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Review

PGC-1 coactivators in the control of energy metabolism

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Chronic disruption of energy balance, where energy intake exceeds expenditure, is a major risk factor for the development of metabolic syndrome. The latter is characterized by a constellation of symptoms including obesity, dyslipidemia, insulin resistance, hypertension, and non-alcoholic fatty liver disease. Altered expression of genes involved in glucose and lipid metabolism as well as mitochondrial oxidative phosphorylation has been implicated in the pathogenesis of these disorders. The peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) family of transcriptional coactivators is emerging as a hub linking nutritional and hormonal signals and energy metabolism. PGC-1α and PGC-1β are highly responsive to environmental cues and coordinate metabolic gene programs through interaction with transcription factors and chromatin-remodeling proteins. PGC-1α has been implicated in the pathogenic conditions including obesity, type 2 diabetes, neurodegeneration, and cardiomyopathy, whereas PGC-1β plays an important role in plasma lipoprotein homeostasis and serves as a hepatic target for niacin, a potent hypotriglyceridemic drug. Here, we review recent advances in the identification of physiological and pathophysiological contexts involving PGC-1 coactivators, and also discuss their implications for therapeutic development.

Keywords transcriptional coactivator; metabolic syndrome; PGC-1; mitochondrial biogenesis; energy metabolism

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Introduction

The prevalence of contemporary life style, characterized by increased consumption of high-fat, high-fructose food and reduced physical activity, has driven a dramatic increase in the incidence of metabolic syndrome. It has been projected that, by 2025, one in every three American children born in the year 2000 will carry a significant lifetime risk of developing type 2 diabetes, and therefore become prone to premature cardiovascular disease, blindness, kidney failure, and amputations. A cardinal feature of metabolic syndrome is severe obesity, which arises from chronic imbalance between energy intake and energy consumption. As such, restoration of the energy balance is a major strategy for the therapy of metabolic disease including obesity, diabetes, hypertension, atherosclerosis, and fatty liver diseases.

Peroxisome proliferator-activated receptor (PPAR) γ coactivator-1 (PGC-1) family members are multifunctional transcriptional coregulators that act as 'molecular switches' in many metabolic pathways. PGC-1α and PGC-1β have been shown to regulate adaptive thermogenesis, mitochondrial biogenesis, glucose/fatty-acid metabolism, peripheral circadian clock, fiber-type switching in skeletal muscle, and heart development. Their versatile actions are achieved by interacting with different transcription factors in a tissue-specific manner. The potent effects of PGC-1 coactivators in coordinating various metabolic processes underscore their significant role in the control of energy metabolism as well as their potential as targets for pharmacological intervention.

Structure and function of PGC-1 coactivators

The PGC-1α gene is located on chromosome 5 in mice (chromosome 4 in humans) and encodes a protein containing 797 (mouse) or 798 (human) amino acids [1]. Structural and functional studies have indicated that PGC-1α has a strong transcriptional activation domain at the N terminus, which interacts with several histone acetyltransferase (HAT) complexes including 3'-5'-cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB)-binding protein, p300, and steroid receptor coactivator-1 [2]. These proteins acetylate histones and

remodel chromatin structure into a state that is permissive for transcriptional activation. Adjacent to the N-terminal domain is a regulatory region that roughly spans 200 amino acids. Toward the C terminus, PGC-1α recruits the thyroid receptor-associated protein/vitamin D receptor-interacting protein/mediator complex that facilitates direct interaction with the transcription initiation machinery [3]. This region also interacts with the switch/sucrose non-fermentable (SWI/SNF) chromatin-remodeling complex through its interaction with BAF60a [4]. The Ser/Arg-rich domain and an RNA-binding domain toward C terminus have been demonstrated to couple pre-mRNA splicing with transcription [5]. As such, PGC-1α serves as a platform for the recruitment and assembly of various chromatin-remodeling and histone-modifying enzymes to alter local chromatin state. Importantly, the PGC-1α transcriptional activator complex is also able to displace repressor proteins, such as histone deacetylase and small heterodimer partner, on its target promoters, providing an alternative mechanism for gene activation [6]. PGC-1α and PGC-1β share extensive domain similarity and several clusters of conserved amino acids, such as the LXXLL motif that interacts with nuclear receptors and host cell factor 1 interacting motif [7]. The third family member, PRC (PGC-1-related coactivator), also contains the activation domain and RNA-binding domain, but overall has more limited homology to PGC-1α and PGC-1β [8]. The PGC-1 family members are conserved in higher vertebrates, including mammals, birds, and fish. Interestingly, a PGC-1 family homologue named Spargel was recently identified in *Drosophila* that could regulate mitochondrial activity and insulin signaling [9].

Both PGC-1α and PGC-1β robustly regulate mitochondrial oxidative metabolism (**Fig. 1**). PGC-1α was initially identified as a PPARγ-interacting protein from the brown adipose tissue (BAT) that could regulate adaptive thermogenesis in response to cold [1]. Subsequent studies revealed that the core function of PGC-1α was to stimulate mitochondrial biogenesis and oxidative metabolism. PGC-1α is abundantly expressed in tissues with high energy demand, including the BAT, heart, skeletal muscle, kidney, and brain [10–12]. In fact, when ectopically expressed in fat or muscle cells, PGC-1α strongly stimulates the program of nuclear and mitochondrial-encoded mitochondrial genes as well as organelle biogenesis [10]. The stimulatory effects of PGC-1α on mitochondrial genes are achieved through its coactivation of nuclear respiratory factors 1 and 2 (NRF1 and NRF2, respectively) and the estrogen-related receptor α (ERRα) [10,13,14]. The induction of NRF1 and NRF2 subsequently leads to the increased expression of mitochondrial transcription factor A (mtTFA) [10] as well as other mitochondrial subunits of the electron transport chain complex such as β-adenosine-triphosphate (ATP) synthase, cytochrome *c*, and cytochrome oxidase IV [15,16]. mtTFA translocates to mitochondrial matrix, where it stimulates mitochondrial DNA replication and mitochondrial gene expression [17].

As mentioned above, a critical aspect of PGC-1α is that it is highly versatile and has the ability to increase the transcriptional activity of many nuclear receptor families, including members of the estrogen, PPAR, retinoid X, mineralocorticoid, glucocorticoid (GR), liver X (LXR), pregnane X, the constitutive androstane, vitamin D, and thyroid hormone receptor families [18,19]. PGC-1α can also bind to unliganded nuclear receptors, as in the case of the orphan hepatic nuclear factor (HNF) 4α, farnesoid X receptor (FXR), and ERRα, suggesting that their conformations are conductive to ligand-independent mechanisms of gene regulation [20]. PGC-1α transcriptional partners are not limited to the nuclear receptor superfamily; however, this coactivator also associates with a diverse array of other transcription factors, including forkhead/winged helix protein family member FOXO1, as well as a number of zinc-finger proteins identified through a genome-wide coactivation screen [4,20]. The docking interface for these interacting

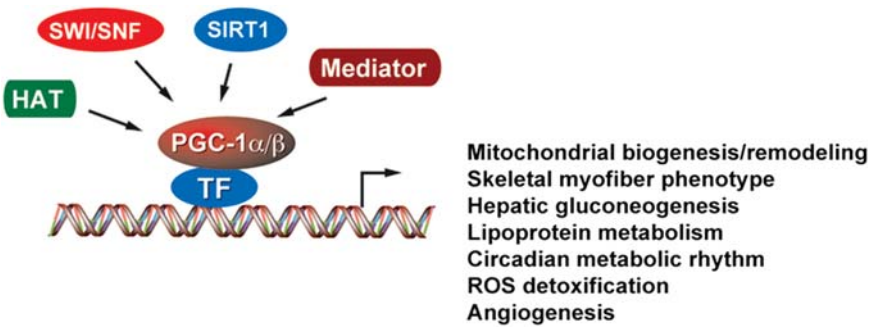

Figure 1 The working model of PGC-1 coactivators PGC-1α and PGC-1β regulate diverse metabolic programs through coactivating selective transcriptional factors (TF) associated with regulatory elements of target genes. PGC-1 recruits HAT, SWI/SNF chromatin-remodeling, Sirt1 deacetylase, and mediator complexes to modulate the epigenetic status of chromatin.

proteins appears to distribute throughout the length of PGC-1α. In addition, PGC-1α has three functional LXXLL motifs that are responsible for docking nuclear receptors [18]. The diversity of PGC-1α-interacting proteins enables PGC-1α to regulate various metabolic processes in a tissue-specific manner.

Tissue-specific metabolic actions of PGC-1 coactivators

The following section reviews PGC-1 functions in oxidative tissues including the brain, heart, brown fat, skeletal muscle, liver, and pancreatic islets, based on gain and loss-of-function analysis both in cultured cells and *in vivo*. A summary of tissue-specific PGC-1 functions and the phenotype of PGC-1 transgenic mouse models are included in **Tables 1 and 2**, respectively.

Brain

PGC-1α null mice display spongioform lesions in several brain areas, predominantly in the striatum, and exhibit behavioral abnormalities including marked hyperactivity and frequent limb clasping [39]. Recent studies of mice with neuron-specific PGC-1α inactivation support a crucial role of this factor in neuronal function and energy balance. Similar brain lesions are observed when PGC-1α is selectively ablated in CaMKIIα-positive neurons, providing direct evidence for its action in neurons. Of note, striatal degeneration with hyperactivity is reminiscent of Huntington's disease (HD) in humans, potentially implicating PGC-1α in the selective vulnerability of striatal neurons in HD. To date, the specific role of PGC-1α in linking mitochondrial dysfunction to HD pathogenesis has been explored. The mutant huntingtin protein accumulated in HD brain interferes with PGC-1α function by repressing its transcription [44]. Impaired PGC-1α expression and mitochondrial function contributes to neurodegeneration in susceptible neurons [21]. In addition, PGC-1α plays an important role in the regulation of genes responsible for the detoxification of reactive oxygen species (ROS), including copper/zinc superoxide dismutase (SOD1), manganese SOD (SOD2), and glutathione peroxidase 1 [22]. In this case, PGC-1α protects dopaminergic neurons from degeneration caused by oxidative stress. Taken together, the finding that PGC-1α expression is impaired in the striatum of HD patients raises the possibility that molecules activating PGC-1α may be therapeutically useful.

Heart

Heart is an organ with an extremely high and dynamic demand for ATP. Much of this supply comes from fatty-acid β-oxidation, though glucose also serves as fuel source. Several studies have demonstrated that PGC-1α is a crucial regulator of oxidative metabolism in the heart. PGC-1α mRNA levels are strongly induced in the neonatal heart, along with the activation of mitochondrial biogenesis and the metabolic switch from glycolysis to oxidative phosphorylation in cardiac muscle [24]. Overexpression of PGC-1α both *in vitro* and *in vivo* powerfully induces mitochondrial gene expression and biogenesis [24]. PGC-1α expression is reduced in several animal models of cardiac dysfunction, which is typically accompanied by a metabolic switch from fat oxidation to glycolysis [45]. PGC-1α null mice exhibit significantly lower cardiac reserve in response to electrical or chemical stimulation [46].

Table 1 Tissue-specific functions of PGC-1α and PGC-1β

Tissues	Biological functions	
	PGC-1α	PGC-1β
Brain	Maintenance of mitochondrial function [21], ROS detoxification [22], GABAergic neuronal function [23]	Unknown
Heart	Mitochondrial oxidative metabolism [24], fatty-acid β-oxidation [24]	Mitochondrial OXPHOS [25], mediating the effects of adrenergic stimulation on heart rate [26]
Brown fat	Mitochondrial biogenesis and fat oxidation [1]; Adaptive thermogenesis [1]	Brown adipocyte differentiation [27]; Adaptive thermogenesis [28]
Skeletal muscle	Slow-switch muscle fiber [29], mitochondrial biogenesis [29], skeletal muscle atrophy [30]	Type IIX fiber formation [31]
Liver	Hepatic fasting response [18,32], homocysteine metabolism [33], integration of circadian clock and metabolism [34]	Hepatic lipogenesis and VLDL secretion [35], regulation of lipoprotein catabolism [36]
Pancreatic islets	Suppression of GSIS and membrane depolarization [37]	Suppression of GSIS [38]

VLDL, very-low-density lipoprotein.

Table 2 Phenotypes of PGC-1 knockout and transgenic mouse models

Models	Manipulations	Phenotypes
PGC-1α	Whole-body ablation [39]	Hyperactive, cold-sensitive, resistant to diet-induced obesity, lesions in the striatum
	Whole-body ablation [40]	Reduced muscle performance and exercise capacity, impaired adaptive thermogenesis, hepatic steatosis
	Muscle-specific ablation [41]	Impaired glucose tolerance, normal peripheral insulin sensitivity
	Muscle-specific overexpression [29]	Switch of type II muscle fiber to type IIa and I muscle fibers, resistance to electrically stimulated fatigue
	Cardiac-specific overexpression [24]	Loss of sarcomeric structure, dilated cardiomyopathy
	Tetracycline-inducible, cardiac-specific overexpression [42]	Increased mitochondrial biogenesis, derangements of mitochondrial ultrastructure, cardiomyopathy
PGC-1β	Whole-body ablation [28]	Impaired mitochondrial function, reduced body weight and fat mass, increased thermogenesis, blunted chronotropic response to dobutamine in the heart, hepatic steatosis, reduced lipoprotein-associated triglyceride and cholesterol content
	Whole-body ablation [26]	Decreased activity during the dark cycle, abnormal hypothermia and morbidity, hepatic steatosis, increased serum triglyceride and cholesterol
	Deletion of exons 3–4 [43]	Mitochondrial dysfunction in liver and skeletal muscle, hepatic steatosis, hepatic insulin resistance
	Muscle-specific overexpression [31]	Increased fatty-acid oxidation, hyperphagia, reduced body weight and adipose tissue, increased exercise capacity, increased IIX fiber content
PGC-1α/β	Double knockout [25]	Neonatal lethality, bradycardia, intermittent heart block, reduced cardiac output, reduced growth, a late fetal arrest in mitochondrial biogenesis

Moreover, PGC-1α null mice develop early symptoms of heart failure, such as activation of the fetal program of cardiac gene expression and a significant increase in circulating levels of atrial natriuretic peptide, a hallmark of cardiac dysfunction [46]. These mice also exhibit lower treadmill-running capacity and diminished cardiac function after exercise. However, it should be noted that superphysiological expression of PGC-1α in the heart leads to robust mitochondrial proliferation and myofibrillar displacement, and dilated cardiomyopathy ensues [24]. As such, therapeutic regulation of PGC-1α in heart failure should aim at restoring PGC-1α function in cardiac muscle within a therapeutically beneficial window.

PGC-1β is also abundantly expressed in the heart [47]. Heart function in PGC-1β-deficient mice is largely unaffected under normal conditions [26]. However, PGC-1β ablation reduces mitochondrial content in cardiac muscle and blunts the effect of adrenergic stimulation on heart rate [26]. Remarkably, mice with combined deficiency of PGC-1α and PGC-1β (PGC-1α$\beta^{-/-}$) die shortly after birth with small hearts, bradycardia, intermittent heart block, and a markedly reduced cardiac output [25]. Cardiac-specific ablation of PGC-1β on a PGC-1α-deficient background results in cardiac defects including reduced growth, a late fetal arrest in mitochondrial biogenesis, and persistence of a fetal pattern of gene expression [25]. These observations suggest that PGC-1α and PGC-1β collectively are required for the postnatal metabolic and functional maturation of the heart.

Brown fat

In rodents, BAT is the major organ responsible for adaptive thermogenesis during cold exposure. In contrast to white adipose tissue, whose primary physiological function is energy storage, the main function of BAT is energy dissipation, largely in the form of heat. The expression of PGC-1α is strongly induced in BAT by cold temperature; PGC-1α is downstream of the β-adrenergic receptor/cAMP pathway and sympathetic nervous system activity [1]. In this case, PGC-1α turns on several key components involved in the adaptive thermogenic program, including the stimulation of fuel uptake, mitochondrial fatty-acid β-oxidation, and stimulation of uncoupling protein 1 (UCP1) expression [1]. PGC-1α interacts with other nuclear hormone receptors such as PPARα, retinoic acid receptor, and thyroid receptor to enhance UCP1 expression. UCP1 dissipates mitochondrial proton gradient by generating heat and uncouples oxidative phosphorylation from ATP production. PGC-1α-deficient mice are unable to defend against cold stress due to thermogenic defects [39].

PGC-1β mRNA is induced during white and brown adipocyte differentiation [27]. Interestingly, while the expression of PGC-1β is not cold inducible, its deficiency

also impairs adaptive thermogenesis [28], suggesting that these two coactivators play non-redundant function in fuel oxidation and thermogenic response.

Skeletal muscle

PGC-1α is abundantly expressed in skeletal muscle, particularly slow-twitch myofibers, and is rapidly inducible by exercise training in rodents and humans [48–50]. It is clear that calcium signaling pathways play important roles in the induction of PGC-1α through calcineurin and calcium-dependent protein kinases and the subsequent activation of CREB and myocyte-enhancing factor 2 [51,52]. In addition, p38 mitogen-activated protein kinase (p38 MAPK) and AMP-dependent kinase (AMPK) are also required for exercise-induced PGC-1α expression [51,53]. Interestingly, muscle-specific overexpression muscle creatine kinase (MCK) of PGC-1α in mice turns white, glycolytic skeletal muscles (fast-twitch muscle fibers) into red, oxidative muscles (slow-twitch muscle fibers) with increased mitochondrial biogenesis as well as the expression of contractile proteins characteristic of slow-twitch myofibers [29]. In addition to the regulation of mitochondrial function, PGC-1α increases mRNA content of enzymes involved in fat metabolism such as fatty-acid translocase/CD36, carnitine palmitoyltransferase I, and medium-chain acyl-coenzyme A dehydrogenase (MCAD) in skeletal muscle [54]. Consistent with the molecular changes, PGC-1α transgenic muscle has increased fatigue resistance following electrical stimulation [29]. In contrast, both whole-body and muscle-specific PGC-1α knock out (KO) mice show reduced mRNA and/or protein content of mitochondrial respiratory chain proteins and ATP synthase. They are exercise intolerant and their skeletal muscles are prone to contraction-induced fatigue [40].

In primary cultures of rat muscle cells, PGC-1β increases the expression of glucose transporter 4, myosin heavy chain Ib, and other slow-twitch muscle markers [55]. While PGC-1β also stimulates mitochondrial biogenesis in skeletal muscle, it appears to drive a program of gene expression that is reminiscent of type IIx fibers [31]. In addition, the expression of PGC-1β, but not PGC-1α, is decreased along with reduced ERRα activity and MCAD expression in skeletal muscle of senescence-accelerated mice [56].

Liver

Hepatic PGC-1α expression reaches its peak during early postnatal period [7]. In adults, starvation induces PGC-1α expression in the liver through glucagon and GR signaling [32]. PGC-1α orchestrates a complex program of metabolic changes that occur during the transition of a fed to a fasted liver, including gluconeogenesis, fatty-acid β-oxidation, ketogenesis, heme biosynthesis, and bile-acid homeostasis. These effects of PGC-1α on fasting adaption are achieved by coactivating key hepatic transcription factors, such as HNF4α, PPARα, GR, FOXO1, FXR, and LXR [18]. In accordance with these observations, PGC-1α KO mice and RNAi-mediated liver-specific PGC-1α knockdown mice display the impairment of gluconeogenic gene expression and hepatic glucose production [39,57]. These mice develop hypoglycemia and hepatic steatosis upon fasting [40]. In addition, PGC-1α regulates the genes encoding homocysteine synthesis enzymes in the liver and modulates plasma homocysteine levels [33]. Forced expression of PGC-1α *in vivo* leads to elevated plasma homocysteine levels.

In mammals, circadian clock regulates major aspects of energy metabolism, including glucose and lipid homeostasis and mitochondrial respiration. Our recent work revealed that PGC-1α is a key component of the circadian oscillator that integrates the peripheral clock and energy metabolism [34]. PGC-1α stimulates the expression of Bmal1, a core clock gene, in hepatocytes and muscle cells through coactivation of the ROR family of orphan nuclear receptors. Mice lacking PGC-1α have abnormal diurnal rhythms of activity, body temperature, and metabolic rate. As PGC-1α expression is regulated by nutritional and hormonal cues, it is likely that it links these signals to the clockwork and synchronizes tissue metabolism with circadian pacemaker.

PGC-1β expression is increased in response to dietary intake of fats and leads hyperlipidemia through activating hepatic lipogenesis and very-low-density lipoprotein (VLDL) secretion [35]. Several factors are involved in mediating the effects of PGC-1β on plasma triglyceride metabolism, including sterol response element-binding protein (SREBP), LXR, and Foxa2 [35,58]. Recent studies demonstrated that PGC-1β and its target gene apolipoprotein C3 (ApoC3) are downstream of nicotinic acid, a widely used hypotriglyceridemic drug [36]. Both acute injection and chronic feeding of mice with nicotinic acid suppress PGC-1β and ApoC3 expression in the liver [36]. These studies illustrated a new role for PGC-1β in modulating lipoprotein catabolism and the relevance of this pathway in therapeutic action of nicotinic acid. Remarkably, systemic delivery of antisense oligonucleotide targeting PGC-1β improved systemic metabolic homeostasis in the model of fructose-induced insulin resistance [59].

Pancreatic islets

β-Cell dysfunction is cardinal for the development of type 2 diabetes. PGC-1α is expressed in pancreatic β-cells and is elevated in animal models of type 2 diabetes [37]. Ectopic expression of PGC-1α impairs both early and delayed glucose-stimulated insulin secretion (GSIS) and suppresses membrane depolarization without affecting baseline insulin secretion. Altered PGC-1α expression is accompanied by increased glucose-6-phosphatase and reduced glucokinase gene expression. Furthermore, UCP2

may be another effector downstream of PGC-1; UCP2 mediates mitochondrial proton leak, decreases ATP production, and negatively regulates GSIS [60]. Although the mechanism through which PGC-1α is induced in diabetic animal models is not understood, fatty acids [61] and incomplete inactivation of FOXO1 [62] may contribute to this process. In contrast to animal data, studies in human type 2 diabetic islets showed that PGC-1α mRNA expression is markedly reduced and correlated with the reduction in insulin secretion in those islets [63]. DNA methylation of the PGC-1α gene promoter is increased in human diabetic islets. Therefore, the exact function of PGC-1α in pancreatic islets needs further study.

The function of PGC-1β in islets is less studied. A recent study indicated that PGC-1β, in contrast to PGC-1α, directly binds to and acts as a coactivator of SREBPs and Foxa2 involved in pancreas development and function [38]. The authors also showed that PGC-1β suppresses GSIS via upregulation of UCP2 and granuphilin gene expression in INS-1E cells [38].

Post-translational modifications of PGC-1 coactivators

PGC-1α undergoes extensive post-translational modifications, including acetylation, phosphorylation, methylation, and SUMOylation, in response to nutritional and hormonal signals. These modifications allow fine-tuning of PGC-1α activities in a context-dependent manner. The acetyl transferase general control of amino-acid synthesis 5 acetylates PGC-1α at several lysine residues, alters its localization within the nucleus, and inhibits its transcriptional activity [64]. On the contrary, deacetylation of PGC-1α through sirtuin 1 (Sirt1) increases PGC-1α activity on gluconeogenic gene transcription in the liver [65]. PGC-1α is phosphorylated by both p38 MAPK and AMPK in skeletal muscle [66,67], leading to a more stable and active protein. In contrast, phosphorylation of PGC-1α by Akt/protein kinase B downstream of the insulin signaling cascade in the liver decreased its stability and transcriptional activity [68]. In addition, PGC-1α also undergoes methylation at several arginine residues in the C-terminal region by protein arginine methyltransferase 1 [69]. Finally, PGC-1α can undergo SUMOylation in conserved lysine residue 183 and its transcriptional activity is attenuated [70]. Interestingly, experiments using C_2C_{12} cells have indicated that AMPK-mediated phosphorylation primes PGC-1α for deacetylation by Sirt1 [71], suggesting that different modifications of PGC-1α likely communicate with each other to coordinately regulate its activity. PGC-1β is also acetylated at multiple sites [72]; however, the biological significance of these events is less well defined.

PGC-1α and metabolic diseases

As PGC-1α regulates multiple aspects of energy metabolism, it is not surprising that PGC-1α has been found to be dysregulated in several pathological conditions. The expression of PGC-1α and its target genes involved in mitochondrial oxidative phosphorylation (OXPHOS) is significantly decreased in the skeletal muscle of patients with type 2 diabetes [73]. Similar reduction of PGC-1α expression was also observed in the adipose tissue of insulin-resistant and morbidly obese individuals [74]. Interestingly, thiozolidinedione, an important class of antidiabetic drugs, can enhance the expression of PGC-1α and mitochondrial biogenesis in white adipose tissue [75]. While these observations support a potentially beneficial role of PGC-1α in insulin resistance and type 2 diabetes, several studies suggested distinct actions of PGC-1α in other tissues. For example, PGC-1α expression is elevated in the liver of both type 1 and type 2 diabetic mouse models [76]. Furthermore, PGC-1α has been shown to stimulate hepatic glucose production and suppress β-cell energy metabolism and insulin release in mice [32,37]. Paradoxically, transgenic expression of PGC-1α in skeletal muscle leads to robust mitochondrial biogenesis but also causes insulin resistance, likely the result of imbalance of lipid uptake and oxidation [77]. In addition, a common polymorphism of the PGC-1α gene (Gly482Ser), which apparently reduces PGC-1α activity, has been linked to increased risk of type 2 diabetes [78].

In the cardiovascular system, PGC-1α expression is also decreased in hypertrophic heart [45]. PGC-1α null mice display accelerated cardiac dysfunction and clinical signs of heart failure [46]. In contrast, PPARα ligand-dependent transcriptional activity and coactivation by PGC-1α are enhanced in the heart by stress including ischemia and hypoxia [79]. In peripheral vessel tissues, downregulation of PGC-1α expression was observed in vascular smooth muscle cells (VSMCs) treated by oleic acid [80] and high glucose [81]. Restoration of PGC-1α has beneficial effects on VSMCs and endothelial cells [82]. In this context, PGC-1α appears to play an important role in ROS metabolism and defense against oxidative stress. These observations indicate that PGC-1α is an important factor in the regulation of cardiovascular function.

Abnormalities in mitochondrial function are associated with neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, and HD. Levels of PGC-1α are reduced in the brain of HD patients due to repression of PGC-1α gene expression by mutant huntingtin, leading to mitochondrial defects and increased oxidative stress [83]. Expression of PGC-1α partially reverses the toxic effects and provides neuroprotection in the HD mutant

mouse [44]. In the peripheral nervous system, PGC-1α has been shown to regulate gene expression at the neuromuscular junction and influences expression of acetylcholine receptors in muscle fibers [84]. In addition, elevated PGC-1α levels protect neural cells in culture from cell death caused by oxidative-stressor through its induction of antioxidant genes [22].

Energy metabolism in cancer cells differs fundamentally from that in its normal counterparts. In general, cancer cells have high glycolytic activity and prefer glucose as a fuel source, a phenomenon known as the Walburg effect. The switch from OXPHOS to glycolysis occurs even in the presence of sufficient oxygen. This aerobic glycolysis has been postulated to enhance cancer cell proliferation and survival. Interestingly, reduced expression of PGC-1α has been observed in human breast cancer [85], colon cancer [86], liver cancer [87], and ovarian cancer [88]. Adenoviral-mediated overexpression of PGC-1α induces E-cadherin expression while decreasing motility of human hepatoma $HepG_2$ cells [89]. Such manipulation also causes cell apoptosis in human ovarian cancer cells through a PPARγ-dependent pathway [88]. These findings suggest that PGC-1α is a potentially important regulator of cancer cell metabolism and contributes to altered metabolic function in cancer cells. A causal relationship between PGC-1α and cancer development, however, remains to be established.

Summary and perspective

The PGC-1 family of transcriptional coactivators has emerged as a regulatory hub within the transcriptional networks that maintain metabolic homeostasis. The dynamic regulation of PGC-1 expression and/or post-translational modification in response to nutritional and hormonal signals provides a highly versatile regulatory platform for metabolic control. A major challenge is to map out tissue-specific activities of PGC-1α and PGC-1β as well as the transcriptional partners that mediate PGC-1 actions. Of note, recent genome-wide coactivation analyses provide a global view of potential PGC-1α interacting proteins in humans. While the biological function of nuclear receptor targets of PGC-1 is better understood, very little is known about a large number of zinc-finger proteins that associate with PGC-1α. The identification of PGC-1α splicing isoforms also adds additional complexity [90]. Dysregulation of PGC-1 expression has been observed in a wide variety of pathological conditions. As such, proper modulation of PGC-1α expression/activity has great potential in the prevention and treatment of diseases associated with impaired mitochondrial function and oxidative metabolism. Although targeting a coactivator could be challenging, certain features of coactivator action can be exploited for clinical use. For example, coactivators have kinetic benefits in controlling biological programs in that they coordinate different steps in biological programs through the integration of the activity of various transcription factors. As such, significant biological effects can be achieved by quantitatively modulating coactivator function. The diversity of post-translational modifications of PGC-1 potentially allows targeting specific protein–protein interaction interface. As discussed above, tissue-specific modulation of PGC-1 function is essential for metabolic modulation without causing deleterious side effects.

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