PGC1α and mitochondrial metabolism – emerging concepts and relevance in ageing and neurodegenerative disorders

Shane Austin and Julie St-Pierre*

Department of Biochemistry and Goodman Cancer Research Centre, McGill University, 3655 Promenade Sir William Osler, Montréal, QC, H3G 1Y6, Canada

*Author for correspondence (julie.st-pierre@mcgill.ca)

Journal of Cell Science 125, 4963–4971

doi: 10.1242/jcs.113662

Summary

PGC1α is a transcriptional coactivator that is a central inducer of mitochondrial biogenesis in cells. Recent work highlighted that PGC1α can also modulate the composition and functions of individual mitochondria. Therefore, it is emerging that PGC1α is controlling global oxidative metabolism by performing two types of remodelling: (1) cellular remodelling through mitochondrial biogenesis, and (2) organelle remodelling through alteration in the intrinsic properties of mitochondria. The elevated oxidative metabolism associated with increased PGC1α activity could be accompanied by an increase in reactive oxygen species (ROS) that are primarily generated by mitochondria. However, increasing evidence suggests that this is not the case, as PGC1α is also a powerful regulator of ROS removal by increasing the expression of numerous ROS-detoxifying enzymes. Therefore, PGC1α, by controlling both the induction of mitochondrial metabolism and the removal of its ROS by-products, would elevate oxidative metabolism and minimize the impact of ROS on cell physiology. In this Commentary, we discuss how the biogenesis and remodelling of mitochondria that are elicited by PGC1α contribute to an increase in oxidative metabolism and the preservation of ROS homeostasis. Finally, we examine the importance of these findings in ageing and neurodegenerative disorders, conditions that are associated with impaired mitochondrial functions and ROS balance.

Key words: PGC1α, Mitochondrial remodelling, Mitochondrial biogenesis, Reactive oxygen species (ROS), Ageing, Neurodegeneration

Introduction

The regulation of cellular and mitochondrial metabolism is controlled by numerous transcriptional networks. In recent years, the peroxisome proliferator-activated receptor γ coactivator 1 (PGC1) family of transcriptional coactivators has emerged as central regulators of metabolism. The PGC1 family consists of three members, namely PGC1α, PGC1β and the PGC related coactivator (PRC), which interact with transcription factors and nuclear receptors to exert their biological functions (Handschin and Spiegelman, 2006). The most well-known and studied member of the PGC1 family is PGC1α (encoded by the *PPARGC1A* gene). PGC1α is a positive regulator of mitochondrial biogenesis and respiration, adaptive thermogenesis, gluconeogenesis as well as many other metabolic processes (Handschin and Spiegelman, 2006). Importantly, the expression of PGC1α is highly inducible by physiological cues, including exercise, cold and fasting (Handschin and Spiegelman, 2006). A central function of PGC1α that is intimately linked to mitochondrial biogenesis is the detoxification of reactive oxygen species (ROS) (St-Pierre et al., 2006; St-Pierre et al., 2003; Valle et al., 2005). Indeed, ROS are generated during mitochondrial respiration, and PGC1α has emerged as a key player, controlling their removal by regulating the expression of numerous ROS-detoxifying enzymes. Therefore, it appears that PGC1α both increases mitochondrial functions and minimizes the buildup of its by-products, ensuring a global positive impact on oxidative metabolism.

The other two members of the family, PGC1β and PRC, were discovered on the basis of similarity in sequence identity. PGC1β possesses a large degree of sequence identity and homology to PGC1α (Kressler et al., 2002; Lin et al., 2002a), whereas PRC has less homology to PGC1α and shares only some structural features (Andersson and Scarpulla, 2001). Functionally, PGC1β is a powerful inducer of mitochondrial biogenesis and respiration (Lin et al., 2002a; St-Pierre et al., 2003). It is also involved in the expression of the lipogenic programme in liver (Lin et al., 2005) and of type IIX fibres in muscle (Arany et al., 2007), as well as playing a central role in interferon-γ-induced host defence (Sonoda et al., 2007) and osteoclast activation (Ishii et al., 2009). PRC has been implicated in the regulation of the expression of several components of the respiratory chain (Vercauteren et al., 2009). Taken together, the PGC1 family of proteins regulate a wide array of metabolic functions, enabling them to act as global orchestrators of metabolism. However, one common metabolic function for the three members of the PGC1 family is mitochondrial metabolism. More advances have been made in elucidating the impact of PGC1α on mitochondrial metabolism compared with the other two members of the family, and for this reason, this Commentary will focus on PGC1α. We will highlight recent developments indicating that PGC1α has a profound impact on the intrinsic properties and functions of individual mitochondria, in addition to stimulating mitochondrial biogenesis. This mitochondrial remodelling might have important physiological consequences because it could be an effective way to fine-tune mitochondrial metabolism. We will focus our analysis on the effect of PGC1α on mitochondrial respiration

Journal of Cell Science

and ROS metabolism, two physiological processes that are tightly interconnected. Finally, we will discuss the potential beneficial effects of elevating PGC1α activity in neurodegenerative disorders and ageing, pathological conditions that have a strong association with mitochondrial dysfunctions.

PGC1α and the regulation of oxidative metabolism

There are two ways by which PGC1α can increase global oxidative metabolism. First, it can perform cellular remodelling through organelle biogenesis (mitochondria and peroxisomes). Second, an increasing number of studies highlight that PGC1α can coordinate organelle remodelling, resulting in substantial modification of the composition and function of individual organelles.

Cellular remodelling

Organelle biogenesis

The original discovery of PGC1α in brown fat cells revealed an important function for this transcriptional coactivator in mitochondrial metabolism (Box 1). Indeed, ectopic expression of PGC1α in white adipose cells results in a drastic increase in mitochondrial biogenesis, as well as induction of the expression of the mitochondrial uncoupling protein 1 (UCP1), two characteristics that are reminiscent of brown adipocytes (Puigserver et al., 1998). Immediately following this discovery, it was shown that PGC1α increases the expression of the nuclear respiratory factors (NRFs), which are transcription factors that regulate the expression of numerous mitochondrial genes (Wu et al., 1999). In addition, PGC1α coactivates and increases the transcriptional activity of NRF1 on target genes (Wu et al., 1999). It was later revealed that the main physiological consequence on mitochondria for this PGC1α-mediated increase in mitochondrial gene expression is a substantial induction of uncoupled respiration (St-Pierre et al., 2003). Together, these studies identified PGC1α as a master inducer of mitochondrial biogenesis and respiration.

Mouse models further highlighted the importance of PGC1α in mitochondrial physiology. Tissues from *Ppargc1a*-null mice display reduced expression of mitochondrial genes, notably those encoding various subunits of the electron transport chain, and lowered respiration (Leone et al., 2005; Lin et al., 2004). This reduced mitochondrial function impairs physiological processes that rely on mitochondrial metabolism. Indeed, *Ppargc1a*-null mice exhibit sensitivity to cold that is associated with an impaired capacity to upregulate the expression of UCP1 upon exposure to cold (Leone et al., 2005; Lin et al., 2004). They also show decreased capacity to exercise compared with wild-type controls (Leone et al., 2005). Contrary to *Ppargc1a*-null mice, transgenic mice ectopically expressing PGC1α in the heart and muscle tissues display increased expression of mitochondrial genes as well as elevated mitochondrial biogenesis (Lehman et al., 2000; Lin et al., 2002b; Wende et al., 2007). These studies demonstrate that gain and loss of PGC1α have important consequences for mitochondrial physiology *in vivo*.

A central organelle that supports mitochondrial functions during oxidative metabolism is the peroxisome. The main function of the peroxisome in mammalian cells is to metabolize complex fatty acids that cannot be metabolized by mitochondria. Importantly, peroxisomes cannot degrade fatty acids to completion, and export fatty acids with shortened chains to the mitochondria for the final breakdown reactions. Therefore, mitochondria and peroxisomes cooperate in the metabolism of lipids, which are very important fuels during oxidative metabolism (Schrader and Yoon, 2007). The connection between mitochondria and peroxisomes has been further strengthened in recent years by the discovery of vesicles that travel between the two organelles (Andrade-Navarro et al., 2009). Furthermore, a recent study demonstrated that PGC1α is a positive regulator of peroxisomal biogenesis (Bagattin et al., 2010), illustrating that mitochondria and peroxisomes share a common factor for their biogenesis.

Together, these data demonstrate that one central way by which PGC1α orchestrates changes in cellular metabolism is through organelle biogenesis (Fig. 1). Given that mitochondria are the main producers of ROS in cells, with peroxisomes also contributing, cells that display an induction of PGC1α in response to various physiological stimuli must adapt to an elevated generation of ROS mediated by the increased number of mitochondria and peroxisomes, or else suffer the deleterious consequences of increased oxidative metabolism. Next, we examine the effect of PGC1α on ROS metabolism.

ROS metabolism

Cells generate various forms of ROS, including superoxide and hydrogen peroxide, which if not properly removed, can attack DNA, lipids and proteins. To protect themselves from the potential deleterious effects of ROS, cells contain ROS-detoxifying enzymes in various compartments, notably mitochondria, peroxisomes and the cytoplasm. PGC1α has been shown to positively affect the expression of numerous ROS-detoxifying enzymes (St-Pierre et al., 2006; St-Pierre et al., 2003; Valle et al., 2005). The initial investigation supporting a role for PGC1α in ROS metabolism reported that ectopic expression of PGC1α in muscle cells increases the expression of superoxide dismutase 2 (SOD2), which removes superoxide, and glutathione peroxidase 1 (GPX1), which removes hydrogen peroxide (St-Pierre et al., 2003). Further studies extended the repertoire of ROS-detoxifying enzymes, whose expression is regulated by PGC1α, to include various mitochondrial, cytoplasmic as well as peroxisomal ROS-detoxifying enzymes (St-Pierre et al., 2006; Valle et al., 2005). These studies also revealed the physiological relevance of the ROS metabolic programme that is regulated by PGC1α. Ectopic

Box 1. Fat cell metabolism

White adipocytes are cells that contain a large fat droplet and few mitochondria. These cells are responsible for storing energy.

Brown adipocytes are cells that contain multiple small lipid droplets and numerous mitochondria. The main function of these cells is to generate heat mainly through uncoupling of mitochondrial respiration by the mitochondrial protein uncoupling protein 1 (UCP1). Uncoupled respiration refers to respiration that is not coupled to ATP production, thereby generating heat through the dissipation of the mitochondrial proton gradient. There is basal uncoupling as well as inducible uncoupling, notably through the UCPs (Jastroch et al., 2010). Coupled respiration refers to respiration that is coupled to ATP production. For mammals under standard conditions (i.e. awake but resting, not digesting food, at thermoneutrality and stress free), ~80% of mitochondrial respiration is coupled and 20% is uncoupled (Rolfe and Brown, 1997).

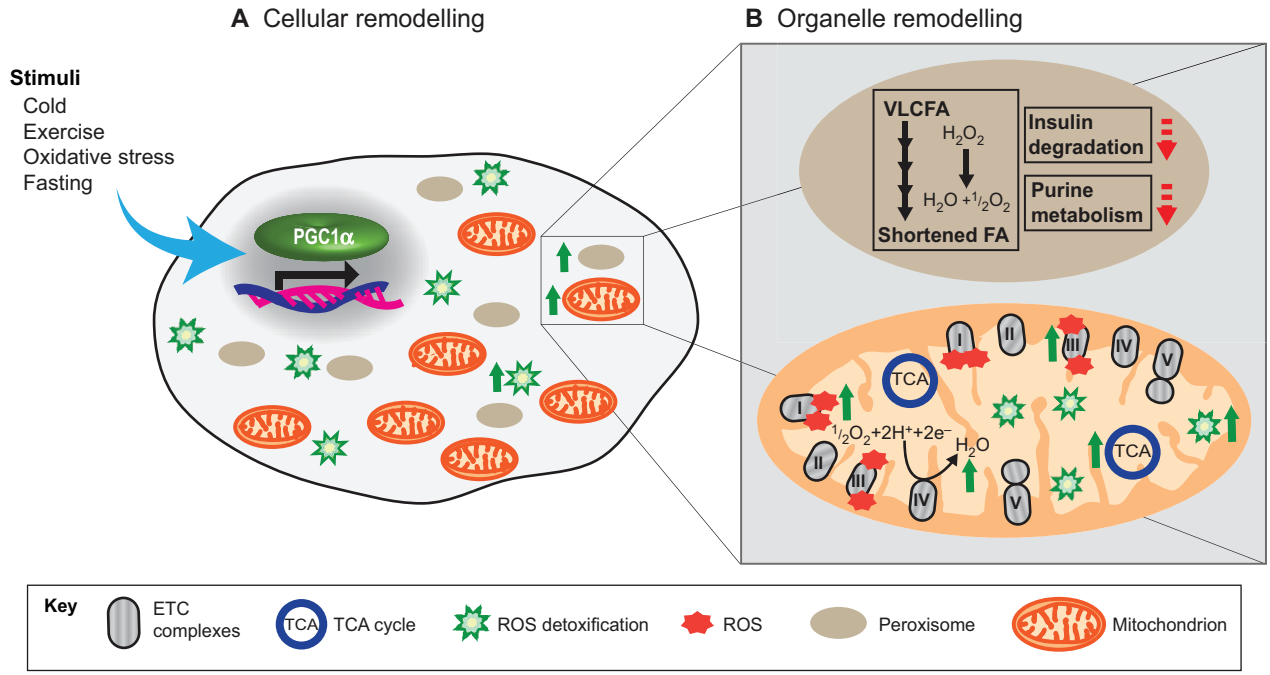


Fig. 1. Regulation of oxidative metabolism by PGC1α. Physiological stimuli induce expression of PGC1α leading to increased oxidative metabolism through cellular and organelle remodelling. (**A**) The impact of PGC1α on cellular remodelling: elevated PGC1α levels increase mitochondrial and peroxisomal biogenesis as well as ROS-detoxifying enzymes (illustrated by green arrows). (**B**) The impact of PGC1α on remodelling of peroxisomes and mitochondria. Elevated levels of PGC1α change the composition of peroxisomes, so that they might exhibit decreased insulin degradation and purine metabolism (dashed lines represent the proposed functional changes). Elevated levels of PGC1α alter the composition and functions of individual mitochondria. High levels of PGC1α result in elevated activity of TCA cycle enzymes, changes in the subunit composition of the various ETC complexes, increased content of ROS-detoxifying enzymes as well as elevated respiratory and ROS production capacities. The increases are illustrated by green arrows. VLCFA, very long chain fatty acid; FA, fatty acid.

expression of PGC1α in cells improves survival during conditions of oxidative stress (St-Pierre et al., 2006; Valle et al., 2005), whereas reduced expression of PGC1α sensitises cells to oxidative stress (St-Pierre et al., 2006). In support of these experiments, transgenic mice ectopically expressing PGC1α in muscle have a lower accumulation of oxidative damage with age compared with wild-type controls (Wenz et al., 2009), whereas the hippocampus and substantia nigra of *Ppargc1a*-null mice display enhanced sensitivity to oxidative stressors (St-Pierre et al., 2006).

Overall, the studies on the effect of PGC1α on oxidative metabolism reveal that it increases mitochondrial biogenesis in parallel to elevating the cellular ROS-detoxifying capacity, such that cells can benefit from increased respiration and ATP production without suffering from oxidative damage. For these reasons, PGC1α has been suggested to coordinate a 'clean energy programme' (Finkel, 2006), in which the generation of mitochondrial high energy metabolites (ATP) and removal of toxic derivatives (ROS) are coordinately regulated.

Organelle remodelling

As mentioned above, PGC1α positively regulates the expression of diverse mitochondrial, peroxisomal and ROS-detoxifying gene networks. The elevated expression of these genes in cells that ectopically express PGC1α has been mostly attributed to increased organelle biogenesis. Indeed, it is expected that if an enzyme is located in mitochondria and there is a proliferation of mitochondria, the cellular content of this enzyme will increase. However, there is growing evidence that PGC1α also modulates the intrinsic composition of mitochondria and peroxisomes. In other words, the new mitochondria and peroxisomes that are generated in the presence of PGC1α have different properties compared with the original organelles. These changes in the intrinsic properties of mitochondria and peroxisomes will have a central impact on cellular gene expression profiles and oxidative metabolism, as discussed below.

Mitochondrial respiratory capacity

The first study that investigated the impact of PGC1α on the respiratory capacity of individual mitochondria revealed that mitochondria isolated from muscle tissues of transgenic mice that ectopically express PGC1α (MCK–PGC1α Tg mice) have a higher capacity for substrate oxidation than those from wild-type controls (St-Pierre et al., 2003). Two recent studies performed comprehensive bioenergetics analyses of mitochondria isolated from muscle tissues of MCK–PGC1α Tg mice (Austin et al., 2011; Hoeks et al., 2012). Austin and collaborators (Austin et al., 2011) reported increased resting (state 4) and active (state 3) respiration on carbohydrates (malate and pyruvate) for muscle mitochondria from MCK–PGC1α Tg mice compared with those from wild-type controls (Box 2). Hoeks and collaborators (Hoeks et al., 2012) reported an intriguing substrate preference in that muscle mitochondria from MCK–PGC1α Tg mice display increased active respiration when they respire on lipid (palmitoyl CoA plus carnitine), but not on carbohydrate (in this case pyruvate). In addition, they observed no difference in resting respiration between muscle mitochondria from MCK–PGC1α Tg mice and wild-type controls when respiring on lipid or carbohydrate (Hoeks et al., 2012). This substrate preference has

Box 2. Respiration states in isolated mitochondria

In order to experimentally determine the respiratory capacity of mitochondria, they are incubated in the presence of various substrates and/or drugs. Common substrates include pyruvate (carbohydrate) and palmitoyl carnitine (lipid). Malate is often added to ensure that the citric acid cycle intermediates are not limiting. The obtained respiration measurements are normalised per milligram of mitochondrial protein. The most commonly assessed respiration states are state 3 and state 4 (Brand and Nicholls, 2011).

State 3: respiration rate in the presence of substrates and ADP. Mitochondria convert ADP into ATP by the ATP synthase. State 3 respiration represents the active state of mitochondria.

State 4: respiration rate after ADP has been converted into ATP. Often, the drug oligomycin is added to inhibit ATP synthase, so that the respiration is not linked to production of ATP. This respiration rate represents the basal state of mitochondria.

also been reported in mitochondria isolated from muscle tissues of mice containing an inducible PGC1α transgene (Wende et al., 2007). These mitochondria display increased resting and active respiration rates when respiring on palmitoyl carnitine, but not pyruvate (Wende et al., 2007). The absence of an elevated respiration in mitochondria isolated from muscle tissues that ectopically express PGC1α when they respire on pyruvate alone (Hoeks et al., 2012; Wende et al., 2007) could be owing to the fact that malate was not added in parallel to pyruvate, which could limit citric acid cycle intermediates (Box 2). Nevertheless, taken together, these studies illustrate that mitochondria isolated from muscle tissues that ectopically express PGC1α can display increased respiratory capacity. By contrast, mitochondria isolated from muscle tissues lacking PGC1α have diminished state 3 respiration rates when respiring on pyruvate or palmitoyl carnitine (Zechner et al., 2010).

The PGC1α-mediated changes in the respiratory capacity of mitochondria could be explained by alterations in either the levels or activity of various mitochondrial enzymes, or a combination of both. In support of this point, muscle mitochondria isolated from MCK–PGC1α Tg mice have elevated activity of citrate synthase, a citric acid cycle enzyme, and β-hydroxyacyl CoA dehydrogenase, a fatty acid oxidation enzyme (Hoeks et al., 2012). Furthermore, they have elevated amounts of several subunits of the various electron transport chain (ETC) complexes as well as ATP synthase (Austin et al., 2011; Wenz et al., 2009). These studies nicely demonstrate that PGC1α affects the content and activity of numerous proteins within mitochondria that are involved in diverse pathways, supporting the idea that PGC1α has a global effect on mitochondrial functions.

Finally, it emerges that PGC1α can control cellular mitochondrial respiration in two ways, first by changing the number of mitochondria in cells, and second by altering the respiratory capacity of individual mitochondria.

Mitochondrial ROS generation capacity

The respiratory and ROS-generating capacities of mitochondria are inextricably linked to the activity of the ETC. The main sites of ROS production by the electron transport chain are complexes I and III of the ETC. The topology of ROS for these complexes is such that complex I generates ROS on the matrix side of the membrane whereas complex III generates ROS on both the matrix and cytoplasmic sides of the membrane (see Box 3) (Brand, 2010). Only recently, functional studies were performed to quantitate the impact of PGC1α on the capacity of mitochondria to generate ROS (Austin et al., 2011; Hoeks et al.,

Box 3. Assays to measure ROS production in isolated mitochondria

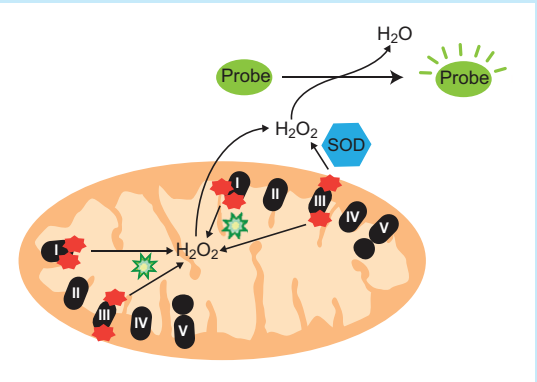
During mitochondrial respiration, electrons can escape the mitochondrial electron transport chain and react with oxygen to form superoxide anions.

Fluorometric methods

These methods indirectly measure superoxide production. The basis of this technique is the reaction of hydrogen peroxide (H_2O_2) with horseradish peroxidase and a substrate (e.g. Amplex red) that becomes fluorescent. Isolated mitochondria are incubated in the presence of substrates to activate respiration. Superoxide that is generated in the mitochondrial matrix cannot cross the mitochondrial membrane and is converted by SOD2 into H_2O_2, which then diffuses out of the mitochondria into the assay medium and is detected by the assay (see figure). Superoxide generated on the cytoplasmic face of the mitochondrial membrane can be quantified by adding exogenous SOD in the assay medium, which converts it into H_2O_2. Importantly, this method permits the quantification of ROS that originate from both the matrix and cytoplasmic face of the mitochondrial membrane. Furthermore, this assay is used to determine the topology of superoxide production by mitochondria, that is, determining the side of the mitochondrial membrane on which superoxide is generated. If the rate of H_2O_2 production increases during the assay upon addition of exogenous SOD, it means that superoxide is released on the cytoplasmic face of the membrane. If the rate of H_2O_2 production is insensitive to exogenous SOD, it means that superoxide is coming from the matrix.

Electron spin resonance

This method directly measures molecules with unpaired electrons, such as the superoxide anion, by using spin traps. Isolated mitochondria are incubated in the presence of substrates to activate respiration. Superoxide generated on the cytoplasmic face of the mitochondrial membrane can be directly detected and quantified. Superoxide that is generated in the mitochondrial matrix cannot cross the mitochondrial membrane, and hence, is not readily detected. However, new spin traps that accumulate inside mitochondria have been developed and might prove useful in assessing ROS generated in the mitochondrial matrix (Spasojević, 2011).



2012). Mitochondria isolated from muscle tissues of MCK–PGC1α Tg mice display an increased capacity to generate ROS at complexes I and III of the ETC, in agreement with their increased respiratory capacity (Austin et al., 2011). Importantly, the fraction of electrons that escape the ETC to generate ROS per unit of respiration is unaltered by PGC1α, indicating a tight association between respiration and production of ROS at the mitochondrial level. Also, PGC1α does not affect the topology of ROS production by complexes I and III (Austin et al., 2011; Brand, 2010). The second study on the impact of PGC1α on mitochondrial production of ROS using the same PGC1α transgenic mouse model found that PGC1α does not impact the capacity of mitochondria to generate ROS (Hoeks et al., 2012). However, that study provides only a partial assessment of the mitochondrial ROS production sites because the authors used electron spin resonance (ESR) with a specific spin trap that can only detect ROS generated on the cytoplasmic face of the mitochondrial membrane (see Box 3). The study by Austin and colleagues (Austin et al., 2011) used fluorescent probes that permit the quantification of ROS production from both the matrix and the cytoplasmic face of the mitochondrial membrane, thereby providing a greater coverage of the ROS-production sites (see Box 3). These differences in experimental approaches to detect and quantify mitochondrial ROS production are likely to be the main reason for the variation in the reported results.

The elevated capacity of mitochondria isolated from muscle tissues of MCK–PGC1α Tg mice to generate ROS could be explained by a higher content of subunits from complexes I and III (Austin et al., 2011; Wenz et al., 2009). Another key factor that could contribute to the greater release of ROS from these mitochondria is their elevated content of SOD2 (Wenz et al., 2009). Indeed, the most common assay used to measure production of ROS by mitochondria is to quantify the amount of H_2O_2 they release (Box 3). This method was used in our study (Austin et al., 2011), in which muscle mitochondria from MCK–PGC1α Tg mice showed an increased capacity to produce ROS. The elevated content of SOD2 in muscle mitochondria from MCK–PGC1α Tg mice will increase the dismutation rate of superoxide into H_2O_2 inside the mitochondrial matrix, causing the release of elevated levels of H_2O_2 into the medium. Importantly, however, in a cellular context, this elevated release of H_2O_2 by mitochondria will be removed by various cytoplasmic ROS-detoxifying enzymes, whose expression is upregulated by PGC1α (St-Pierre et al., 2006). In fact, it appears that the increase in ROS detoxification mediated by PGC1α is greater than the increase in mitochondrial production of ROS mediated by PGC1α, indicating that PGC1α could be associated with reduced steady-state levels of ROS in cells. In support of this hypothesis, cells that ectopically express PGC1α display reduced levels of ROS, whereas PGC1α null cells show increased ROS content (St-Pierre et al., 2006; Valle et al., 2005). Furthermore, muscle tissues from PGC1α transgenic mice display reduced accumulation of oxidative damage with age compared with wild-type controls, illustrating that globally PGC1α protects against oxidative damage (Wenz et al., 2009).

Collectively, the studies exploring the impact of PGC1α on the respiration and ROS-production capacities of mitochondria highlight that PGC1α causes substantial remodelling of mitochondrial composition and functions. This remodelling of mitochondria will work in concert with PGC1α-mediated biogenesis of mitochondria, as well as with the increase in content of ROS-detoxifying enzymes, to establish a new state of cellular oxidative metabolism (Fig. 1).

Possible effect of PGC1α on the composition of peroxisomes

The only evidence of peroxisomal remodelling by PGC1α is on the basis of gene expression data (Bagattin et al., 2010). Ectopic expression of PGC1α in various cell lines increases the expression of some peroxisomal enzymes, such as those involved in fatty acid oxidation, whereas the expression of other enzymes is unaffected, for example the insulin-degrading enzyme involved in insulin degradation, or even reduced, such as the xanthine dehydrogenase involved in purine metabolism (Bagattin et al., 2010). Given that PGC1α regulates peroxisomal biogenesis (Fig. 1) (Bagattin et al., 2010), these data suggest that the new peroxisomes generated in the presence of PGC1α differ in their intrinsic composition, so that they would be specialised in specific metabolic functions, notably fatty acid oxidation (Fig. 1). However, no functional study has been performed on peroxisomes isolated from tissues or cells that ectopically express PGC1α to determine the impact of these changes in gene expression on peroxisomal metabolism. Furthermore, it remains to be elucidated how the peroxisomal remodelling that is elicited by PGC1α works in concert with mitochondrial remodelling as well as with organelle biogenesis to regulate global cellular energy metabolism.

Mechanisms of cellular and organelle remodelling

Mitochondria consist of proteins that are encoded both by nuclear and mitochondrial genes. The mammalian mitochondrial genome encodes ETC subunits, ribosomal RNAs (rRNAs) and several transfer RNAs (tRNAs), all of which are localised to the mitochondria (Scarpulla, 2008). The mitochondrial proteins that are encoded by nuclear genes are imported into the mitochondria, and the regulation of global mitochondrial metabolism implicates a coordinated control of the expression of proteins encoded by the mitochondrial and nuclear genomes. Nuclear respiratory factor 1 (NRF1), nuclear respiratory factor 2 [(NRF2), also known as GA-binding protein (GABPA)], and the oestrogen related receptors (ERRs) are important transcription factors that regulate the expression of mitochondrial genes encoded in the nucleus (Giguère, 2008; Handschin and Spiegelman, 2006). PGC1α has been shown to increase the expression and/or coactivate these transcription factors to regulate the expression of genes involved in mitochondrial metabolism (Giguère, 2008; Handschin and Spiegelman, 2006). Notably, PGC1α increases the expression and acts as a coactivator for NRF1 to regulate the expression of transcription factor A, mitochondrial (TFAM), which is primarily responsible for the transcription and replication of mitochondrial genes from the mitochondrial genome (Wu et al., 1999).

Recently, evidence has emerged that PGC1α itself might also be localised to mitochondria where it would interact with TFAM (Aquilano et al., 2010; Safdar et al., 2011). The exact function of PGC1α inside mitochondria remains to be fully elucidated. Nevertheless, it is tempting to speculate that PGC1α is a proximal factor coordinating the expression of mitochondrial genes that are encoded by both nuclear and mitochondrial genomes. This way, PGC1α could provide a unified control over mitochondrial metabolism.

Finally, it is important to appreciate that although PGC1α can regulate various mitochondrial functions and other metabolic programmes, they do not necessarily need simultaneous

Table 1. Post-translational modifications of PGC1α and their biological consequences

Post-translational modifications	Biological outcome	References
Phosphorylation		
AKT	Inhibition of activity affecting the expression of gluconeogenic and lipid oxidation genes	(Li et al., 2007)
AMPK	Increase in activity and regulation of genes involved in mitochondrial functions and glucose metabolism	(Jäger et al., 2007)
CLK2	Decrease in expression of gluconeogenic genes	(Rodgers et al., 2010)
GSK3B	In combination with phosphorylation of p38 MAPK, GSK3B designates PGC1α for proteasomal degradation	(Olson et al., 2008)
p38 MAPK	Increase in activity leading to expression of mitochondrial genes	(Puigserver et al., 2001)
S6 kinase	Decrease in the induction of gluconeogenic genes while maintaining the expression of mitochondrial genes	(Lustig et al., 2011)
Acetylation		
GCN5	Inhibition of transcriptional activity	(Lerin et al., 2006)
Deacetylation		
SIRT1	Increase in expression of gluconeogenic genes	(Rodgers et al., 2005)
SUMOylation		
SUMO1	Decrease in transcriptional activity	(Rytinki and Palvimo, 2009)
Methylation		
PRMT1	Increase in activity leading to expression of mitochondrial biogenesis genes	(Teyssier et al., 2005)

regulation under a given physiological condition. In this context, post-translational modifications might impart specificity to the metabolic functions that are mediated by PGC1α. Indeed, the activity of PGC1α is controlled by several post-translational modifications (Table 1), including phosphorylation (Jäger et al., 2007; Li et al., 2007; Lustig et al., 2011; Olson et al., 2008; Puigserver et al., 2001; Rodgers et al., 2010), acetylation (Lerin et al., 2006), deacetylation (Rodgers et al., 2005), small ubiquitin-like modifier (SUMO)-ylation (Rytinki and Palvimo, 2009) as well as methylation (Teyssier et al., 2005). Deacetylation and methylation of PGC1α increase its activity, whereas acetylation and sumoylation negatively impact its function. Phosphorylation of PGC1α can increase or decrease its activity depending on the phosphorylating kinase. Importantly, these post-translational modifications could confer specificity to PGC1α for specific target genes. In support of this hypothesis, cytokine-mediated phosphorylation of PGC1α by p38 mitogen-activated protein kinase (p38 MAPK) robustly increases the expression of uncoupling protein 3 (UCP3) (Puigserver et al., 2001). Also, a recent study has shown that phosphorylation of PGC1α by S6 kinase decreases its capacity to induce the expression of gluconeogenic genes in the liver, while preserving its ability to regulate the expression of mitochondrial genes (Lustig et al., 2011). Collectively, these studies elegantly demonstrate that these post-translational modifications can be important modulators of PGC1α activity.

The functions of PGC1α in pathological conditions

Given the central importance of mitochondria in energy homeostasis, it is perhaps not surprising that PGC1α has been implicated in many pathological conditions, such as diabetes and heart disease (Handschin and Spiegelman, 2006). Here, we focus on conditions that have been associated with mitochondrial dysfunctions for a long time, namely ageing and neurodegenerative disorders (see Fig. 2).

Ageing

Ageing is a complex and heterogeneous condition that encompasses several changes that are occurring over time. Indeed, a failure to meet energetic demands, dysfunctions in several physiological processes and increased stress contribute to the condition of ageing. Mitochondria have been at the core of ageing theories for a long time, owing to the fact that mitochondrial functions generally decline during ageing (Quinlan et al., 2011). For example, mitochondrial functions, along with the expression of

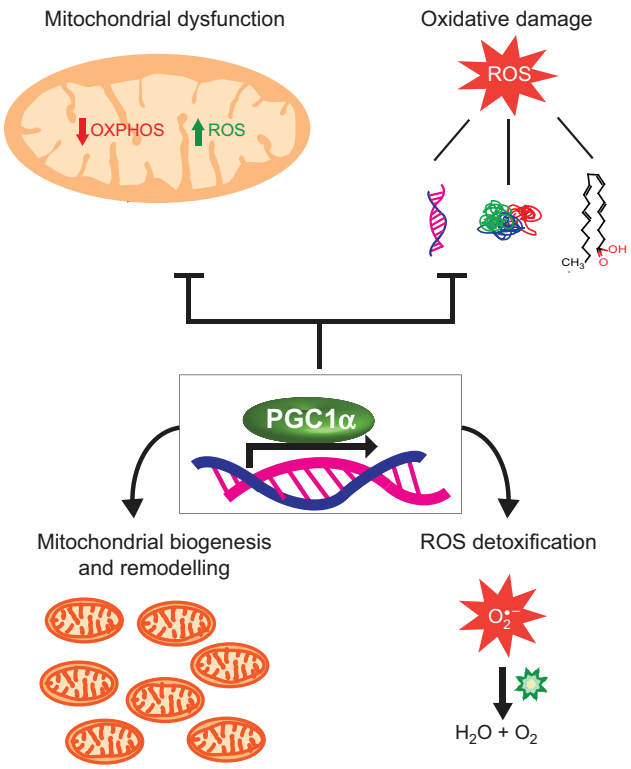


Fig. 2. Impact of PGC1α in ageing and neurodegenerative disorders. For a long time, ageing and neurodegenerative disorders have been associated with mitochondrial dysfunctions, such as decreased respiratory capacity and increased production of ROS, as well as oxidative damage. Elevated PGC1α levels ameliorate the phenotype of numerous mouse models of these pathological conditions, probably by increasing mitochondrial metabolism and ROS detoxification.

PGC1α and PGC1β, are reduced during telomere dysfunction, a condition associated with ageing (Sahin et al., 2011).

A prominent theory in ageing research is the 'free radical theory of ageing', which states that increased production of ROS by mitochondria and the resulting oxidative damage are important determining factors in ageing (Quinlan et al., 2011). Specifically, mutations to the mitochondrial DNA (mtDNA) are thought to have a central role in the age-associated decline of mitochondrial functions. The mitochondrial polymerase γ (POLG) mouse model (Kujoth et al., 2005; Trifunovic et al., 2004) has been instrumental in highlighting the importance of mitochondria in ageing. POLG is a DNA polymerase that is localised to the mitochondria, where it replicates mtDNA and is also involved in DNA repair. Mice with mutant POLG have increased mtDNA mutations and display alopecia (hair loss), osteoporosis and cardiomyopathy, all conditions associated with ageing (Kujoth et al., 2005; Trifunovic et al., 2004). In order to test whether increasing mitochondrial metabolism through PGC1α expression could ameliorate the phenotype of POLG mice, these mice were crossed with MCK–PGC1α Tg mice (Lin et al., 2002b). Mice that express both mutant POLG and PGC1α have increased mitochondrial activity in heart and skeletal muscle, which leads to improved functions of these tissues compared with mice expressing mutant POLG alone (Dillon et al., 2012). These data highlight that elevated mitochondrial functions can have beneficial effects in ageing that are independent of the presence of mutations to the mtDNA. Importantly though, elevated expression of PGC1α in muscle tissues throughout lifespan has been shown to delay the onset of some conditions associated with ageing such as sarcopenia (loss of muscle mass) (Wenz et al., 2009). These improved functions were attributed to a lower decrease in mitochondrial functions with age, as well as with reduced accumulation of oxidative damage (Wenz et al., 2009). Taken together, these studies illustrate that PGC1α can delay the onset of conditions that are associated with ageing and help attenuate the impact of oxidative damage once it is present.

Neurodegenerative disorders

The first evidence of the involvement of PGC1α in neurodegenerative disorders came from the *Ppargc1a*-null mice (Leone et al., 2005; Lin et al., 2004), which display neurodegeneration associated with hyperactivity reminiscent of symptoms of Huntington's disease (HD) (Lin et al., 2004). Neurodegeneration in HD is characterised by the production of the mutant huntingtin (HTT) protein. HD is associated with reduced mitochondrial functions, and HD patients, as well as HD mice, show reduced expression of several mitochondrial genes and of PGC1α (Chaturvedi et al., 2009; Chaturvedi et al., 2010; Cui et al., 2006; Weydt et al., 2006). Moreover, it has been shown that mutant HTT associates with the PGC1α promoter and limits its expression, thus providing a further mechanistic link between HD and PGC1α (Cui et al., 2006). Finally, breeding of HD mice with *Ppargc1a*-null mice exacerbates their neurodegeneration, whereas ectopic expression of PGC1α in the striatum of transgenic HD mice protects these neurons from neuronal atrophy (Cui et al., 2006).

Several studies also support a protective role for PGC1α in Parkinson's disease (PD). PD is characterised by the loss of dopaminergic neurons in the substantia nigra and the presence of inclusions, referred to as Lewy bodies, which contain α-synuclein and ubiquitin (Lin and Beal, 2006). The expression of numerous PGC1α target genes, such as those of the respiratory chain, is decreased in PD patients (Zheng et al., 2010). In support of this observation, *Ppargc1a*-null mice are more sensitive to MPTP, a drug used to model PD in experimental studies (St-Pierre et al., 2006). Furthermore, PGC1α protects against neuronal loss in cell culture models of PD (Wareski et al., 2009; Zheng et al., 2010). Recently, it has been shown that PARIS, a novel substrate of the E3 ubiquitin ligase Parkin, which is often mutated in PD (Lin and Beal, 2006), represses the expression of PGC1α (Shin et al., 2011). Stereotaxic injection of PARIS in the substantia nigra of mice leads to neuronal loss that can be attenuated by co-injection with PGC1α (Shin et al., 2011). However, prolonged ectopic expression of PGC1α is unable to protect against neuronal loss *in vivo* mediated by α-synuclein (Ciron et al., 2012), which might be explained by a potential dose-dependent effect of PGC1α in neurons, with modest expression providing beneficial effects, and moderate to substantial overexpression having deleterious consequences.

PGC1α has also been implicated in Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy. Expression of PGC1α is reduced in AD patients and in the transgenic 2576 mouse model of AD (Gong et al., 2010; Qin et al., 2009; Sheng et al., 2012). Importantly, ectopic expression of PGC1α in cell models of AD ameliorates their phenotype (Qin et al., 2009; Sheng et al., 2012). In ALS, it has been shown that PGC1α improves the overall phenotype of various mouse models of ALS (Da Cruz et al., 2012; Liang et al., 2011; Zhao et al., 2011). Lastly, PGC1α has been shown to regulate the expression of neuromuscular junction genes, such as utrophin and laminin, as well as decrease damage to muscle tissue in a mouse model of Duchenne muscular dystrophy (Handschin et al., 2007). Overall, these data highlight a potential protective role for PGC1α in different neurodegenerative conditions.

Conclusions and future perspectives

In this Commentary, we have highlighted that PGC1α orchestrates global aerobic metabolism by controlling both organelle biogenesis and remodelling. Studies of the impact of PGC1α on cellular metabolism have been ongoing for some time. However, only recently a focus has emerged on integrative studies that examine the impact of PGC1α on the composition and function of organelles, such as mitochondria and peroxisomes. It will be of great importance to understand how these PGC1α-mediated changes in organelles contribute to the cellular adjustments in metabolism that occur during physiological or pathological conditions (Fig. 2). Also, the effect of the other members of the PGC family, PGC1β and PRC, on organelle remodelling remains largely unexplored. Furthermore, much work is still needed to elucidate the physiological consequences of the post-translational modifications of PGC1α and the underlying molecular mechanisms.

Finally, we discussed the role of PGC1α in ageing and neurodegenerative disorders, conditions that are associated with altered mitochondrial metabolism. In general, increased PGC1α levels appear to improve the phenotype of various murine models of these conditions, possibly by improving mitochondrial functions and ROS detoxification. However, importantly, even though PGC1α is a central regulator of metabolism, its beneficial impact in ageing and neurodegeneration might be independent of its effect on metabolism. The potential deleterious consequences of large increases in PGC1α will need to be considered in the development of drugs or therapeutic interventions where the aim is to elevate PGC1α levels. Indeed, the beneficial therapeutic

window for PGC1α could be narrow, and achieving precise induction levels might present a substantial clinical challenge. Nevertheless, it is the hope that discoveries on PGC1α regulation and functions will eventually translate into benefits for patients.

Acknowledgements

Disclosure of Potential Conflicts of Interest: no potential conflicts of interest are disclosed.

Funding

This work is supported by a National Development Scholarship from the Ministry of Education and Human Resource Management, Barbados (NDS2010/05 to S.A.); and grants from the Canadian Institutes of Health Research [grant number MOP-106603 to J.St-P.] and Terry Fox Foundation [grant number TFF-116128 to J.St-P.]. J.St-P. is a FRSQ research scholar.

References

Andersson, U. and Scarpulla, R. C. (2001). Pgc-1-related coactivator, a novel, serum-inducible coactivator of nuclear respiratory factor 1-dependent transcription in mammalian cells. *Mol. Cell. Biol.* **21**, 3738-3749.

Andrade-Navarro, M. A., Sanchez-Pulido, L. and McBride, H. M. (2009). Mitochondrial vesicles: an ancient process providing new links to peroxisomes. *Curr. Opin. Cell Biol.* **21**, 560-567.

Aquilano, K., Vigilanza, P., Baldelli, S., Pagliei, B., Rotilio, G. and Ciriolo, M. R. (2010). Peroxisome proliferator-activated receptor gamma co-activator 1alpha (PGC-1alpha) and sirtuin 1 (SIRT1) reside in mitochondria: possible direct function in mitochondrial biogenesis. *J. Biol. Chem.* **285**, 21590-21599.

Arany, Z., Lebrasseur, N., Morris, C., Smith, E., Yang, W., Ma, Y., Chin, S. and Spiegelman, B. M. (2007). The transcriptional coactivator PGC-1beta drives the formation of oxidative type IIX fibers in skeletal muscle. *Cell Metab.* **5**, 35-46.

Austin, S., Klimcakova, E. and St-Pierre, J. (2011). Impact of PGC-1α on the topology and rate of superoxide production by the mitochondrial electron transport chain. *Free Radic. Biol. Med.* **51**, 2243-2248.

Bagattin, A., Hugendubler, L. and Mueller, E. (2010). Transcriptional coactivator PGC-1alpha promotes peroxisomal remodeling and biogenesis. *Proc. Natl. Acad. Sci. USA* **107**, 20376-20381.

Brand, M. D. (2010). The sites and topology of mitochondrial superoxide production. *Exp. Gerontol.* **45**, 466-472.

Brand, M. D. and Nicholls, D. G. (2011). Assessing mitochondrial dysfunction in cells. *Biochem. J.* **435**, 297-312.

Chaturvedi, R. K., Adhihetty, P., Shukla, S., Hennessy, T., Calingasan, N., Yang, L., Starkov, A., Kiaei, M., Cannella, M., Sassone, J. et al. (2009). Impaired PGC-1alpha function in muscle in Huntington's disease. *Hum. Mol. Genet.* **18**, 3048-3065.

Chaturvedi, R. K., Calingasan, N. Y., Yang, L., Hennessey, T., Johri, A. and Beal, M. F. (2010). Impairment of PGC-1alpha expression, neuropathology and hepatic steatosis in a transgenic mouse model of Huntington's disease following chronic energy deprivation. *Hum. Mol. Genet.* **19**, 3190-3205.

Ciron, C., Lengacher, S., Dusonchet, J., Aebischer, P. and Schneider, B. L. (2012). Sustained expression of PGC-1α in the rat nigrostriatal system selectively impairs dopaminergic function. *Hum. Mol. Genet.* **21**, 1861-1876.

Cui, L., Jeong, H., Borovecki, F., Parkhurst, C. N., Tanese, N. and Krainc, D. (2006). Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. *Cell* **127**, 59-69.

Da Cruz, S., Parone, P. A., Lopes, V. S., Lillo, C., McAlonis-Downes, M., Lee, S. K., Vetto, A. P., Petrosyan, S., Marsala, M., Murphy, A. N. et al. (2012). Elevated PGC-1α activity sustains mitochondrial biogenesis and muscle function without extending survival in a mouse model of inherited ALS. *Cell Metab.* **15**, 778-786.

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

Finkel, T. (2006). Cell biology: a clean energy programme. *Nature* **444**, 151-152.

Giguère, V. (2008). Transcriptional control of energy homeostasis by the estrogen-related receptors. *Endocr. Rev.* **29**, 677-696.

Gong, B., Chen, F., Pan, Y., Arrieta-Cruz, I., Yoshida, Y., Haroutunian, V. and Pasinetti, G. M. (2010). SCFFbx2-E3-ligase-mediated degradation of BACE1 attenuates Alzheimer's disease amyloidosis and improves synaptic function. *Aging Cell* **9**, 1018-1031.

Handschin, C. and Spiegelman, B. M. (2006). Peroxisome proliferator-activated receptor gamma coactivator 1 coactivators, energy homeostasis, and metabolism. *Endocr. Rev.* **27**, 728-735.

Handschin, C., Kobayashi, Y. M., Chin, S., Seale, P., Campbell, K. P. and Spiegelman, B. M. (2007). PGC-1alpha regulates the neuromuscular junction program and ameliorates Duchenne muscular dystrophy. *Genes Dev.* **21**, 770-783.

Hoeks, J., Arany, Z., Phielix, E., Moonen-Kornips, E., Hesselink, M. K. and Schrauwen, P. (2012). Enhanced lipid-but not carbohydrate-supported mitochondrial respiration in skeletal muscle of PGC-1α overexpressing mice. *J. Cell. Physiol.* **227**, 1026-1033.

Ishii, K. A., Fumoto, T., Iwai, K., Takeshita, S., Ito, M., Shimohata, N., Aburatani, H., Taketani, S., Lelliott, C. J., Vidal-Puig, A. et al. (2009). Coordination of PGC-1beta and iron uptake in mitochondrial biogenesis and osteoclast activation. *Nat. Med.* **15**, 259-266.

Jäger, S., Handschin, C., St-Pierre, J. and Spiegelman, B. M. (2007). AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. *Proc. Natl. Acad. Sci. USA* **104**, 12017-12022.

Jastroch, M., Divakaruni, A. S., Mookerjee, S., Treberg, J. R. and Brand, M. D. (2010). Mitochondrial proton and electron leaks. *Essays Biochem.* **47**, 53-67.

Kressler, D., Schreiber, S. N., Knutti, D. and Kralli, A. (2002). The PGC-1-related protein PERC is a selective coactivator of estrogen receptor alpha. *J. Biol. Chem.* **277**, 13918-13925.

Kujoth, G. C., Hiona, A., Pugh, T. D., Someya, S., Panzer, K., Wohlgemuth, S. E., Hofer, T., Seo, A. Y., Sullivan, R., Jobling, W. A. et al. (2005). Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science* **309**, 481-484.

Lehman, J. J., Barger, P. M., Kovacs, A., Saffitz, J. E., Medeiros, D. M. and Kelly, D. P. (2000). Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. *J. Clin. Invest.* **106**, 847-856.

Leone, T. C., Lehman, J. J., Finck, B. N., Schaeffer, P. J., Wende, A. R., Boudina, S., Courtois, M., Wozniak, D. F., Sambandam, N., Bernal-Mizrachi, C. et al. (2005). PGC-1alpha deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. *PLoS Biol.* **3**, e101.

Lerin, C., Rodgers, J. T., Kalume, D. E., Kim, S. H., Pandey, A. and Puigserver, P. (2006). GCN5 acetyltransferase complex controls glucose metabolism through transcriptional repression of PGC-1alpha. *Cell Metab.* **3**, 429-438.

Li, X., Monks, B., Ge, Q. and Birnbaum, M. J. (2007). Akt/PKB regulates hepatic metabolism by directly inhibiting PGC-1alpha transcription coactivator. *Nature* **447**, 1012-1016.

Liang, H., Ward, W. F., Jang, Y. C., Bhattacharya, A., Bokov, A. F., Li, Y., Jernigan, A., Richardson, A. and Van Remmen, H. (2011). PGC-1α protects neurons and alters disease progression in an amyotrophic lateral sclerosis mouse model. *Muscle Nerve* **44**, 947-956.

Lin, M. T. and Beal, M. F. (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* **443**, 787-795.

Lin, J., Puigserver, P., Donovan, J., Tarr, P. and Spiegelman, B. M. (2002a). Peroxisome proliferator-activated receptor gamma coactivator 1beta (PGC-1beta), a novel PGC-1-related transcription coactivator associated with host cell factor. *J. Biol. Chem.* **277**, 1645-1648.

Lin, J., Wu, H., Tarr, P. T., Zhang, C. Y., Wu, Z., Boss, O., Michael, L. F., Puigserver, P., Isotani, E., Olson, E. N. et al. (2002b). Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature* **418**, 797-801.

Lin, J., Wu, P. H., Tarr, P. T., Lindenberg, K. S., St-Pierre, J., Zhang, C. Y., Mootha, V. K., Jäger, S., Vianna, C. R., Reznick, R. M. et al. (2004). Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. *Cell* **119**, 121-135.

Lin, J., Yang, R., Tarr, P. T., Wu, P.-H., Handschin, C., Li, S., Yang, W., Pei, L., Uldry, M., Tontonoz, P. et al. (2005). Hyperlipidemic effects of dietary saturated fats mediated through PGC-1beta coactivation of SREBP. *Cell* **120**, 261-273.

Lustig, Y., Ruas, J. L., Estall, J. L., Lo, J. C., Devarakonda, S., Laznik, D., Choi, J. H., Ono, H., Olsen, J. V. and Spiegelman, B. M. (2011). Separation of the gluconeogenic and mitochondrial functions of PGC-1alpha through S6 kinase. *Genes Dev.* **25**, 1232-1244.

Olson, B. L., Hock, M. B., Ekholm-Reed, S., Wohlschlegel, J. A., Dev, K. K., Kralli, A. and Reed, S. I. (2008). SCFCdc4 acts antagonistically to the PGC-1alpha transcriptional coactivator by targeting it for ubiquitin-mediated proteolysis. *Genes Dev.* **22**, 252-264.

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

Puigserver, P., Rhee, J., Lin, J., Wu, Z., Yoon, J. C., Zhang, C. Y., Krauss, S., Mootha, V. K., Lowell, B. B. and Spiegelman, B. M. (2001). Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. *Mol. Cell* **8**, 971-982.

Qin, W., Haroutunian, V., Katsel, P., Cardozo, C. P., Ho, L., Buxbaum, J. D. and Pasinetti, G. M. (2009). PGC-1alpha expression decreases in the Alzheimer disease brain as a function of dementia. *Arch. Neurol.* **66**, 352-361.

Quinlan, C. L., Treberg, J. R. and Brand, M. D. (2011). Mechanisms of mitochondrial free radical production and their relationship to the aging process. In *Handbook of the Biology of Aging (Seventh Edition)* (ed. J. M. Edward and N. A. Steven), pp. 47-61. San Diego, CA: Academic Press.

Rodgers, J. T., Lerin, C., Haas, W., Gygi, S. P., Spiegelman, B. M. and Puigserver, P. (2005). Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. *Nature* **434**, 113-118.

Rodgers, J. T., Haas, W., Gygi, S. P. and Puigserver, P. (2010). Cdc2-like kinase 2 is an insulin-regulated suppressor of hepatic gluconeogenesis. *Cell Metab.* **11**, 23-34.

Rolfe, D. F. and Brown, G. C. (1997). Cellular energy utilization and molecular origin of standard metabolic rate in mammals. *Physiol. Rev.* **77**, 731-758.

Rytinki, M. M. and Palvimo, J. J. (2009). SUMOylation attenuates the function of PGC-1alpha. *J. Biol. Chem.* **284**, 26184-26193.

Safdar, A., Little, J. P., Stokl, A. J., Hettinga, B. P., Akhtar, M. and Tarnopolsky, M. A. (2011). Exercise increases mitochondrial PGC-1alpha content and promotes nuclear-mitochondrial cross-talk to coordinate mitochondrial biogenesis. *J. Biol. Chem.* **286**, 10605-10617.

Sahin, E., Colla, S., Liesa, M., Moslehi, J., Müller, F. L., Guo, M., Cooper, M., Kotton, D., Fabian, A. J., Walkey, C. et al. (2011). Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature* **470**, 359-365.

Scarpulla, R. C. (2008). Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiol. Rev.* **88**, 611-638.

Schrader, M. and Yoon, Y. (2007). Mitochondria and peroxisomes: are the 'big brother' and the 'little sister' closer than assumed? *Bioessays* **29**, 1105-1114.

Sheng, B., Wang, X., Su, B., Lee, H. G., Casadesus, G., Perry, G. and Zhu, X. (2012). Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. *J. Neurochem.* **120**, 419-429.

Shin, J.-H., Ko, H. S., Kang, H., Lee, Y., Lee, Y.-I., Pletinkova, O., Troconso, J. C., Dawson, V. L. and Dawson, T. M. (2011). PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. *Cell* **144**, 689-702.

Sonoda, J., Laganière, J., Mehl, I. R., Barish, G. D., Chong, L.-W., Li, X., Scheffler, I. E., Mock, D. C., Bataille, A. R., Robert, F. et al. (2007). Nuclear receptor ERR alpha and coactivator PGC-1 beta are effectors of IFN-gamma-induced host defense. *Genes Dev.* **21**, 1909-1920.

Spasojević, I. (2011). Free radicals and antioxidants at a glance using EPR spectroscopy. *Crit. Rev. Clin. Lab. Sci.* **48**, 114-142.

St-Pierre, J., Lin, J., Krauss, S., Tarr, P. T., Yang, R., Newgard, C. B. and Spiegelman, B. M. (2003). Bioenergetic analysis of peroxisome proliferator-activated receptor gamma coactivators 1alpha and 1beta (PGC-1alpha and PGC-1beta) in muscle cells. *J. Biol. Chem.* **278**, 26597-26603.

St-Pierre, J., Drori, S., Uldry, M., Silvaggi, J. M., Rhee, J., Jäger, S., Handschin, C., Zheng, K., Lin, J., Yang, W. et al. (2006). Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell* **127**, 397-408.

Teyssier, C., Ma, H., Emter, R., Kralli, A. and Stallcup, M. R. (2005). Activation of nuclear receptor coactivator PGC-1alpha by arginine methylation. *Genes Dev.* **19**, 1466-1473.

Trifunovic, A., Wredenberg, A., Falkenberg, M., Spelbrink, J. N., Rovio, A. T., Bruder, C. E., Bohlooly-Y, M., Gidlöf, S., Oldfors, A., Wibom, R. et al. (2004). Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* **429**, 417-423.

Valle, I., Alvarez-Barrientos, A., Arza, E., Lamas, S. and Monsalve, M. (2005). PGC-1alpha regulates the mitochondrial antioxidant defense system in vascular endothelial cells. *Cardiovasc. Res.* **66**, 562-573.

Vercauteren, K., Gleyzer, N. and Scarpulla, R. C. (2009). Short hairpin RNA-mediated silencing of PRC (PGC-1-related coactivator) results in a severe respiratory chain deficiency associated with the proliferation of aberrant mitochondria. *J. Biol. Chem.* **284**, 2307-2319.

Wareski, P., Vaarmann, A., Choubey, V., Safiulina, D., Liiv, J., Kuum, M. and Kaasik, A. (2009). PGC-1alpha and PGC-1beta regulate mitochondrial density in neurons. *J. Biol. Chem.* **284**, 21379-21385.

Wende, A. R., Schaeffer, P. J., Parker, G. J., Zechner, C., Han, D. H., Chen, M. M., Hancock, C. R., Lehman, J. J., Huss, J. M., McClain, D. A. et al. (2007). A role for the transcriptional coactivator PGC-1alpha in muscle refueling. *J. Biol. Chem.* **282**, 36642-36651.

Wenz, T., Rossi, S. G., Rotundo, R. L., Spiegelman, B. M. and Moraes, C. T. (2009). Increased muscle PGC-1alpha expression protects from sarcopenia and metabolic disease during aging. *Proc. Natl. Acad. Sci. USA* **106**, 20405-20410.

Weydt, P., Pineda, V. V., Torrence, A. E., Libby, R. T., Satterfield, T. F., Lazarowski, E. R., Gilbert, M. L., Morton, G. J., Bammler, T. K., Strand, A. D. et al. (2006). Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. *Cell Metab.* **4**, 349-362.

Wu, Z., Puigserver, P., Andersson, U., Zhang, C., Adelmant, G., Mootha, V., Troy, A., Cinti, S., Lowell, B., Scarpulla, R. C. et al. (1999). Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* **98**, 115-124.

Zechner, C., Lai, L., Zechner, J. F., Geng, T., Yan, Z., Rumsey, J. W., Collia, D., Chen, Z., Wozniak, D. F., Leone, T. C. et al. (2010). Total skeletal muscle PGC-1 deficiency uncouples mitochondrial derangements from fiber type determination and insulin sensitivity. *Cell Metab.* **12**, 633-642.

Zhao, W., Varghese, M., Yemul, S., Pan, Y., Cheng, A., Marano, P., Hassan, S., Vempati, P., Chen, F., Qian, X. et al. (2011). Peroxisome proliferator activator receptor gamma coactivator-1alpha (PGC-1α) improves motor performance and survival in a mouse model of amyotrophic lateral sclerosis. *Mol. Neurodegener.* **6**, 51.

Zheng, B., Liao, Z., Locascio, J. J., Lesniak, K. A., Roderick, S. S., Watt, M. L., Eklund, A. C., Zhang-James, Y., Kim, P. D., Hauser, M. A. et al. (2010). PGC-1α, a potential therapeutic target for early intervention in Parkinson's disease. *Sci. Transl. Med.* **2**, 52ra73.

Journal of Cell Science