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Review

PGC-1 family coactivators and cell fate: Roles in cancer, neurodegeneration, cardiovascular disease and retrograde mitochondria–nucleus signalling

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ABSTRACT

Over the past two decades, a complex nuclear transcriptional machinery controlling mitochondrial biogenesis and function has been described. Central to this network are the PGC-1 family coactivators, characterised as master regulators of mitochondrial biogenesis. Recent literature has identified a broader role for PGC-1 coactivators in both cell death and cellular adaptation under conditions of stress, here reviewed in the context of the pathology associated with cancer, neurodegeneration and cardiovascular disease. Moreover, we propose that these studies also imply a novel conceptual framework on the general role of mitochondrial dysfunction in disease. It is now well established that the complex nuclear transcriptional control of mitochondrial biogenesis allows for adaptation of mitochondrial mass and function to environmental conditions. On the other hand, it has also been suggested that mitochondria alter their function according to prevailing cellular energetic requirements and thus function as sensors that generate signals to adjust fundamental cellular processes through a retrograde mitochondria-nucleus signalling pathway. Therefore, altered mitochondrial function can affect cell fate not only directly by modifying cellular energy levels or redox state, but also indirectly, by altering nuclear transcriptional patterns. The current literature on such retrograde signalling in both yeast and mammalian cells is thus reviewed, with an outlook on its potential contribution to disease through the regulation of PGC-1 family coactivators. We propose that further investigation of these pathways will lead to the identification of novel pharmacological targets and treatment strategies to combat disease.

Contents

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1. PGC-1 family coactivators and transcriptional regulation of mitochondrial biogenesis and function

Cellular control of the complex signalling network responsible for maintaining a proper and functional mitochondrial population is currently emerging as a central conundrum associated with a growing number of pathophysiological processes. Novel research fields converge upon this central theme, encompassing mitochondrial dynamics, selective mitochondrial autophagy, maintenance of the mitochondrial genome (mtDNA), and quality control of mitochondrial protein complexes. At the level of the whole organelle, it has been proposed that dysfunctional mitochondria, flagged by loss of their membrane potential ($\Delta\Psi_m$), are separated from the intact, polarised network by fission and can either be recycled by subsequent fusion with 'healthy' mitochondria or degraded through autophagy, representing the 'mitochondrial life cycle' (reviewed in (Twig et al., 2008)). Similarly at the molecular level, misfolded and damaged mitochondrial proteins are degraded by organelle specific proteases (for reviews see (Luce et al., 2010; Tatsuta and Langer, 2008)), and defective mtDNA can be segregated, a phenomenon which may lead to major depletion of mtDNA copy number (Holt, 2010). Indeed, radioactive ^{14}C pulse-chase experiments (Miwa et al., 2008) have estimated the half-life of the cellular mitochondrial pool in hepatocytes *in vivo* to be only ≈40 h. If left unopposed these quality control mechanisms would lead to rapid depletion of mitochondrial mass, thus an equally active biogenesis system must be in operation in order to constantly replenish the healthy cellular mitochondrial pool. The biogenesis of mitochondria involves multiple processes, including: (i) formation of the double membrane boundary from phospholipids, which are either imported from other organelles or synthesised locally (Horibata and Sugimoto, 2010; Potting et al., 2010; Tamura et al., 2009; Vance and Vance, 2004); (ii) import of mitochondrial proteins which are encoded by nuclear genes, representing the large majority of the mitochondrial proteome; (iii) synthesis of the few, but nonetheless fundamental, mtDNA encoded protein components of the electron transport chain (ETC) in the matrix (Calvo and Mootha, 2010; Schmidt et al., 2010; Sickmann et al., 2003); and (iv) replication of the mitochondrial genome and translational machinery (Shutt and Shadel, 2010; Wallace, 2007). These four processes are inherently interrelated in order to achieve a balanced assembly of the organelle (Gohil and Greenberg, 2009; Scarpulla, 2006). Moreover, since mitochondrial function is dynamically regulated to facilitate adaptation to cellular activity, mitochondrial biogenesis requires the concerted regulation of the expression of nuclear encoded genes, which ultimately enable each of these processes.

Reflecting the complexity and importance of the control of the mitochondrial biogenesis machinery, expression of the mitochondrial proteome, estimated to comprise approximately 1500 protein species (Pagliarini et al., 2008), is regulated by a plethora of nuclear factors in a hierarchical manner. Early work, pioneered by the group of Scarpulla, identified a set of DNA binding transcription factors (TFs) responsible for the induction of cytochrome *c* and cytochrome oxidase subunit genes, thus named nuclear respiratory factor 1 and 2 (NRF-1 and 2, the latter is a homologue of the mouse GA binding protein [GABP], for reviews see (Scarpulla, 2006, 2008a)). In addition, NRFs also indirectly control the expression of mtDNA encoded genes by potently inducing the nuclear encoded mitochondrial transcription factors A, B1 and B2 (TFAM, TFB1M and TFB2M, respectively), regulators of the transcription and replication of the mitochondrial genome (Scarpulla, 2008b). Further TFs were consequently associated with regulation of mitochondrial genes, such as the cAMP response element binding protein (CREB) (Gopalakrishnan and Scarpulla, 1994) and initiator element binding factor (YY1) (Basu et al., 1997). Importantly, the transcriptome regulated by these TFs extends beyond transcripts encoding mitochondrial proteins (Cam et al., 2004) to those required for broad cellular function, and cell type specific TFs exist, such as myocyte enhancer factor-2 (MEF2) and E-box binding factors in striated muscle (Lenka et al., 1996; Wan and Moreadith, 1995). In addition, taking the transcriptional regulation of mitochondrial biogenesis to a higher level, the expression of specific sets of mitochondrial proteins is controlled as part of larger transcriptional networks directed by diverse extracellular and intracellular signalling pathways responsible for regulating cellular lipid and carbohydrate metabolism, the detoxification of harmful agents, cell growth and differentiation. These factors, acting in *cis*- or *trans*-, regulate the expression of mitochondrial proteins either directly in their specific promoter region or indirectly, acting through modulation of the expression of primary TFs, such as NRF-1 and 2. Control of mitochondrial biogenesis by thyroid and steroid hormones is achieved through nuclear receptors (NRs) for thyroid hormones (TRs) (Marin-Garcia, 2010), glucocorticoids (GR) (Connaughton et al., 2010), testosterone (Qin et al., 2010) and estradiol (ERα) (Klinge, 2008), along with a series of orphan NRs: peroxisome proliferator-activated receptor (PPARα and γ), estrogen related receptor NRs (ERRα and γ), hepatocyte nuclear factor 4α (HNF-4α) and the liver X receptor (LXR) (Hock and Kralli, 2009). In addition, NRs activated by xenobiotics have also been suggested to modulate mitochondrial function by transcriptional regulation, such as the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR)(Wada et al., 2009). Finally, c-myc mediated induction of mitochondrial biogenesis orchestrates the integration of mitochondrial function with cellular growth and proliferation, whilst both direct and indirect repression of mitochondrial metabolism and oxidative activity by hypoxia inducible factor (HIF-1α) aids adaptation to hypoxic conditions.

Investigation into a further level of integration in nuclear transcriptional regulation of mitochondrial biogenesis has been instigated by the discovery of the nuclear coactivator PPARγ coactivator-1α (PGC-1α), a member of the ever-growing family of nuclear coregulators. Coregulators exist and function in large multiprotein complexes, in which rather than binding to DNA, they engage NRs and TFs and modulate their transcriptional potency by promoting the subsequent biochemical interactions required for induction or repression of gene transcription. These interactions include allosteric modification of DNA binding by TFs and NRs, chromatin modification and remodelling, initiation of transcription and mRNA editing (see (O'Malley and Kumar, 2009) and references therein). PGC-1α was cloned first in the mouse (Puigserver et al., 1998) and subsequently in humans (Esterbauer et al., 1999) as a coregulator of the NRs PPARγ and TR driving adaptive thermogenesis in brown adipocytes, and as a factor playing a role in the differentiation of this cell type (reviewed in (Kajimura et al., 2010; Spiegelman et al., 2000)). This seminal finding was soon followed by the identification of a series of TFs (NRF1 and 2α, YY1 and MEF2C acting directly on the ETC; the SREBP family

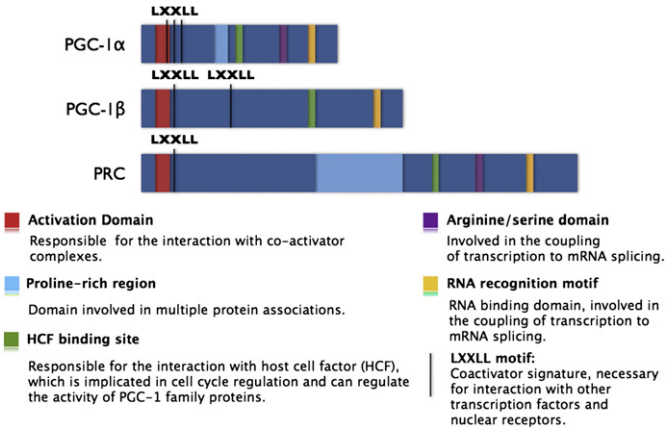

Fig. 1. Structure of the PGC-1 family coactivators. Schematic comparison of PGC-1α, PGC-1β and PRC with the identities and function of the conserved sequence motifs shown in the key at the bottom.
Modified from (Scarpulla, 2011).

controlling lipid metabolism (Lin et al., 2005b)) and NRs (ERRα and γ, PPARα and FXR (Zhang et al., 2004) also acting on lipid metabolism) coregulated by PGC-1α, establishing its role as the 'master regulator' of mitochondrial biogenesis (Wu et al., 1999). Further members of a small family of structurally related transcriptional coactivators have also been cloned via their homology to PGC-1α (Fig. 1.), named PGC-1β (Kressler et al., 2002; Lin et al., 2002a) and PGC-1α related coactivator (Andersson and Scarpulla, 2001) (PRC), as well as a truncated alternatively spliced isoform, NT-PGC-1α (Zechner et al., 2010; Zhang et al., 2009). Genetic approaches have established the complimentary function of PGC-1α and PGC-1β in maintaining an appropriate mitochondrial density in tissues with high energy demand, as clearly demonstrated by the recently created double knockout mice, which show markedly reduced mitochondrial number and size in brown adipose tissue, skeletal muscle and cardiac muscle, associated with cardiac failure soon after birth (Lai et al., 2008; Zechner et al., 2010). On the contrary, although PRC also shares the core mitochondrial biogenetic function of PGC-1α and PGC-1β, its tissue specific expression levels do not correlate with mitochondrial density, rather with the proliferative status of the cell (Andersson and Scarpulla, 2001; Vercauteren et al., 2006).

Whilst the principal function of the PGC-1 family of coactivators – master regulators of mitochondrial biogenesis – is now relatively well established, at least three further lines of evidence indicate that a broader spectrum of cellular activities is also under their surveillance, namely: (i) In addition to acting as coactivators to NRs, PGC-1 family members engage in interactions with other nuclear coactivators and corepressors, representing a further level of complexity in the regulation of cellular functions in a tissue specific manner, the implications of which remain to be elucidated. These interactions mediate chromatin remodelling and either promote (CBP/p300, SIRT1, Baf60a, Lipin) or repress (Rip140, GCN5, Sin3A) PGC-1 family function (reviewed in (Hock and Kralli, 2009; Lin, 2009)); (ii) The PGC-1 family is responsible for the regulation of a broad range of additional related metabolic functions not themselves intrinsic to mitochondria. For instance, PGC-1α activates a large set of genes, termed oxidative phosphorylation (OXPHOS)-coregulated genes, mediating insulin-dependent glucose disposal primarily in the heart, brown adipose tissue and skeletal muscle (Mootha et al., 2003), in addition to a strong dependence of hepatic gluconeogenesis and fatty acid oxidation on PGC-1β (Ling et al., 2004), PGC-1α additionally coordinates heme biosynthesis (Handschin et al., 2005) and triglyceride metabolism (Zhang et al., 2009); (iii) Finally, the complex hierarchical nuclear regulatory network outlined above is a target for a range of fundamental cellular signalling pathways, which modulate the activity of the PGC-1 family members either by regulating their expression levels or through post-translational modifications (recently reviewed in (Hock and Kralli, 2009; Lin et al., 2005a; Scarpulla, 2011)). Energy deprivation, that is decreased intracellular ATP/AMP and NADH/NAD^+ ratios, activates PGC-1α both by phosphorylation through the AMP activated protein kinase (AMPK) pathway or by sirtuin (SIRT1) mediated deacetylation. Cellular energy status also signals to PGC-1α through mammalian target of rapamycin (mTOR) and YY1, and intriguingly, the regulation of PGC-1α activity by exercise and cold exposure is also under the control of stress signalling via the MAPK pathway, as well as through cellular Ca^{2+} and cAMP signalling (Hock and Kralli, 2009). An additional route of signalling from mitochondria to NRs and coregulators might also operate in a retrograde manner to directly couple the functional status and requirements of these organelles to the nuclear transcription programme. The final section of this review will further elaborate upon this concept.

Altogether, the highly complex function and regulatory network of the PGC-1 family which has been unravelled during the last decade may well be only the tip of the iceberg, but nonetheless clearly indicate that these transcriptional coregulators are engaged in fundamental mechanisms determining cellular activity, and ultimately cell fate. Indeed, deregulation of PGC-1 family function now appears to underlie major pathologies. Loss of the PGC-1 family activity will inevitably lead to metabolic derangements, which in turn will affect cell growth, proliferation and cell survival. Alternatively, nuclear rearrangement of gene regulatory elements associated with the function of these coregulators might directly modify the expression of components of cell death and pro-survival pathways. In the next two sections we shall: (i) briefly summarise the existing data in which PGC-1 family activity may exert an influence upon cell fate, and the associated pathologies which may result, and (ii) examine the hypothesis that primary mitochondrial dysfunction leading to energy deprivation could signal to the nuclear transcriptome through the PGC-1 family, instigating either protective or maladaptive mechanisms contributing to disease. We believe that critical evaluation of these studies is necessary to assess the suitability of these molecules or pathways as pharmacological targets.

2. PGC-1 family coactivators and cell survival

The regulation of cell fate is a complex process, and relies upon the balance and integration of multiple opposing 'pro-survival' and 'pro-death' signalling pathways. Should signals promoting cell death come to predominate over those for continued growth and survival, cellular elimination may occur through several defined routes. The best characterised of these routes is apoptosis, a genetically encoded cell death programme which leads to the ordered dismantling of cellular architecture and proceeds through a set of distinct morphological stages, including chromatin condensation and nuclear fragmentation (Galluzzi et al., 2007; Kroemer et al., 2009). This dismantling is mediated through the action of caspase enzymes, a class of cysteine-dependent aspartate-specific proteases, which may be activated after the release of pro-apoptotic factors from the mitochondrial inter-membrane space during the intrinsic pathway of apoptosis. The release of such factors occurs only after permeabilisation of the outer mitochondrial membrane, the integrity of which is in turn regulated by the competing action of members of the BCL-2 family of proteins (reviewed in (Chipuk et al., 2010; Youle and Strasser, 2008)) upon which both survival and death signals converge. Cell death may also occur via necrosis, the abrupt swelling and rupture of cellular organelles and the plasma membrane, which may follow loss of $\Delta\Psi_m$ during mitochondrial permeability transition (Galluzzi et al., 2007; Halestrap, 2009; Kroemer et al., 2009). Mitochondria are thus key regulators of cell fate.

The mitochondrial route to cell death may be activated by multiple stimuli including the developmental programme, DNA damage, ER stress, growth factor and nutrient deprivation, viral infection and oxidative stress (Youle and Strasser, 2008). However, abnormalities in invoking cell death pathways lie at the heart of distinct pathologies. Aberrant induction of cell death may result in conditions as diverse as neurodegeneration, ischemia reperfusion injury and autoimmune disease (Fadeel and Orrenius, 2005), whilst conversely failure to undergo death is a key stage in the malignant transformation of cancer cells (Hanahan and Weinberg, 2000). Recent evidence has begun to identify a role for the PGC-1 family of nuclear coregulators in cell fate determination, and in diseases which may arise from dysregulation of this function.

2.1. Neurodegenerative diseases

Neurodegenerative disorders result from progressive loss of function and cell death within neuron populations, exemplified by Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) amongst others. The systemic manifestation of these diseases results from loss of specific subsets of neurons. The PGC-1 family was directly implicated in neurodegeneration with the creation of the PGC-1α knockout (PGC-$1\alpha^{-/-}$) transgenic mouse model. PGC-$1\alpha^{-/-}$ mice display marked hyperactivity accompanied by neuronal degeneration and lesions predominantly in the striatum, with less prominent lesions in cortical regions (Lin et al.,

2004). These results were confirmed by an independently generated PGC-1α$^{-/-}$ mouse model in which vacuolar lesions of the central nervous system were observed (Leone et al., 2005), positing a role for PGC-1α in the maintenance of neuronal function.

The involvement of PGC-1 family coactivators in neurodegenerative disorders has been further implied by genetic studies. The regulation of lifespan and increased risk of the development of both PD and HD have been shown to be associated with single nucleotide polymorphisms in the gene encoding PGC-1α (*PPARGC1A*) (Clark et al., 2011; Weydt et al., 2009), whilst sequence variations in PGC-1α target genes such as TFAM and NRF-1 were identified in AD and HD patients (Maruszak et al., 2011; Taherzadeh-Fard et al., 2011). Decreased expression of PGC-1α has also been reported in AD, HD and PD patients, as well as in mouse models of HD and spinal and bulbar muscular atrophy (Cui et al., 2006; Qin et al., 2009; Ranganathan et al., 2009; Weydt et al., 2006; Xiang et al., 2011; Zheng et al., 2010). Such repression of PGC-1α has been attributed to mutant nuclear huntingtin (Cui et al., 2006) or a parkin dysfunction mediated mitochondrial-nuclear pathway (Shin et al., 2011). Accordingly, forced expression of PGC-1α in neuronal cell cultures significantly abrogated cell death induced by both 3-nitropropionic acid (a pharmacological model of HD) (Weydt et al., 2006). Overexpression of PGC-1α in HD mouse muscle fibres restored the muscular capacity for oxidative phosphorylation under chronic energy deprivation conditions (Chaturvedi et al., 2009), while up-regulation of the coactivator by the kinase MSK-1 attenuated neuronal cell death induced by mutant huntingtin protein (Martin et al., 2011). Furthermore, overexpression of PGC-1α also improved the motor performance and survival of a SOD-1 G93A transgenic ALS mouse model (Zhao et al., 2011). Due to the emerging role of PGC-1α in multiple neurodegenerative pathologies, strategies for pharmacological activation of the coactivator have recently gained much attention as a potential novel avenue of treatment for these diseases (Handschin, 2009; Wenz, 2009, 2011; Wenz et al., 2010; Zorzano et al., 2010).

Both PGC-1α and PGC-1β have been demonstrated to trigger protective mechanisms under conditions of oxidative stress, providing an appealing hypothesis to explain their beneficial role in preventing degenerative diseases. In murine myoblasts the abundance of mitochondrial respiratory complexes and uncoupling proteins was increased through overexpression of exogenous PGC-1α or PGC-1β, accompanied by a concomitant increase in the expression of genes associated with detoxification of both mitochondrial and cytosolic reactive oxygen species (ROS) (St-Pierre et al., 2003). PGC-1α overexpression in SH-SY5Y neuroblastoma cells also resulted in increased expression of manganese superoxide dismutase (MnSOD) (Cowell et al., 2009). Furthermore, exposure to H_2O_2 augmented both PGC-1α and PGC-1β gene expression in mouse embryonic fibroblasts, along with the previously reported increase in antioxidant capacity, whilst silencing of PGC-1α alone or simultaneous silencing of PGC-1α and PGC-1β blunted the enhanced expression of ROS detoxification enzymes (St-Pierre et al., 2006), suggesting a potential cytoprotective role for these coregulators during oxidative stress. Accordingly, PGC-1α$^{-/-}$ mice were shown to be sensitised to neuronal cell death caused by MPTP or kainic acid, whilst overexpression of PGC-1α in murine striatal neuron progenitor cells significantly decreased cell death induced by H_2O_2 or paraquat, a superoxide generating agent (St-Pierre et al., 2006). SH-SY5Y cells overexpressing PGC-1α were also protected from H_2O_2 treatment, with a reduction in caspase-3 activation (Cowell et al., 2009; St-Pierre et al., 2006). The neuroprotective effects of PGC-1α were recently potentially extended to conditions of oxygen and glucose deprivation, under which PGC-1α overexpression suppressed apoptosis in primary mouse cortical neurons (Luo et al., 2009).

2.2. Cardiovascular diseases

The ability of PGC-1 family coactivators to increase cellular antioxidant defences also underpins a protective effect in the vascular endothelium. As for neuron models, increased expression of PGC-1α in human vascular endothelial cells (HUVEC) led to mitochondrial biogenesis and an increased complement of ROS detoxification proteins, including MnSOD (Valle et al., 2005). Exposure to ROS also upregulated PGC-1α expression and the cellular antioxidant capacity of bovine endothelial cells (Borniquel et al., 2006). HUVEC overexpressing PGC-1α produced fewer intracellular ROS and displayed an inhibition of caspase-3 activation with increased cell viability after oxidative stress induced by DMNQ, H_2O_2 and high glucose conditions (Valle et al., 2005). Suppression of ROS detoxification by post-translational inhibition of the transactivation activity of PGC-1α may lie behind vascular hypertrophy induced by angiotensin II (Xiong et al., 2010). PGC-1α was further seen to prevent apoptosis of endothelial cells triggered by fatty acids, apparently mediated through increased expression of the adenine nucleotide transporter 1 (Won et al., 2010).

Gene knockout models of the PGC-1 family coactivators have also revealed a role in maintaining proper cardiac function. Both PGC-1α$^{-/-}$ and PGC-1β knockout (PGC-1β$^{-/-}$) transgenic mice present with modest heart defects and are less able to increase cardiac work output in response to either chemical or electrical stimulation (Arany et al., 2006; Lelliott et al., 2006; Leone et al., 2005). Moreover, double transgenic knockout of PGC-1α and PGC-1β in mice results in early postnatal heart failure as the primary cause of lethality (Lai et al., 2008). Similarly, diminished PGC-1α expression correlates with stress induced cardiac failure (Arany et al., 2006; Sano et al., 2004) and cardiomyocyte cell death in a mouse model of congestive heart failure (Garnier et al., 2003). Indeed, PGC-1α has been suggested to play a key role in physiological cardiomyocyte metabolism and growth (Arany et al., 2005; Czubryt et al., 2003; Huss and Kelly, 2004). However, in contrast to neuronal models, forced expression of PGC-1 family proteins is not necessarily beneficial in cardiac cells. Whilst overexpression of PGC-1α was shown to block PARP cleavage, caspase-3 activation and apoptosis of cardiomyocytes in an *in vitro* model of stress-induced cardiac failure (Arany et al., 2006; Sano et al., 2004), it also delayed mouse cardiac contractile recovery after an ischemic episode, and increased cardiomyocyte cell death under anoxia (Lynn et al., 2010) and caused transient cardiomyopathy during development (Russell et al., 2004).

2.3. Cancer

Cancer results from the imbalance of cell proliferation over cell death. Acquired resistance to the initiation of cell death processes is a key stage in tumour development (Hanahan and Weinberg, 2000), and increased levels of expression of the PGC-1 family coactivators have been observed in cancer cells (Savagner et al., 2003; Shiota et al., 2010; Srivastava et al., 2007), which may be associated with a pro-survival effect. Mitochondrial cell death pathways can be triggered by pathological Ca^{2+} accumulation in the mitochondrial matrix (Duchen et al., 2008; Orrenius et al., 2003). Overexpression of PGC-1α in both a cervical cancer (HeLa) cell line and rat skeletal myotubes markedly reduced mitochondrial Ca^{2+} uptake during Ca^{2+} signalling stimulated by physiological ligands; importantly, this modification of organelle Ca^{2+} homeostasis also protected HeLa cells from death induced by C_2 ceramide and staurosporine (Bianchi et al., 2006). The protective effect was related to increased mitochondrial biogenesis, providing a direct link between PGC-1α transcriptional activity and cell fate. The transactivation activity of PGC-1β may also influence the sensitivity of cancer cells to death inducing stimuli. PGC-1β is required for increased gene expression activity at the 17q12-21 chromosomal region, a set of genes often amplified in breast cancer and associated with a poor prognosis. Silencing of PGC-1β mediated by siRNA in tamoxifen-resistant MCF-7 breast cancer cells restored the tamoxifen sensitivity in this cell line (Deblois et al., 2010). However, no direct mechanistic link between the extrinsic pathway of apoptotis and the PGC-1 family of coactivators has yet been found.

Alongside suppression of the cell death programme, cancer cells must also alter intracellular metabolism to meet the demands of rapid cellular proliferation in the unique tumour microenvironment, referred to as metabolic reprogramming (DeBerardinis et al., 2008). As master regulators of cellular metabolism, the PGC-1 family members may orchestrate changes in metabolism capable of sustaining a rapid growth phenotype. The PGC-1β dependent amplicon at the 17q12-21 chromosomal region has also been associated with the growth of certain types of breast cancer, and silencing of PGC-1β reduced the proliferative rate of a breast cancer cell line (Deblois et al., 2010). Similarly, silencing of PRC in osteosarcoma cells inhibited proliferation in both glucose and galactose based culture medium, accompanied by cell cycle arrest in G1 phase, suggesting that PRC function may support both mitochondria dependent and independent cell growth and proliferation (Vercauteren et al., 2009). Functional PGC-1α might be required for efficient growth and proliferation of prostate cancer cells, since siRNA mediated PGC-1α silencing reduced proliferative rates and caused G1 phase cell cycle arrest in both hormone-sensitive and hormone-insensitive prostate cancer cell lines (Shiota et al., 2010). Significantly increased PGC-1α expression levels were measured in tumour samples obtained from arsenic-induced skin cancer patients, and may be associated with increased cellular proliferation (Lee et al., 2011), whilst a similar mechanism, triggered by a mitochondria-nucleus retrograde signalling pathway, has been proposed to drive oncocytic tumorigenesis. PGC-1α stimulation may also be capable of activating the biosynthetic PI3K/Akt growth pathway, since pharmacological activation of PGC-1α promoted proliferation and Akt activation in H1838 and H2106 non-small cell lung cancer cell lines (Han et al., 2009). Overexpression of PGC-1α also increased the expression of uridine phosphorylase, an enzyme involved in the pyrimidine salvage pathway often upregulated by cancer cells, and increased proliferation in both breast and colon cancer cell lines (Kong et al., 2009). PGC-1α may potentially stimulate both cell growth and cancer cell survival through HIF TFs, since PGC-1α overexpression in rat skeletal myotubes upregulated HIF-2α, a TF previously associated with tumourigenesis and chemoresistance (Majmundar et al., 2010; Rasbach et al., 2010; Roberts et al., 2009).

However, the role of the PGC-1 family in controlling cancer cell fate appears to be complex, and not invariably beneficial. Indeed, forced expression of PGC-1α resulted in apoptosis of human epithelial ovarian cancer cells (Zhang et al., 2007b), and several studies have revealed significantly decreased PGC-1 coactivator expression in tumour samples (Feilchenfeldt et al., 2004; Jiang et al., 2003; Watkins et al., 2004). Accordingly, PGC-1 driven mitochondrial biogenesis impeded cancer cell proliferation under glycolytic conditions (Wang and Moraes, 2011), and miRNA mediated downregulation of PGC-1 was shown to mediate coordinated changes in the hepatocyte metabolic network promoting hepatocarcinogenesis (Burchard et al., 2010).

2.4. Summary: An emerging cohesive role of the pgc-1 family in cell survival, growth and proliferation?

As summarised in Table 1, the expression of the PGC-1 family coactivators plays a broadly cytoprotective role in cellular physiology, promoting cell growth, proliferation and survival after apoptotic stimuli. Accordingly, expression of PGC-1α improves several neurodegenerative, cardiovascular and other age related pathologies, as discussed above. Moreover, recent pharmacological approaches in a number of pathologies have been aimed at exploiting the activation of PGC-1α through multiple routes, including the PPARγ pathway using fibrates, the SIRT1 pathway using resveratrol and the AMPK pathway using AICAR. A detailed summary of these works is beyond the scope of this review, for recent updates see (Handschin, 2009; Wenz, 2009, 2011; Zorzano et al., 2010). It should be noted however that PGC-1 family expression may not always be beneficial. As several examples discussed above demonstrate, overactivation of the metabolic and signalling networks controlled by these coactivators might lead to reduced proliferation and even cytotoxicity in cardiac tissue as well as in cancer cells, thus it is plausible that the specific effects of PGC-1 family coactivators depend upon the actual environmental and metabolic context of the cell. Fine tuning of the activation different members of the family and their interactions with other TFs might thus have differential effects on cell fate, leaving outstanding open questions for future research.

3. Mitochondrion–nucleus retrograde signalling and its role in cell fate and disease pathology

As discussed above, PGC-1 family coactivators play an important role in influencing cell fate, and their deregulation is frequently associated with disease states. Regulation of both the expression and the activity of PGC-1α and PGC-1β is under the control of cellular energy and redox status, which in turn is ultimately governed by mitochondrial activity. We thus propose that primary mitochondrial dysfunction may contribute to alterations in the activity of the PGC-1 family through a retrograde mitochondrion–nucleus signalling pathway and play a part in the pathomechanism of at least a subset of mitochondria related diseases. These alterations might represent adaptive changes to re-establish normal mitochondrial function, but may also directly regulate cellular fate, leading either to cellular survival or to maladaptive responses, aggravating disease. Here we first briefly review the available information on mitochondrion–nucleus retrograde signalling, then discuss its certain pathological aspects, with emphasis on the potential role of PGC-1 family coactivators.

3.1. The prototypic mitochondrion–nucleus retrograde signalling pathways in yeast

A mitochondrial homeostatic system in yeast, involving mitochondrial-nuclear intergenomic communication was first demonstrated by the group of Butow (Parikh et al., 1987). Interestingly, these early observations revealed that loss of mtDNA triggered the upregulation not only of nuclear encoded mitochondrial genes such as cytochrome oxidase subunit VI, as may be expected as part of an adaptive negative feedback loop, but also several genes encoding non-mitochondrial proteins, and even non-translated nuclear ribosomal RNAs (Butow et al., 1988). Accordingly, the *CIT2* gene encoding the peroxisomal isoform of citrate synthase has been identified as a prototypical target of the mitochondrion–nucleus signal transduction pathway (Liao et al., 1991). The backbone of the pathway comprises two transcription factors, Rtg1p and Rtg3p, which bind the R-box consensus site (GTCAC). The assembly, nuclear translocation and consequent activation of these TFs are controlled by a cascade of cytoplasmic regulators (reviewed in (Liu and Butow, 2006)). Importantly, amongst these cytoplasmic factors the activator Rtg2p requires ATP binding, and was suggested to respond to NH_4^+, glutamine and glutamate levels, compatible with a putative role as a metabolic sensor, whilst the inhibitor Lst8p is an essential component of both target of rapamycin (TOR) complexes 1 and 2, the evolutionarily conserved hubs of the yeast nutrient sensing pathway (Chen and Kaiser, 2003; Liu et al., 2001). Indeed, the set of Rtg target genes identified thus far aligns with metabolic pathways responsible: (i) adaptation to the dysfunction of mitochondrial respiration by upregulating the partly peroxisomal glyoxylate cycle for the oxidation of fatty acids and two carbon sources, (ii) maintenance of mtDNA by the bifunctional TCA cycle enzyme aconitase (encoded by *ACO1*) (Chen et al., 2005) and (iii) the anaplerosis of a truncated TCA cycle in the absence of succinate dehydrogenase activity in order to provide substrates for glutamate and lysine synthesis, ensuring the requirement for nitrogen for anabolic reactions is fulfilled (Epstein et al., 2001; Magasanik and Kaiser, 2002).

However, several lines of evidence indicate that while the pathway thus far described plays an essential role in cellular homeostasis, it might represent only one arm of mitochondrion–nucleus signalling.

Table 1
Modulation of cell fate by PGC-1 family coactivators in neuronal, cancer and cardiovascular models. Listing studies reporting the effects of experimental modulation of the expression/activity of PGC-1α, β or PRC.

Family member	Experimental system			Effect on cell fate	Reference
	Modification	Cell type	PGC-1 promotes cell survival?		
Neurodegeneration					
PGC-1α	Knockout	Mouse dopaminergic neurons	✓	Sensitises to MPTP and kainic acid induced cell death.	(St-Pierre et al., 2006)
	Overexpression	Mouse striatal neuronal progenitor cells	✓	Protects against paraquat and H_2O_2 induced cell death.	
PGC-1α	Overexpression	SH-SY5Y neuroblastoma cell line	✓	Protects against H_2O_2-induced cell death and inhibits caspase 3 activation.	(Cowell et al., 2009)
PGC-1α	Overexpression	STHdh-q111 cell line	✓	Protects against loss of $\Delta\Psi_m$ induced by 3-nitropropionic acid.	(Weydt et al., 2006)
PGC-1α	Overexpression	Mouse primary cortical neurons	✓	Protects against cell death induced by oxygen and glucose derivation.	(Luo et al., 2009)
PGC-1α	Overexpression	Rabbit renal proximal tubular cells	✓	Promotes recovery from mitochondrial dysfunction when expressed after oxidative insult.	(Rasbach et al., 2010)
PGC-1α	Upregulation induced by PPARγ agonists	SH-SY5Y neuroblastoma cell line	✓	Protects against glucose deprivation induced cell death.	(Miglio et al., 2009)
PGC-1α	Overexpression	Mouse primary cortical neurons (Tg2576 AD)	✓	Protects against amyloidogenic Aβ accumulation	(Qin et al., 2009)
PGC-1α	Overexpression	In vivo injection in mouse brain	✓	Prevents the loss of DA neurons induced by PARIS overexpression	(Shin et al., 2011)
PGC-1α	Overexpression	STHdh-q111 cell line, primary mouse striatal neurons	✓	Protects against mutant huntingtin induced toxicity.	(Cui et al., 2006)
Cancer					
PGC-1α	Overexpression	HepG2 cell line	✓	Reduces troglitazone-induced cell death.	(Liao et al., 2010)
PGC-1α	Overexpression	HeLa cervical cancer cell line	✓	Inhibits C_2 ceramide induced death. Partial inhibition of staurosporine induced cell death.	(Bianchi et al., 2006)
PGC-1α	Overexpression	SK-BR-3 breast cancer cell line	✓	Increases expression of uridine phosphorylase.	(Kong et al., 2009)
PGC-1α	Upregulation induced by PPAR-β/ δ agonist	H1838 and H2106 non-small cell lung carcinoma cell lines	✓	Stimulates cell growth through PI3K/AKT pathway.	(Han et al., 2009)
PGC-1α	siRNA silencing	Prostate cancer cell lines	✓	Inhibits cell proliferation and induces G1 phase cell cycle arrest.	(Shiota et al., 2010)
PGC-1β	siRNA silencing	SK-BR-3 and MCF7 breast cancer cell lines	✓	Inhibits proliferation. Restores antiproliferative effect of tamoxifen to tamoxifen-resistant MCF7 cells.	(Deblois et al., 2010)
PRC	shRNA silencing	U20S osteosarcoma cell line	✓	Decreases proliferation in glucose and galactose only medium.	(Vercauteren et al., 2009)
PRC	Overexpression	FTC-133, XTC.UC1 and RO 82 W-1 thyroid cell lines	✓	Promotes cell growth.	(Mirebeau-Prunier et al., 2010)
PGC-1α	Upregulation induced by PPAR-β/ δ agonist	HeLa, 143B, MDA-MD-231	x	Decreases growth rates in glucose-containing medium	(Wang and Moraes, 2011)
PGC-1α	Overexpression	HO8910 epithelial ovarian cancer cell line	x	Induces apoptosis.	(Zhang et al., 2007b)
Cardiovascular system					
PGC-1β	Knockout	Mouse heart	✓	Required for normal chronotopic response	(Lelliott et al., 2006)
PGC-1α	Knockout	Mouse heart	✓	Required for postnatal growth of the the heart	(Leone et al., 2005)
PGC-1α	Knockout	Mouse heart	✓	Protects against traverse aortic constriction induced cardiac stress (apoptosis)	(Arany et al., 2006)
PGC-1α PGC-1β	Knockout	Mouse heart	✓	Lack of both coactivators lead to perinatal heart failure	(Lai et al., 2008)
PGC-1α	Overexpression	Rat cardiomyocytes	✓	Protects from apoptosis in a stress induced cardiac failure model	(Sano et al., 2004)
PGC-1α	siRNA silencing	Primary mouse vascular smooth muscle cells	✓	Augments angiotensin II induced rise in intracellular ROS and hypertrophy.	(Xiong et al., 2010)
PGC-1α	Overexpression/knockout	Mouse	✓	Angiogenesis	(Arany et al., 2008)
PGC-1α	Overexpression	Human aortic endothelial cells	✓	Inhibits linoleic acid-induced apoptosis.	(Won et al., 2010)
PGC-1α	Overexpression	Human umbilical vein endothelial cells	✓	Protects against H_2O_2 or high glucose induced apoptosis.	(Valle et al., 2005)
PGC-1α	In vivo transgene expression	Mouse heart	x	Cardiomyopathy in adult heart	(Russell et al., 2004)
PGC-1α	Overexpression	Mouse cardiac-derived H9c2 cell line	x	Increases cell death after anoxia-reoxygenation injury.	(Lynn et al., 2010)

Firstly, a large set of genes which show altered patterns of expression in yeast cells with compromised mitochondrial function is not under the control of the Rtg1p/Rtg3p complex. Secondly, genome wide profiling of different yeast strains or of yeast under altered metabolic states, for example under glucose repression of mitochondrial respiration, showed modified expression of a largely different set of genes than in response to mtDNA depletion (Traven et al., 2001). Moreover, overlapping but distinct sets of genes are responsive to inhibition of mitochondrial function by means of directly inhibiting respiratory complex III by antimycin, the ATP synthase by oligomycin, uncoupling of the electron

transport chain by FCCP or mutations in TCA cycle enzymes compared to those genes of which expression is altered following mtDNA depletion, further indicating that response pathways specific to the site of a metabolic defect exist (Epstein et al., 2001; McCammon et al., 2003). The upregulation of the multidrug resistance transporter Pdr5p, mediated by the Pdr1p and Pdr3p transcription factors in response to comprised F_o function of the ATP synthase represents an example of retrograde mitochondrion–nucleus signalling not controlled by the Rtg1p/Rtg3p complex (Zhang and Moye-Rowley, 2001), and further studies will be essential to identify additional mediators of such signalling. Of note, Rtg2p, the main 'switch' of the yeast retrograde response pathway, also functions as a nuclear coregulator, forming part of the SLIK (SAGA-like) transactivation complex at the promoters of retrograde response target genes (Pray-Grant et al., 2002).

3.2. Diverse pathways of mitochondrial-nuclear retrograde signalling in mammalian cells

While the existence of a fundamental yeast mitochondria–nucleus retrograde signalling pathway is well established, at least two further outstanding questions still remain largely elusive; 'What are the primary signals leading to the activation of the pathway?' and 'How well are these retrograde signalling pathways conserved in multicellular organisms, particularly in mammals?'. Studies on the mammalian mitochondrial-nuclear retrograde signalling pathways have revealed a remarkable heterogeneity in both the primary signals resulting from mitochondrial dysfunction and in the downstream nuclear TFs consequently activated (Fig. 2). To date at least four key primary signals have been recognised to directly result from mitochondrial dysfunction: (i) reduction of mitochondrial and cellular ATP levels; (ii) changes in the cellular $NADH/NAD^+$ ratio; (iii) disequilibrium of free radical production and cellular oxidative defences; and (iv) deregulation of cellular Ca^{2+} homeostasis. These signals are less studied in yeast, but they appear to play a key role in retrograde signalling in mammalian cells. In addition, glutamate might also function as a primary metabolic signal, given its role as a potent suppressor of Rtg2p signalling in yeast. In response to these primary triggers, several nutrient sensing and stress signalling pathways have been implicated in the mammalian mitochondria-nuclear communication, targeting a wide range of transcriptional factors in the nucleus. Interestingly, no clear homologies to the components of the yeast system have yet been identified.

Up-regulation of nuclear encoded mitochondrial (citrate synthase, Cox-Va, (Marusich et al., 1997)) and non-mitochondrial (ß-actin, myc, GAPDH (Wang and Morais, 1997)) genes in response to mitochondrial dysfunction was first demonstrated in different mammalian cell types at the end of the 1990's, followed by a series of studies exploring the nature of the retrograde signalling pathway, also referred to as the mitochondrial stress pathway, in C2C12 myoblasts and A549 human lung cancer cells by the group of Avadhani (Amuthan et al., 2002; Biswas et al., 1999). These studies found elevated basal cytosolic $[Ca^{2+}]$, together with the overexpression of ER Ca^{2+} release channels, and reduced cellular [ATP] in spite increased glycolytic pathways in mtDNA depleted cells, setting the paradigm of primary mitochondrial signals triggering the retrograde response in mammalian cells. Of note, the causal relationship between mitochondrial dysfunction and deregulated Ca^{2+} signalling has been shown by independent studies, in which Ca^{2+} chelation alone was sufficient to abolish the changes observed (Arnould et al., 2002; Luo et al., 1997).These studies showed marked activation of heterogeneous cellular stress responses linking mitochondrial dysfunction to the activation of a set of nuclear

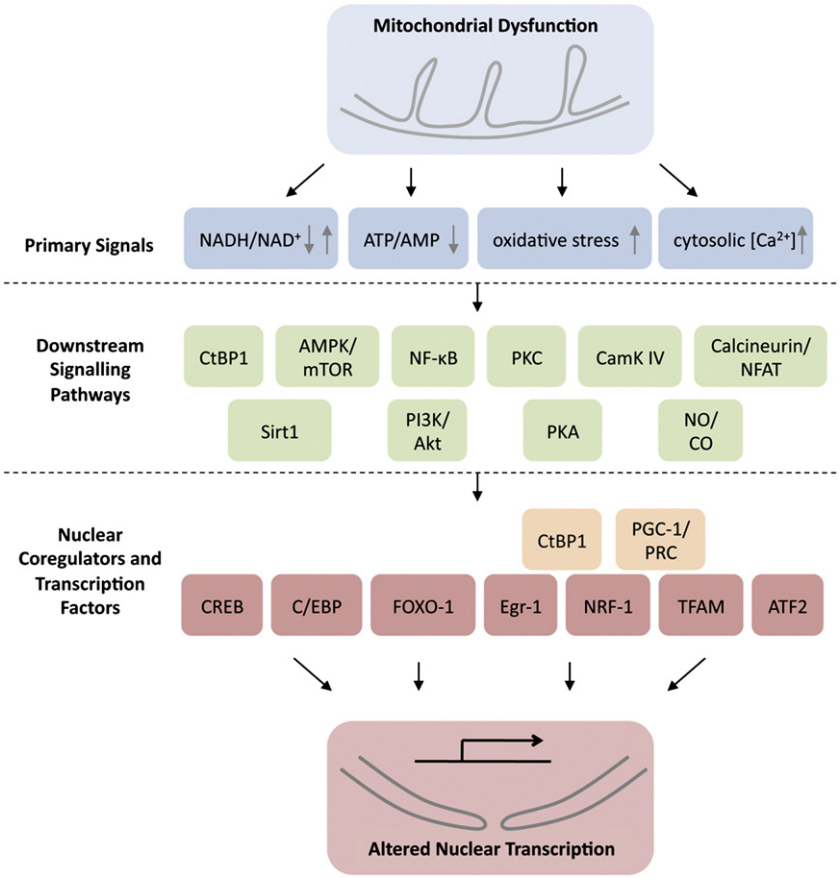

Fig. 2. Key regulators of mitochondrion–nucleus retrograde signalling. Mitochondrial dysfunction may alter cellular Ca^{2+}, redox and energetic homeostasis, and modulate the activity of key signalling pathways which in turn regulate the expression and function of multiple nuclear coregulators and TFs. A wide array of signalling molecules have been implicated in this retrograde response, a number of which are here highlighted.

transcription factors, demonstrating *bona fide* communication between the mitochondrial and nuclear genomes. These pathways include calcineurin mediated activation of NFAT signalling coupled to increased activity of ATF2, activation of NFκB (Biswas et al., 1999; Biswas et al., 2008), MAPK (Amuthan et al., 2002; Luo et al., 1997) and protein kinase C (PKC) (Amuthan et al., 2001), as well as CamKIV mediated CREB activation (Arnould et al., 2002). The involvement of the transcription factors Egr-1 and CEBP downstream of MAPK and PKC signalling has also been suggested (Butow and Avadhani, 2004).

More recent studies on the mitochondrial stress response following both acute and chronic depletion of mtDNA or pharmacological inhibition of mitochondrial function further confirmed the remarkable diversity of such signalling in mammalian cells. While the role of Ca^{2+} mediated CREB activation in adaptive mitochondrial biogenesis in rho0 cells has been further confirmed (Mercy et al., 2005), novel mediators have also been identified. Dissipation of $\Delta\Psi_m$ was shown to specifically inhibit tyrosine phosphorylation of a defined set of proteins (Luo and Ingram, 2001), likely reflecting calcineurin mediated upregulation and activation of the insulin like growth factor-1 receptor, triggering increased glucose uptake and utilisation by aerobic glycolysis (Guha et al., 2007). Similarly, a pathway acting through PI3K and Akt activation was shown to enhance the formation of a transcriptional activator complex, mediated by the phosphorylation of heterogeneous nuclear ribonucleoprotein (hnRNP) A2 as a coactivator. This complex, formed by NFκB c-Rel/p50, C/EBPβ, CREB, and NFAT, is responsible for upregulation of *Glut4*, *Cathepsin L* and the *RyR1* gene expression, prototypical genes upregulated by mitochondrial stress in C2C12 cells and other cancer cell lines (Guha et al., 2010; Guha et al., 2009). Alongside activation of novel signalling pathways, a series of studies have also considered other primary signals resulting as direct consequence of mitochondrial dysfunction in mitochondrion–nucleus retrograde signalling. An imbalance between the supply of reducing equivalents and flow through the electron transport chain due to compromised function of respiratory complexes is one of the main sources of cellular reactive oxygen species (Murphy, 2009), and indeed increased ROS generation has been shown to convey signals to a wide array of cellular targets (for reviews see e.g. (Droge, 2002; Jones, 2008)). Mitochondrial ROS have thus also been implicated in crosstalk between the mitochondria and nucleus, regulating cytochrome c_1 and *b* expression (Suzuki et al., 1998), a response which probably involves NFκB, NRF-1 and TFAM (Miranda et al., 1999; Piantadosi and Suliman, 2006). Still, there is no clear understanding of the components involved in this ostensibly pleiotropic pathway, reflected by studies involving H_2O_2 as a primary trigger in AMP kinase-mediated (Irrcher et al., 2009) or CREB-mediated (St-Pierre et al., 2006) mediated mitochondrial biogenesis, or even retrograde regulation of the Drosophila cell cycle, in which AMP and ROS appear to act independently through ASK-1, FOXO and p27 (Dacapo) (Owusu-Ansah et al., 2008), as well as stem cell proliferation and differentiation (Mandal et al., 2011). In addition to ROS, the involvement of nitric oxide and carbon monoxide signalling pathways has also been suggested to play a part in mammalian retrograde signalling (Butow and Avadhani, 2004; Le Pennec et al., 2011; Rhodes et al., 2009). These factors undoubtedly can function as triggers of mitochondrial biogenesis (see e.g. (Nisoli et al., 2003)), but their role as *bone fide* retrograde signals awaits verification.

Finally, even though they have not yet been demonstrated to play a direct role in mitochondrion–nucleus communication, we should mention two recently characterised pathways linking changes in cytosolic NADH/NAD^+ ratios to alterations in nuclear transcriptional activity. First, an attractive hypothesis would associate reduced cellular energy levels, characterised by diminished NADH/NAD^+ ratios, to NAD^+ mediated activation of the sirtuin family of deacetylases. According to this pathway, activation of Sirt1 in turn would lead to the activation of PGC-1α, mediating mitochondrial biogenesis to re-establish cellular energy levels (Nemoto et al., 2005). However, since the free cytoplasmic and presumably nuclear NADH/NAD^+ ratio was estimated to approximately 1:700 (Williamson et al., 1967), even substantial reduction in NADH levels would not lead to significant changes in the absolute [NAD^+]. Alternatively, it has been recently proposed that increased AMP/ATP ratios, due to mitochondrial dysfunction would lead to activation of AMPK, which has been shown to signal energy depletion to Sirt1 by increasing absolute NAD^+ levels (reviewed in (Jeninga et al., 2010)). On the other hand, cytosolic NADH was proven to specifically bind to carboxyl-terminal binding protein (CtBP), a transcriptional corepressor (Fjeld et al., 2003), leading to its translocation to the nucleus (Verger et al., 2006). Since inhibition of the mitochondrial electron transfer chain leads to elevated NADH levels, and CtBP was shown to modify the activity of a series of TFs and coregulators, including PGC-1α and Sirt1 (Kajimura et al., 2008; Zhang et al., 2007a), this pathway might represent a genuine mitochondrion–nucleus feedback loop.

3.3. Evolutionarily conserved, common features of mitochondrion–nucleus signalling

The studies of retrograde signalling in mammalian model systems summarised above have demonstrated the fundamental role of mitochondrial function in controlling cellular homeostasis through interaction with the nuclear genome. Moreover, they also reflect the evolutionary divergence from the yeast retrograde signalling pathway, which primarily concerns metabolic adaptation, to a much broader framework of stress signalling, ultimately governing cell fate. Although not within the strict scope of the review, we must mention two related trends in the field substantiating this view. Firstly, the intimate link with NFκB controlled stress signalling has led to the proposal of evolution of yeast retrograde signalling into the cellular defence pathways of innate immunity, oxidative defence and the unfolded protein response, while the homology of the bHLH/zip domain of Rtg1/3 proteins with the Myc/Max/Mad related protein network suggests further links to cellular proliferation, metabolism and cell death (Srinivasan et al., 2010). Secondly, mitochondrial dysfunction elicited in a manner similar to the unfolded protein response (UPR) of the endoplasmic reticulum has recently gained attention. Accumulation of misfolded proteins in the mitochondrial matrix, partly as a consequence of compromised expression of the mitochondrially encoded proteins, has been shown to induce an organelle specific mitochondrial UPR (UPRmt) (Martinus et al., 1996), and a series of studies have unveiled a novel, evolutionarily conserved adaptive signalling pathway between mitochondria and the nucleus (recently reviewed in (Baker and Haynes, 2011; Baker et al., 2011; Broadley and Hartl, 2008). The transcription factors implicated in UPRmt, such as CHOP and CEBP, partially overlap with the proposed mammalian retrograde response targets, but the upstream signals appear to be distinct (e.g. JNK2 (Horibe and Hoogenraad, 2007)). Again, the latter pathway well illustrates the diversity of cellular responses and signalling pathways linked to mitochondrial dysfunction, and for further information on its role in pathologies we refer the reader to (Moisoi et al., 2009; Siegelin et al., 2011)) and the above cited recent reviews.

3.4. Potential pathological implications of mitochondrion–nucleus retrograde signalling involving the PGC-1 family coactivators

The pleiotropic nature of cellular responses induced by mitochondrial stress means that their contribution to pathological states is an overt postulation. For instance, in the case of cancer, several studies have suggested that artificial depletion of mtDNA results in the development of an invasive cancer phenotype. The effect is suggested to be mediated by mitochondrion–nucleus retrograde signalling and includes several mechanisms, e.g. the upregulation of metastatic markers TGFβ1 and cathepsin-L (Amuthan et al., 2002; Amuthan et al., 2001; Guha et al., 2009); conferring resistance to apoptosis by altering the anti- and proapoptotic Bcl-2 family rheostat (Amuthan

et al., 2002; Biswas et al., 2005); mediating a Warburg-like phenotype (Biswas et al., 2008; Guha et al., 2007); and perturbing the p53 network and causing genomic instability (Kulawiec et al., 2008). Similarly, as reviewed recently, mitochondrial dysfunction can contribute to several other major pathologies such as neurodegeneration and cardiovascular disease through multiple, varied mechanisms (Duchen and Szabadkai, 2010). In this section we discuss the small number of available studies where retrograde signalling, triggered by *primary* mitochondrial dysfunction, targets *specifically* the PGC-1 family of coactivators. In general, in these studies the retrograde signals involved are poorly characterised, and the examples presented involve a number of pathways and regulators upstream of PGC-1 family expression and activation, as detailed in the first section and recently reviewed in (Hock and Kralli, 2009; Lin et al., 2005a; Scarpulla, 2011). The outcome of such a signalling, given the broadly cytoprotective role of the PGC-1 family in cellular physiology, follows two general patterns depending upon the particular pathology. In diseases characterised by increased susceptibility to cell death such as neurodegenerative, neuromuscular and cardiovascular diseases, retrograde activation of PGC-1 is expected to play a protective role. In contrast, in cancer, PGC-1 mediated promotion of cell proliferation and survival would contribute to disease progression.

Human mtDNA encodes 37 genes, including 22 mitochondrial tRNAs, 2 mitochondrial rRNAs and 13 proteins, which are essential components for OXPHOS. In addition mtDNA also contains a displacement loop (D-loop) region, which is essential for both the transcription and replication of the mtDNA (Fish et al., 2004; Kelly and Scarpulla, 2004). In comparison to nuclear DNA, mtDNA undergoes a faster rate of mutation due to a variety of factors, notably that mtDNA lacks introns, protective histones and has limited DNA repair capacity. Furthermore, mtDNA is located close to the mitochondrial inner membrane and is therefore vulnerable to oxidative damage due to continuous exposure to ROS generated during OXPHOS (Chandra and Singh, 2011a). Since the identification of the first pathogenic mtDNA mutations in 1988 (Holt et al., 1988) more than 250 pathogenic mtDNA alterations, including point mutations and rearrangements, have been found to cause a range of diseases (Tuppen et al., 2010; Wallace, 2010). Germline mtDNA rearrangements and point mutations may lead to a broad spectrum of diseases, such as mitochondrial myopathies or encephalopathies, Leber's hereditary optic neuropathy (LHON), chronic progressive external ophthalmoplegia (CPEO), Leigh syndrome, Kearns–Sayre syndrome, Myoclonic Epilepsy with Ragged Red Fibers (MERRF), 'Mitochondrial Myopathy, Encephalomyopathy, Lactic Acidosis, Stroke-like Symptoms' (MELAS) maternally-inherited diabetes and deafness, neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome (Swerdlow, 2009; Taylor and Turnbull, 2005; Wallace, 2010). Accumulation of somatic mtDNA mutations is also associated with ageing and age-related diseases such as cancer and neurodegenerative diseases (Reeve et al., 2008; Swerdlow, 2009). Importantly, increased mtDNA mutation load has been reported in sporadic diseases including Alzheimer's disease and Parkinson's disease (Lin et al., 2002b; Simon et al., 2004; Smigrodzki et al., 2004). As pathogenic mtDNA mutations will affect either the maintenance of the mtDNA or alter the function and assembly of core components of the respiratory chain complexes, the ultimate outcome of those mutations is likely to be defects in OXPHOS. A limited number of studies have suggested a possible link between OXPHOS defects and a retrograde signalling pathway to nuclear factors regulating transcription such as PGC-1α to promote mitochondrial biogenesis, although the mechanisms of such signalling require further investigation. In *in vitro* cellular models, exposure to high concentrations of respiratory uncouplers was shown to cause Ca^{2+} mediated up-regulation of PGC-1α (Rohas et al., 2007), whereas ROS was suggested to have the same effect in adaptive responses to even subtle changes in OXPHOS activity caused by common mtDNA sequence variants in different mouse strains (Moreno-Loshuertos et al., 2006) as well as in neurodegenerative disease (St-Pierre et al., 2006). Increased mitochondrial content in the skeletal muscle of patients with impaired OXPHOS due to mtDNA mutations has been reported since the late 1980s (Lombes et al., 1989; Moraes et al., 1989; Shoubridge et al., 1990), which might reflect PGC-1α upregulation, as shown in skeletal muscle of mitochondrial myopathy patients with various mtDNA mutations (Adhihetty et al., 2007). However, other studies suggest that retrograde signalling from mitochondria to the nucleus is not always activated in all cells harbouring pathogenic mtDNA mutations. For example, PGC-1α expression was unaltered in fibroblasts from patients with G13513A, T9185C or A3260C mutations (Menzies et al., 2009) and CREB activation was not observed in skeletal muscle from patients harbouring the A3243G mtDNA mutation or the common 4977 bp mtDNA deletion (Crimi et al., 2005). Similarly, no change in PGC-1α expression was observed in MELAS (Joseph et al., 2004) or NARP (Wojewoda et al., 2011). The lack of a mitochondrion–nucleus compensatory loop in some cases was attributed to its replacement by an intramitochondrial feedback mechanism, comprising the activation of a soluble mitochondrial adenylate cyclase and consequent PKA mediated phosphorylation and activation of complex IV (Acin-Perez et al., 2009). Altogether, these and other studies suggest that the feedback control of nuclear TFs by primary mitochondrial defects may follow a tissue and condition specific pattern, potentially involving PGC-1 family mediated cellular survival. However, no studies have yet directly demonstrated such an inherent protective mechanism in neurodegenerative and cardiovascular disease, warranting further investigation, particularly in view of the beneficial role of direct, experimental activation of mitochondrial biogenesis in these diseases.

Somewhat more information has been obtained on the role of mtDNA integrity, mitochondrial function and retrograde signalling to the PGC-1 family of coactivators in cancer. Extensive sequencing of the mitochondrial genome has revealed that approximately 40–70% of all tumours carry mtDNA alterations, including deletions, insertions and missense mutations (Kaipparettu et al., 2010). In addition to pathogenic mtDNA mutations, certain polymorphisms in mtDNA have also been associated with a predisposition to age-related diseases. For instance, mitochondrial haplogroup U is associated with increased risk of developing prostate cancer and renal cancer (Booker et al., 2006). The A10398G and T16519C polymorphisms increase the risk of developing breast cancer in European–American females, whereas conversely the T3197C and G13708A polymorphisms were found to decrease the risk (Bai et al., 2007). A complete description of all known pathogenic mtDNA mutations and associated diseases is beyond the scope of this review, however a current and updated list of all known mtDNA mutations and polymorphisms can be found in the MitoMAP database (http://www.mitomap.org), and the topic of cancer related mtDNA mutations has been extensively reviewed recently (Brandon et al., 2006; Chandra and Singh, 2011b; Czarnecka et al., 2010; Kulawiec et al., 2010). As discussed above, there is compelling evidence that mitochondrial stress can be causal to the development of various hallmarks of cancer, representing a potential link to primary somatic mtDNA mutations in cancer cells. A specific mutation, unleashing retrograde ROS signalling involving Mcl-1 and HIF1α has been shown to contribute to the development of a metastatic phenotype (Ishikawa et al., 2008a; Ishikawa et al., 2008b), while Akt hyperphosphorylation in the absence of elevated ROS was also able to elicit a similar effect (Kulawiec et al., 2009). Importantly, among the heterogeneous retrograde pathways a few studies have also addressed the role of the PGC-1 family as targets in cancer cells with mtDNA defects. Wenz and colleagues found that the expression of PGC-1α was increased by 3-fold in galactose-resistant clones of a cybrid cell line carrying a homoplasmic mutation (G5703A) in a mtDNA encoded tRNA (Wenz et al., 2010). The same group has also reported upregulation of both PGC-1α and PGC-1β as a consequence of mutations in the ND5 and COXI genes (Srivastava et al., 2007). Furthermore, CREB, a nuclear TF that is known to act at the PGC-1α promoter, was found to be activated in mtDNA-depleted

murine fibrosarcoma cells and human osteosarcoma cells, as well as in cybrid cells harbouring the A8344G mtDNA mutation (Arnould et al., 2002; Mercy et al., 2005). Clinically even more relevant results on this subject were obtained on a subset of tumours with aberrant mitochondrial proliferation, termed oncocytomas. In these neoplasms, mitochondrial defects, mostly due to mtDNA mutations encoding various complex I subunits, trigger compensatory upregulation of mitochondrial biogenesis as recently reviewed (Gasparre et al., 2011). Although the nature of the primary signal is debated, the involvement of PGC-1 family coactivators was demonstrated in this retrograde response. In a subset of thyroid oncocytic tumours PRC was shown to be the primary target of NO and Ca^{2+} mediated signals (Le Pennec et al., 2011; Savagner et al., 2003), whereas in *in vitro* cellular models of oncocytomas, varying the PRC:PGC-1α ratio appears to set the balance between the oxidative and glycolytic phenotypes (Mirebeau-Prunier et al., 2010). Additionally, the occurrence of oncocytic-like foci in the development of endometrial carcinomas was found to be associated with induction of several PGC-1 family target genes (Guerra et al., 2011). Overexpression of PGC-1 family member thus appears to positively correlate with pathogenic changes in cellular function in certain types of cancer cells.

4. Conclusions

Mitochondrial biogenesis is a fundamental cellular process, required both to maintain a functional population of mitochondria capable of meeting cellular energy demands in the face of continual molecular turnover in the mitochondrial network, and as an adaptive mechanism in response to varying energetic requirements. Thus, the ability to synthesise and assemble mitochondrial components is vital for cell survival.

Uniquely amongst the organelles of animal cells, mitochondrial biogenesis falls under the control of two genomic systems, the nuclear genome and mtDNA respectively. The need to co-ordinate the production and assembly of protein components from separate genetic systems, accompanied by the import of further constituents such as lipids from remote sites of synthesis, has lent itself to the development of complex regulatory networks of transcription. Such transcriptional networks rely upon the concerted action and interaction of multiple NRs and TFs for appropriate gene expression. Coregulators acting as part of multiprotein complexes both to promote and to suppress the activity of NRs and TFs directly and through modification of regulatory elements add a further level of fine control, which may exert influence in a cell-type specific manner. Finally, numerous signalling pathways and patterns of gene expression converge upon these biogenesis factors to integrate the energetic needs of the cell, tissue and entire organism into an apposite programme of transcription.

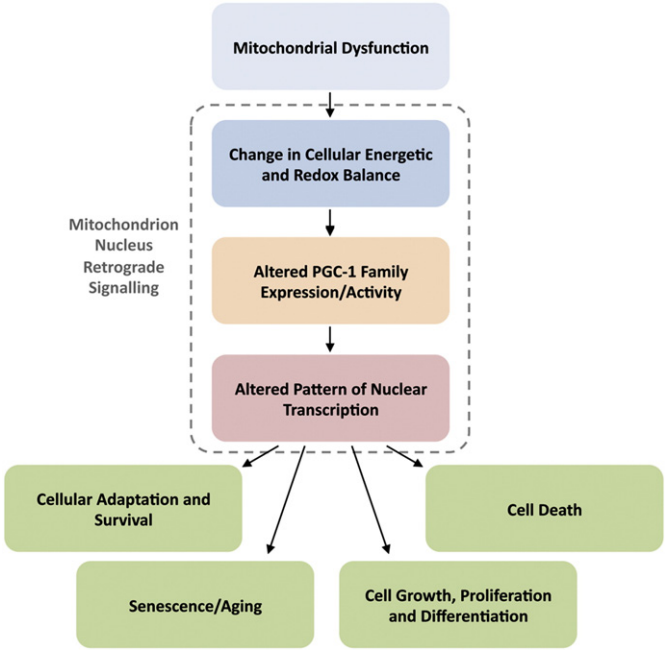

Fig. 3. Retrograde mitochondrion-nuclear regulation of cell fate. Mitochondrial dysfunction may cause fluctuations in cellular Ca^{2+}, energetic and redox homeostasis and in turn modify the expression and/or activity of nuclear TFs. Subsequent alterations in the expression of nuclear target genes regulated by these TFs constitutes a retrograde mitochondrion–nucleus signalling response. This response may promote cellular adaptation, survival, growth or proliferation. Conversely, it can also contribute to senescence or ultimately activate cell death pathways, depending on the genetic or environmental background of the cell. Where deregulation of these processes underpins disease, such retrograde signalling may contribute to pathology.

The PGC-1 family of coactivators function as master regulators of cellular metabolism and mitochondrial biogenesis, and sit at a hub of cellular signalling. Activation or repression of the transactivating function of the PGC-1 family members may drastically alter cellular metabolic activity both directly and indirectly related to mitochondria. Indeed, dysfunction of PGC-1 family coactivators may underlie pathology associated with a diverse range of diseases, including cardiovascular disease, neurodegeneration and cancer. Whilst the normal and pathological regulation of the PGC-1 family remains under investigation, modifications at both the level of transcription and post-translation appear to play a role.

Dysfunction of mitochondria (also termed mitochondrial stress) is now a well-established characteristic of many disease states. These defects are either due to primary mitochondrial alterations, resulting from mutations in mtDNA or nuclear genes encoding mitochondrial proteins, or are the consequence of pathological processes in other cellular compartments. The direct consequences of mitochondrial stress, such as cellular energetic and redox crisis, have a widely recognised pathophysiological role, but the ability of mitochondria to generate signals capable of affecting global patterns of nuclear transcription has not been so widely discussed. Whilst such mitochondria–nucleus retrograde signalling pathways have been described in yeast for some time, the functions and molecular details of comparable communication in mammalian cells have only just begun to emerge. Such mammalian retrograde signalling may be mediated by heterogeneous signals, including altered Ca^{2+} homeostasis, an imbalance in cellular redox state and unsteady ATP levels. Primary mitochondrial dysfunction may also modulate these key parameters, modifying the activity of multiple cellular signalling pathways to finally target a large set of transcriptional coregulators and transcription factors, and consequentially fundamentally alter the transcription of nuclear genes (Fig. 3). We have here discussed the available studies which describe such links between mitochondria and the nucleus, specifically those targeting the PGC-1 family of coactivators. Such retrograde signalling could promote fine and rapid adaptation to changing bioenergetic requirements, however pathophysiological signalling by these means, such as during chronic impairment of OXPHOS produced by mtDNA mutations, may alter the global pattern of gene expression in either a beneficial or maladaptive fashion, depending on the particular pathology. Importantly, a primary mitochondrial defect could conceptually therefore impinge upon cell fate by altering gene expression patterns which are not obviously connected to the initial mutation, and might explain how varied mtDNA mutations converge upon similar phenotypes. Further investigation of the mitochondrion–nuclear signalling thus could yield new treatment strategies and pharmacological targets for a wide range of disorders.

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