Additionally, PGC-1α SNPs are associated with the age of onset of HD. In a PD mouse model, PGC-1α deficiency caused an increased degeneration of dopaminergic neurons in the substantia nigra associated with oxidative damage [91].

Interestingly, activators of PGC-1α such as resveratrol have a neuroprotective effect in acute and chronic brain injury as well as in neurodegenerative diseases suggesting a role for PGC1-α in modulating the outcome of the disease [98].

4.4. Liver and Metabolic Disorders. In liver, PGC-1α 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-1α results in a blunted hepatic fasting response as well as fasting hypoglycemia and hepatic steatosis [86]. PGC-1α associates in liver with several transcription factors such as HNF4-α 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-1α transcription as in muscle and seems to be also necessary for the expression of PGC-1α 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-1α promoter methylation and hence decreased PGC-1α 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-1α 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-1α expression and reduced mitochondrial gene expression [111]. Interestingly, rosiglitazone attenuates age-associated liver pathology in nonalcoholic steatohepatitis [112]. Rosiglitazone is indirectly activating PGC-1α via PPAR, implying that PGC-1α activating is beneficial in liver pathologies.

4.5. Role of PGC-1α Responsive Proteins in Age-Related Pathologies. Also downstream targets of PGC-1α 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-1α, NRF2 (GABP) regulates the NMJ program [75] (see above).

A novel identified target of PGC-1α 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-1α in Antiaging Strategies

There is an abundance of studies that provide indirect and direct evidence in support of a role for PGC-1α and regulation of mitochondrial function in antiaging strategies. As outline above, therapeutic modulation of PGC-1α 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-1α 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-1α 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-1α [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 form 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-1α activation seems to be the mechanism that mediates those beneficial effects and increased PGC-1α 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-1α 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-1α 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-1α and hence mitochondrial biogenesis can be activated by a wide array of pharmacological substances. PGC-1α activity is controlled by the PPARs, AMPK and Sirt1 (Figure 2). Thus, drugs that activate PPARs, AMPK and Sirt1 could potentially result in PGC-1α 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-1α 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-1α expression [46]. In mice, resveratrol prevents the decreased lifespan associated with obesity [52]. It remains to be seen what how pharmaceutical stimulated PGC-1α 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-1α 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-1α cascade in the preventing of age-associated diseases. In the same

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

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