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Mitochondrial regulator PGC-1 α —Modulating the modulator

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Abstract

Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 α) is a central regulator of metabolism that is poised at the intersection of myriad intracellular signaling pathways. In this brief update, we discuss regulation of PGC-1 α at multiple levels, including transcriptional, post-transcriptional, and post-translational modifications. We discuss recently identified small molecule effectors of PGC-1 α that offer translational potential and promise new insight into PGC-1 α biology. We highlight novel mechanistic insights relating to PGC-1 α 's interactions with RNA to enhance transcription and potentially influence transcript processing. Finally, we place these exciting new data in the context of aging biology, offering PGC-1 α as a candidate target with terrific potential in anti-aging interventions.

In addition to their more appreciated role as the primary generators of cellular ATP, mitochondria also serve numerous other functions: to name just a few, they are the site of many of the chemical reactions of intermediary metabolism, act as a buffer for cytosolic calcium, generate ROS, and regulate apoptosis [1]. A few components of complexes of the electron transport system involved in oxidative phosphorylation, 13 genes, are encoded by mitochondrial DNA; however, the remaining >1000 genes are nuclear encoded [2]. Expression of nuclear encoded mitochondrial genes is controlled by a network of transcription factors, transcriptional coactivators, and transcriptional corepressors [3]. Among the best studied of these factors is the transcriptional coactivator peroxisome proliferator activated receptor gamma coactivator-1 alpha (PGC-1 α). PGC-1 α (gene symbol: *PPARGC1A*) is a transcriptional coactivator first discovered as a cold-inducible regulator of mitochondrial energy metabolism [4]. PGC-1 α has no known intrinsic enzymatic activity or DNA binding; instead, it elicits its effects by docking to transcription factors and recruiting other coactivators including SRC-1, CRE-binding protein (CREB), CBP/p300, and the Mediator complex [5–7]. Early studies expanded PGC-1 α interactions to members of the nuclear receptor family transcription factors such as PPARs, TR β , RXRa, RAR α , and ER α [8]. Since then, PGC-1 α has shown to physically interact with or indirectly activate

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numerous other transcriptional regulators involved in diverse cellular functions. Apart from interactions with the AP1 family of general transcription factors [9], the overarching theme among PGC-1 α binding partners and downstream regulatory factors is their involvement in adaptive responses to change. Energy metabolism is impacted by PGC-1 α status through its interactions with ERR α , NRF1, and NRF2/GABP α involved in regulation of nuclear and mitochondrial encoded mitochondrial genes [10,11]. Regulators of the fasting/feeding transition include HNF4 α and FOXO1 [12,13], and those involved in stress or growth signaling including p53, HSF1, and YY1 [14–16]. Elsewhere, PGC-1 α contributes to adaptive changes in patterns of physical activity through myocyte enhancer factor 2 (MEF2) [17], oxygen sensing and signaling through HIF-1 α [18], and many others. PGC-1 α is thought to almost exclusively activate gene expression [9], although repressor activity has also been reported in some cases [19]. Many of these interactions have been identified in specific cell types only or in specific tissues only, and we do not yet have the full picture of how cellular context frames the suite of factors that are accessible to PGC-1 α and/or sensitive to changes in its activity status. All the same, the breadth of cellular functions that are influenced by PGC-1 α is quite extraordinary, arguing that it lies at a central integration point between stimulus and response and as such could be a key player in maintenance of cellular plasticity and adaptation.

PGC-1a is extensively regulated at the transcript and protein levels

Earlier work on PGC-1 α focused primarily on its potential use as a target for diabetes, leading to important discoveries of regulatory mechanisms in tissues that are key for metabolic homeostasis [20]. A great deal of this progress is down to the superb mouse models that have been generated over the years, including global or tissue-specific transgenics and knockouts (Table 1). In skeletal muscle, exercise activates PGC-1 α transcription via calcium signaling activation of the transcription factors MEF2C/MEF2D and CREB. Signaling through the energy-sensing kinase AMPK and the stress-inducible kinase p38 MAPK (mitogen-activated protein kinase) activate PGC-1 α transcription in skeletal muscle. In liver and brown adipose tissue, PGC-1 α transcription is down-stream of glucagon and beta adrenergic signaling, respectively. Since then, there have been new developments of regulation at the transcript level. A number of alternatively spliced isoforms of PGC-1 α have been reported in the literature [21], starting with the description of the isoform NT-PGC-1 α [22]. Much of the recent work regarding this aspect of PGC-1 α biology has focused on four isoforms originally described in muscle, named PGC-1 α 1 (the originally described isoform), PGC-1 α 2, PGC-1 α 3, and PGC-1 α 4 [23]. Brain-specific and liver-specific isoforms have also been described [24,25]. Determining the functional distinctions among these isoforms and the significance of tissue specificity in their expression is an area of active investigation.

PGC-1 α is a modular protein (Figure 1) containing several functional domains, including LXXLL motifs required for docking with several transcription factors, predicted PEST motifs that are associated with protein stability, a nuclear localization sequence, a serine-arginine (SR)-rich domain involved in protein-protein interactions, and an RNA recognition motif (RRM). PGC-1 α is an intrinsically disordered protein, which influences its regulation [26] and may underlie its ability to directly interact with a large range of transcription

factors and cofactors [15]. The modifications decorating intrinsically disordered proteins are thought to impose structural changes which facilitate interactions with binding partners, allowing for broad range of potential regulatory inputs and facilitating engagement with different complexes [27].

Protein stability of PGC-1 α has emerged as an important method of regulation [28]. PGC-1 α has been shown to be modified by the small protein ubiquitin, a process that can be regulated by other marks such as phosphorylation by p38 MAPK and GSK3 β . Several E3 ubiquitin ligases have been implicated in targeting PGC-1 α for 26S proteasomal degradation. F-box and WD repeat domain containing 7 (FBXW7) is a particularly interesting example, with FBXW7 β decreasing PGC-1 α stability and FBXW7 α increasing PGC-1 α stability [29]. FBXW7 expression requires Ewing sarcoma protein (EWS), an RNA-binding protein. EWS inactivation decreases PGC-1 α protein stability and decreases mitochondrial content, a phenotype rescued by PGC-1 α complementation [30]. Although PGC-1 α has both nuclear and cytosolic pools [31,32], its degradation by the 26S proteasome is most likely nuclear [33]. Independent of ubiquitin modification, PGC-1 α can also be degraded by the 20S proteasome [26], an alternative mechanism of protein degradation common for intrinsically disordered proteins. Interestingly, PGC-1 α degradation by the 20S proteasome is prevented by NQO1 (NAD(P)H quinone dehydrogenase 1) in an NADH-dependent manner, providing an additional mechanism of PGC-1 α activation in response to redox state.

Among the best characterized post-translational modifications (PTMs) on PGC-1 α are phosphorylation and acetylation. p38 MAPK phosphorylates PGC-1 α on three residues, increasing its protein stability and transcriptional co-activator activity [28]. These sites all reside within the predicted PEST domain (Figure 1). PGC-1 α is activated by AMPK phosphorylation [34], and the smaller isoform NT-PGC-1 α is activated by PKA phosphorylation [22]. Phosphorylation of PGC-1 α can also be inhibitory, as is the case with AKT [35] and CLK2 [36], which phosphorylate PGC-1 α on multiple sites within the SR domain, blocking interaction between PGC-1 α and MED1 of the mediator complex. PGC-1 α is also phosphorylated by GSK-3 β , a modification that targets PGC-1 α for proteasomal degradation [31,37]. Acetylation on 13 lysines [38,39] is carried out by GCN5, a member of the SAGA complex [40]. Deacetylation of PGC-1 α by SIRT1 has been shown to activate PGC-1 α , and inhibition of SIRT1 has been shown to block PGC-1 α nuclear localization in response to a stress stimulus [31]. Regulation of PGC-1 α by acetylation provides an additional layer of regulation sensitive to energy state in the cell [20]. For example, AMPK activation leads to activation of SIRT1 through modulation of intracellular NAD metabolism [41]. Furthermore, PGC-1 α acetylation may be sensitive to intracellular concentration of acetyl-CoA, providing another link to cellular energy state.

Emerging roles for PGC-1 α in white adipose tissue

The earliest studies of PGC-1 α focused in large part on muscle, liver, and brown adipose tissue, exploring its role in exercise, glucoregulatory function, and the thermogenic response [20] (Figure 2). The importance of mitochondrial adaptation in cellular function has prompted investigations in other tissues, including white adipose tissue. Adipose tissue is derived from several developmental lineages, but it can be broadly categorized as energy-

expending brown adipose tissue (BAT), energy storing white adipose tissue (WAT), and intermediate, inducible ‘beige’ adipocytes. Although PGC-1 α is a well-known regulator of uncoupled respiration in BAT, it is also expressed in WAT where it is required for maintaining expression of mitochondrial genes [43]. More recently, PGC-1 α has been shown to play a central role in the ‘browning’ transition from WAT to beige downstream of an AMPK-SIRT1 signaling axis under high-fat diet feeding conditions [44]. In addition to its function as an energy storage depot, WAT is an important endocrine organ and plays a central role in whole-body metabolism. The secretory profile and metabolic status of adipose tissue was recently shown in mice to be altered by caloric restriction (CR), a dietary regimen that delays or prevents the onset of multiple chronic diseases [45]. Interestingly, CR also increases protein levels of PGC-1 α and positive regulators SIRT1 and AMPK in WAT, suggesting that PGC-1 α activation in adipose tissue may contribute to the mechanisms of CR. PGC-1 α is also a key target of signaling through the adipose-tissue-derived peptide hormone adiponectin [46], suggesting that it operates at both ends in adipose tissue-directed regulation of metabolic homeostasis.

Pharmacological approaches to modulate PGC-1 α

Small molecule modulators of PGC1 α protein expression and activity have been sought as a means to implement targeted metabolic changes. Recently, a number of small molecule screens have been performed with a goal of directly modulating PGC1 α expression or protein stability. Initial screens looked for Ppargc1 α gene activation as a direct assay readout [47,48]. The novel benzimidazole compound, ZLN005, was identified as an activator of PGC1 α gene expression [49] and has been shown to improve metabolic outcomes in a diabetic mouse model and provide protection against cytotoxicity in *in vitro* models of cardiomyopathy [50]. Independent studies have shown protection against macular degeneration [51] and more recently have implicated PGC-1 α in mitigating ischemic-induced neuronal injury in mice [52]. Other small molecule high-throughput screens have been performed to identify compounds that can alter PGC-1 α stability or activity through PTMs. One screen identified a handful of small molecules (specifically, compounds AM80 and AM73) that stabilize PGC1 α protein in different cellular compartments [53]. Treatment with the small molecules not only elicited the classic metabolic pathway transcriptional response but also induced gene expression changes in molecular pathways related to mRNA and general RNA binding. It is unclear if this latter outcome is a direct or indirect effect of targeting PGC-1 α stability, but recent developments in PGC-1 α 's role in RNA processing suggest that this may present a new targetable function.

Inhibitory screens have also found small molecules that can impinge on PGC-1 α PTM status. A recently identified novel compound, SR-18292, was able to elicit beneficial effects in a diabetic mouse model [54]. The compound was found to inhibit hepatic PGC-1 α -induced gluconeogenic transcriptional response linked to HNF4 α , with the proposed mechanism of increased PGC-1 α acetylation. SR-18292 is thought to facilitate the interaction between PGC-1 α and GCN5, allowing hyperacetylation and PGC-1 α protein inhibition (Figure 3). Interestingly, expression of other PGC-1 α targets, including metabolic and mitochondrial genes, was unaltered after treatment with the compound. To date, it remains unclear how PGC-1 α target genes are selectively engaged, and it seems likely that PGC-1 α PTM status

and protein stability at least in part dictate which of the myriad downstream targets are engaged in a given cellular context.

These small molecules show terrific promise for future application in a clinical setting. The next critical steps to realizing their pharmacological potential in human metabolic disease will include research into their bioavailability and delivery efficacy. Apart from their translational potential, these agents will likely prove extremely valuable as tools for discovery in PGC-1 α biology. Agonist and antagonist studies may well lead to better understanding of PGC-1 α 's web of interaction including how upstream signals dictate downstream consequence at the cell type and tissue-specific level.

PGC-1 α engages RNA-based mechanisms

Recent studies shed light on a more nuanced role for PGC-1 α in fine-tuning transcriptional dynamics. In full-length human PGC-1 α , C-terminal K779 has been recently identified as a substrate for methyltransferase SET7/9 and demethylase LSD1 that have been shown to deposit and remove the methylation mark, respectively [55]. This modification is required for the PGC-1 α interaction with MED1 and MED17 of the Mediator complex in both hepatocytes and adipocytes. Methylated PGC1 α was also found to interact with SAGA complex proteins SGF29, ADA2, and ADA3. Interestingly, the affinity of PGC1 α [K799me1] interaction with SGF29 requires the tudor domain of SGF29 (Figure 3). These data suggest a role for PGC-1 α as a scaffold in recruitment of complex subunits, perhaps allowing for complex assembly to be linked to metabolic status. The methyltransferase NSUN7 is a novel PGC-1 α -interacting protein that methylates enhancer RNA (eRNA) (Figure 3). Cooperation between these two proteins may direct the action of eRNA in directing the fate of the mRNA as a means to tailor gene expression to metabolic status. It is not clear that all interactions with RNA are dependent on PGC-1 α methylation status. A nine amino acid CBP-binding motif (CBM) was identified in the human PGC-1 α protein sequence [56]. Both the SR domain and the CBM are required for CBP80 binding to PGC-1 α . The CBM is required for the ability of PGC-1 α to interact with nascent, mature, and noncoding RNA (Figure 3). Unexpectedly, loss of the PGC-1 α RRM did not completely ablate PGC-1 α 's ability to interact with RNA. These findings indicate that after initial contact, stable interaction of PGC-1 α with nascent and mature RNA occurs with assistance from other protein complexes. Besides these biochemically validated interactions, several new interacting partners were identified that may also depend on the K779 methylation status of PGC-1 α , including orphan nuclear pore proteins and RNA processing components [55]. Further investigation of these interactions will, no doubt, provide important insight into PGC-1 α role in RNA processing and transport dynamics in the nucleus.

Translational potential

A growing consensus holds metabolic dysfunction as a unifying underlying mechanism of aging and age-related disease vulnerability [57,58]. Delayed aging by CR offers a window into the biology of aging and here too metabolism has been implicated [59]. A CR-induced transcriptional signature common among diverse tissues involves increased mitochondrial oxidative phosphorylation and redox pathways [60]. This transcriptional signature is

conserved among species on CR and in long-lived genetic mouse models, supporting the concept that mitochondrial function plays a central role in longevity and healthy aging. A further intriguing development is the role of RNA processing in the mechanisms of CR [42] that may, in light of the recent developments described here, be linked to PGC-1 α . Viewed against this backdrop, the importance of advancing what is known about regulators of metabolism such as PGC-1 α is evident. Given the pace of progress to date, we can anticipate in the next few short years a better understanding of how PGC-1 α 's activity might be directed, target specificity determined, and tissue-specific activities selected and optimized. In learning how to harness the beneficial aspects of PGC-1 α function, we will be one step closer to designing effective strategies to delay aging and the onset of age-related disease.

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Figure 1.

PGC-1α protein structure and post-translational modifications. **(a)** Schematic of PGC-1α protein features: SR-rich domain, serine-arginine-rich domain; NLS, nuclear localization sequence; RRM, RNA-recognition motif; CBP80 binding domain. **(b)** FoldIndex prediction of folded and unfolded regions. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha.

Figure 2.

Signaling upstream of PGC-1α and general outcomes of PGC-1α activation. Red arrows indicate changes in PGC-1α activity or intracellular localization, and blue arrows indicate changes in protein stability. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha.

Figure 3.

Recent advances in PGC-1α biology. (a) Methylation of PGC-1α at residue K799. (b) SR-18292 inhibition of PGC-1α. (c, d) PGC-1α interaction with RNA. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha.

Table 1

PGC-1 α transgenic mice.

PMID	Year	PGC-1 α variant	Source	Conditional/whole body
12181572	2002	Mml-PGC-1 α	cDNA	Mml MCK-driver
14726475	2004	Mml-PGC-1 α	cDNA	Tet-inducible
18511502	2008	Mml PGC-1 α -b (GenBank: BB853729) Mml PGC-1 α -c (GenBank: AW012094)	cDNA	Hsa ACTA1-driver
19208857	2009	Hsa-Ppargc1a	BAC	Whole body (Hsa endogenous Ppargc1a promoter)
21984601	2012	Mml-PGC-1 α	cDNA	Mml Thy1-driver
23217713	2012	Mml-PGC-1 α 4	cDNA	Mml MYOG-driver
27910955	2016	Hsa-PGC-1 α	cDNA	Mml VE-Cad-driver
PMID	Year	PGC1 α disruption	Conditional/whole body	
15454086	2004	Flox exons 3–5	Whole body	
15760270	2005	Exon 3 duplication between exons 5–6.	Whole-body hypomorph	
22087241	2011	Flox exons 4–5	Whole-body hypomorph	
30026188	2018	Fused exons 6 & 7	Whole-body hypomorph	

PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator-1 α .