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Peroxisome Proliferator-Activated Receptor γ Coactivator 1 Coactivators, Energy Homeostasis, and Metabolism

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Many biological programs are regulated at the transcriptional level. This is generally achieved by the concerted actions of several transcription factors. Recent findings have shown that, in many cases, transcriptional coactivators coordinate the overall regulation of the biological programs. One of the best-studied examples of coactivator control of metabolic pathways is the peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1) family. These proteins are strong activators of mitochondrial function and are thus dominant regulators of oxidative metabolism in a variety of tissues. The PGC-1 coactivators themselves are subject to powerful regulation at the transcriptional and posttranslational levels. Recent studies have elucidated the function of the PGC-1 coactivators in different tissues and have highlighted the implications of PGC-1 dysregulation in diseases such as diabetes, obesity, cardiomyopathy, or neurodegeneration. (*Endocrine Reviews* 27: 728–735, 2006)

I. Discovery, Function, and Structure of the PGC-1s

A. Discovery

REGULATION OF GENE transcription is a highly orchestrated process that involves multiple steps and a large number of different protein complexes. Transcription factors bind to specific DNA sequences in the promoter or enhancer regions of their target genes upon activation or after being induced themselves. Concomitantly, or in some cases subsequently, large protein complexes are recruited to the transcription factor and facilitate opening of the chromatin structure and initiation of transcription. DNA binding sequences for any given transcription factors can usually be found in the regulatory flanking regions of target genes. However, additional regulatory mechanisms ensure high specificity in the transcriptional induction of genes.

Peroxisome proliferator-activated receptor γ (PPARγ) was found to be a master regulator of adipogenesis (1–3). In addition to being absolutely indispensable for white adipose tissue (WAT) development, PPARγ also plays an important role in brown adipose tissue (BAT). BAT is characterized by small, multilocular lipid droplets and a high number of mitochondria. In contrast to WAT, which is mainly used for fat storage, BAT uses lipids as a fuel for adaptive thermogenesis during cold exposure (4). It was unclear how PPARγ can induce a specific set of genes in WAT, whereas the same transcription factor can regulate different target genes and biological programs in BAT. As examples, the fatty acid binding protein aP2 (also called FABP4) is strongly induced by PPARγ in WAT, whereas other genes, such as the uncoupling protein 1 (UCP-1), are the main PPARγ targets in BAT. Thus, Puigserver *et al.* (5) addressed questions about the molecular mechanisms that determine the specificity of the PPARγ response in these two different tissues. In a yeast two-hybrid screen using a BAT cDNA library, candidate proteins binding to PPARγ were isolated and subsequently tested for BAT *vs.* WAT expression, as well as cold inducibility in BAT. One of the proteins isolated, the PPARγ coactivator 1α (PGC-1α) not only fulfills all of these criteria, but also elevates certain BAT markers when ectopically expressed in murine WAT cell lines, human white adipocytes, or mouse WAT *in vivo* (5, 6). Thus, PGC-1α confers transcriptional specificity to PPARγ by coactivating this nuclear receptor on the UCP-1 but not on the aP2 promoter.

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Abbreviations: ALAS, δ-Aminolevulinate synthase; AMPK, AMP-dependent protein kinase; BAT, brown adipose tissue; CREB, cAMP response element binding protein; DRIP, vitamin D receptor-interacting protein; ERR, estrogen-related receptor; GABP, GA-binding protein; HAT, histone acetyltransferase; HNF4α, hepatocyte nuclear factor 4α; MEF2, myocyte enhancer factor 2; NRF, nuclear respiratory factor; OXPHOS, oxidative phosphorylation; PGC-1, PPARγ coactivator 1; PPARγ, peroxisome proliferator-activated receptor γ; PRC, PGC-1-related coactivator; SREBP, sterol regulatory element-binding protein; TRAP, thyroid receptor-associated protein; UCP-1, uncoupling protein 1; WAT, white adipose tissue.

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B. Function and structure

Analysis of PGC-1α function in BAT and tissue expression patterns immediately suggested that a core function of PGC-1α might be stimulation of mitochondrial number and oxidative metabolism. PGC-1α is strongly expressed in BAT, heart, skeletal muscle, kidney, and brain, all of which are highly oxidative tissues (7–9). Accordingly, when ectopically expressed in fat or muscle cells, PGC-1α strongly promotes increases in mitochondrial DNA as well as the large set of nuclear and mitochondrial-encoded mitochondrial genes (7). Mechanistically, PGC-1α induces mitochondrial genes by increasing the levels of the nuclear respiratory factor 1 and 2 [NRF-1 and NRF-2, alternatively called GA-binding protein (GABP), respectively] and the estrogen-related receptor α (ERRα) (7, 10, 11). When coactivated by PGC-1α, GABP and ERRα promote their own, as well as each others' expression, and subsequently elevate the levels of NRF-1 (10). Subsequently, PGC-1α coactivates NRF-1 and GABP binding to regulatory regions of the mitochondrial transcription factor A promoter (7). Thus, PGC-1α not only initiates elevation of mitochondrial biogenesis and oxidative metabolism, but also participates in the regulation of the downstream steps of this biological program.

This core function of PGC-1α is conserved in the two other members of the PGC-1 family, PGC-1β and the PGC-1-related coactivator (PRC) (12–14). PGC-1α and PGC-1β both strongly increase total mitochondrial respiration; however, PGC-1α elevates uncoupled respiration more than PGC-1β, at least when expressed in cultured myotubes (15). Like PGC-1α, PRC coactivates NRF-1 on the promoters of different mitochondrial genes (14). Orthologs of the PGC-1 family members are found in higher vertebrates, including mammals, birds, and fish (16). No clear PGC-1 orthologs have been found in lower eukaryotes, including nematodes, insects, or yeast. However, recent findings suggest that mediator-15, which integrates transcriptional regulation of fatty acid metabolism in *Caenorhabditis elegans*, might be functionally equivalent to PGC-1α in terms of regulation of lipid metabolism (17).

All three members of the PGC-1 family have a related modular structure. To date, PGC-1α remains the best studied and thus will be discussed in more detail here. PGC-1α has a strong activation domain at the N terminus, which interacts with a histone acetyltransferase (HAT) complex that includes steroid receptor coactivator 1 and cAMP response element binding protein (CREB) binding protein/p300 (18). Adjacent to the N-terminal domain is an inhibitory region that roughly spans 200 amino acids. Toward the C terminus, PGC-1α binds the thyroid receptor-associated protein (TRAP)/vitamin D receptor-interacting protein (DRIP)/Mediator complex that facilitates direct interaction with the transcription initiation machinery (19). Thus, simultaneous recruitment of HAT proteins and the TRAP/DRIP/Mediator complex probably explains the exceptionally powerful transcriptional coactivation capacity of PGC-1α. In addition to TRAP/DRIP/Mediator recruitment, the C terminus of PGC-1α also harbors RNA recognition and splicing domains (20). Thus, PGC-1α can be described as a protein docking platform that, when bound to a transcription factor, recruits histone modifying enzymes, bridges the transcription factor to the basal transcriptional initiation complex, and takes part in processing of the target gene mRNA. Importantly, the recruitment of the HAT complex appears to be stimulated by the binding of PGC-1α to a target transcription factor (18).

II. Specificity of Biological Programs Induced by the PGC-1s in Different Tissues

A. Tissue-specific functions

PGC-1α and PGC-1β are both expressed in tissues with a high oxidative capacity, including brown fat, heart, kidney, skeletal muscle, and brain (5, 12). Whereas PGC-1α and PGC-1β are more restricted in their tissue expression, PRC is expressed fairly ubiquitously (14). In addition to their powerful induction of mitochondrial function, PGC-1 family members activate other tissue-specific functions. For example, PGC-1α is a potent regulator of gluconeogenesis and integrates multiple aspects of the fasting response in the liver, including heme biosynthesis (21–24). Gluconeogenesis is directly regulated by PGC-1α via induction of phosphoenol pyruvate carboxykinase and glucose-6-phosphatase and increased tricarboxylic acid cycle flux, as shown in both gain- and loss-of-function mouse models (21, 24–26). In skeletal muscle, PGC-1α promotes glucose uptake and coordinately induces the expression of skeletal muscle fiber-type I and IIa-specific genes (27, 28). PGC-1α induces expression of UCP-1 in BAT and thus regulates adaptive thermogenesis (5, 29). The tissue-specific functions of PGC-1β are less well studied. In liver, PGC-1β increases lipogenesis and lipoprotein transport but has no major effect on gluconeogenesis (30–32). PGC-1α promotes hepatic lipoprotein metabolism but has no impact on lipogenesis (23, 30).

B. Regulation of PGC-1 activity: induction, posttranslational modifications, and binding partners

The potent induction of mitochondrial function as well as the diverse tissue-specific effects of the PGC-1 family members require a very tight regulation of both expression and activity (16, 33–36). PGC-1α levels are elevated by a number of external stimuli (Fig. 1): cold in BAT, exercise and decreased ATP levels in skeletal muscle, and fasting in liver. A number of different signaling pathways are involved in PGC-1α regulation. In particular, cAMP signaling is a key activator of PGC-1α transcription in many tissues, promoting the binding of CREB or the activating transcription factor-2 to a conserved DNA response element in the PGC-1α promoter. CREB is activated upon glucagon signaling in the liver (22), whereas calcium signaling cascades converge on CREB in skeletal muscle (37). Activating transcription factor-2 is recruited to the PGC-1α promoter after β-adrenergic receptor activation in BAT (38). Interestingly, nitric oxide increases PGC-1α levels and mitochondrial biogenesis via cGMP-dependent pathways (39). In addition, several tissue-specific transcription factors have been implicated in the transcriptional regulation of PGC-1α. In skeletal muscle, myocyte enhancer factor 2 (MEF2) proteins bind to the PGC-1α promoter (37, 40). Importantly, PGC-1α protein can bind to

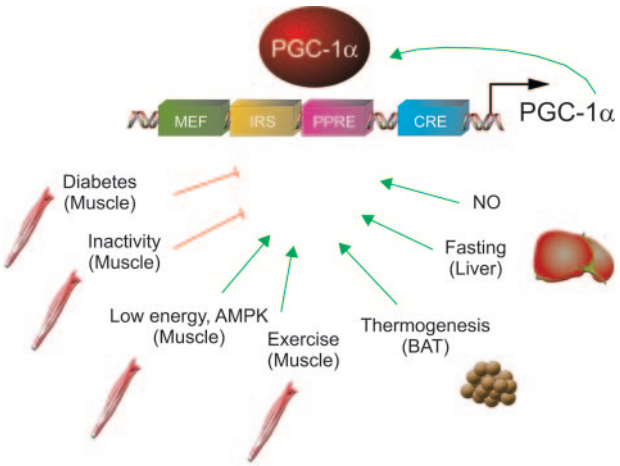

FIG. 1. Regulation of PGC-1α transcription. PGC-1α levels are elevated by various stimuli in different tissues. Many of the signaling pathways activated in these contexts converge on the functional DNA binding elements that have been identified so far in the PGC-1α promoter region. Moreover, PGC-1α regulates its own transcription in a positive autoregulatory loop. Interestingly, many of the transcription factors involved in PGC-1α regulation are also downstream binding partners for PGC-1α, such as Foxo1, PPARγ, or MEF2. NO, Nitric oxide; IRS, insulin responsive sequence (binding site for Foxo1); PPRE, PPAR response element; CRE, cAMP responsive element.

MEF2 on its own promoter and thus regulate its own transcription in a positive autoregulatory loop (37). PGC-1α stimulates its own transcription by coactivating PPARγ binding to the PGC-1α promoter in WAT (41). It therefore seems likely that at least some transcription factors that are binding partners for PGC-1α in the regulation of specific gene expression programs are also upstream of PGC-1α induction. Another example is Foxo1, which is coactivated by PGC-1α in the regulation of gluconeogenic and heme biosynthetic genes (24, 42) and binds to insulin responsive sequences in the PGC-1α promoter (43). Finally, ERRγ has been found to bind to response elements in the PGC-1α promoter (44), and ERRγ is coactivated by PGC-1α in the induction of PGC-1α target genes (45). These biological loops might provide an additional degree of specificity in regulating specific biological pathways. Thus, many of the tissue-specific effects of the PGC-1 family members can be explained by the coexpression of a PGC-1 and the respective tissue-restricted transcription factors, such as regulation of gluconeogenesis and lipoprotein metabolism by PGC-1α and hepatocyte nuclear factor 4α (HNF4α) in the liver (23, 46).

Secondly, the relative activity of the PGC-1s is modulated by posttranslational modifications. The half-life of PGC-1α protein is relatively short (2.28 h) (47). Thus, upon cessation of stimulatory pathways on PGC-1α transcription, the PGC-1α protein is rapidly degraded and the potentially wasteful (and possibly pathogenic) induction of many PGC-1α downstream target genes will return to basal levels. However, subsequent to phosphorylation by p38 MAPK, the half-life of PGC-1α protein is tripled, and thus higher PGC-1α protein levels are observed (47). Moreover, these phosphorylation events lead to release of factors inhibitory toward PGC-1α (48), such as p160 myb binding protein (49). In addition to phosphorylation, PGC-1α protein is also acetylated (50) and methylated (51). Deacetylation of PGC-1α through sirtuin 1 increases PGC-1α activity on gluconeogenic gene transcription in the liver (50). Interestingly, acetylation of PGC-1α by GCN5 not only decreases PGC-1α activity but also relocates PGC-1α within the nucleus (50, 52). Protein arginine methyltransferase 1 methylates PGC-1α in the C-terminal region and enhances its transcriptional activity (51).

Finally, and probably most importantly, PGC-1α activity is controlled by the repertoire of transcription factor binding partners in particular tissues. As mentioned previously, HAT and TRAP/DRIP/Mediator complexes are the major factors by which PGC-1α stimulates transcription. Upon binding to PPARγ, PGC-1α changes conformation that then allows docking of the HAT complex (18). On the other hand, p160 myb binding protein binding to nonphosphorylated PGC-1α represses transcriptional activity, possibly by recruiting histone deacetylase complexes and/or promoting PGC-1α protein degradation (49). In the context of the carnitine palmitoyltransferase-1β (CPT-1β) promoter, the upstream stimulatory factor 2 has been found to bind to the N terminus of PGC-1α and repress coactivation of MEF2A by PGC-1α (53). The orphan nuclear receptor small heterodimer partner competes with PGC-1 for binding to the glucocorticoid receptor on the phosphoenol pyruvate carboxykinase promoter (54). Transcriptional activation of HNF4α by PGC-1α is reduced by the nuclear receptor pregnane X receptor on the cytochrome P450 7A1 promoter (55). Upon ligand activation, pregnane X receptor binds to PGC-1α and thus results in dissociation of PGC-1α from HNF4α (55).

The relative activity of the PGC-1 coactivators in different tissues is thus regulated at multiple different levels. However, regulation and determination of specificity could additionally be mediated by posttranslational modifications of PGC-1 protein that "educate" this transcriptional coactivator. Similar to the "phospho-code" proposed for the steroid receptor coactivators (56), modification of PGC-1 could confer a preference to the PGC-1 proteins to bind to specific transcription factors or recruit particular binding partners that then result in the regulation of selective gene expression programs (Fig. 2). For example, PGC-1α is induced in skeletal muscle by AMP-dependent protein kinase (AMPK) when ATP levels are low (57). However, it would be extremely wasteful to elevate the entire set of PGC-1α-controlled genes in skeletal muscle, including skeletal muscle fiber-type-specific myofibrillar genes. Indeed, AMPK only elevates a subset of genes that are regulated by PGC-1α, such as the glucose transporter GLUT4, cytochrome c, and δ-aminolevulinate synthase (ALAS) (58, 59). No fiber-type switching after AMPK activation has been reported; furthermore, even some metabolic genes like palmitoyltransferase-1β that are activated by PGC-1α remain unchanged upon AMPK signaling (58). Thus, posttranslational modifications of PGC-1α after AMPK activation most likely direct downstream gene induction toward very specific pathways, possibly due to preferential transcription factor binding (Fig. 2B). In the liver, deacetylation of PGC-1α by sirtuin 1 boosts PGC-1α activity on gluconeogenic, but not on oxidative phosphorylation (OXPHOS) gene induction (50). In addition to posttranslational modifications, different splice variants for PGC-1α and PGC-1β have been observed (60, 61). These might arise from

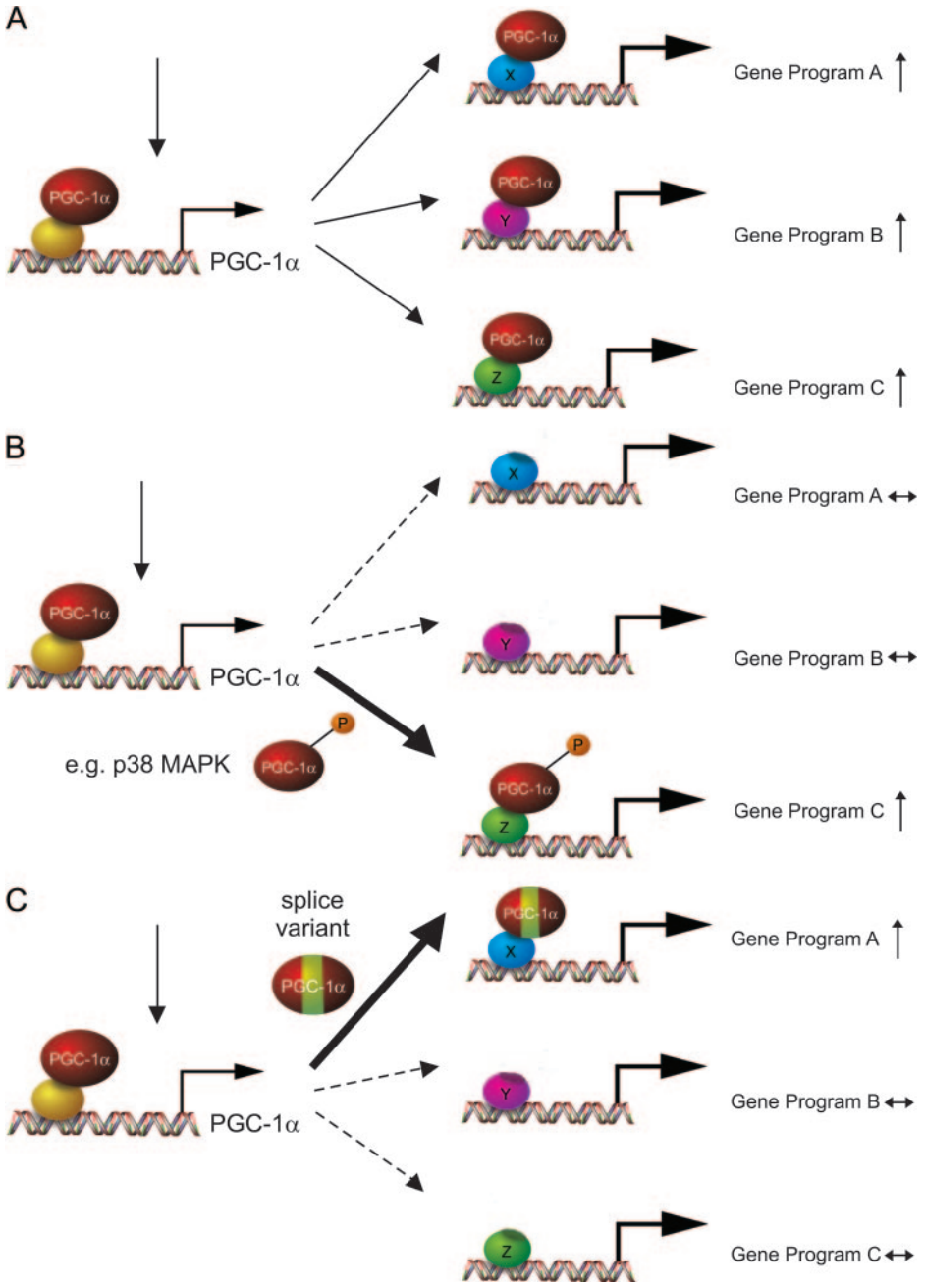

FIG. 2. Specificity of PGC-1-regulated biological programs. A, Ectopic expression of PGC-1α results in the induction of target genes that represent different biological programs. B, In certain contexts, PGC-1α is posttranslationally modified, which might affect its relative binding affinity to transcription factor Z as opposed to X and Y. This will result in preferential induction of gene program C. C, Alternative promoter usage and splicing of the PGC-1α transcript results in different PGC-1α proteins. A PGC-1α splice variant that lacks binding domains for transcription factors Y and Z will only bind to factor X and thus increase transcription of gene program A.

differential internal splicing as well as alternative promoter usage. Intriguingly, PGC-1α is involved in transcription initiation, elongation, and processing (20) and could thus regulate its own mRNA splicing. For example, a PGC-1 splice variant lacking the interaction domain with nuclear receptors would specifically bind to and activate transcription factors of the nonnuclear receptor families (Fig. 2C). A PGC-1β splice variant lacking one of its interaction domains has been described, and this PGC-1β allele exhibits reduced coactivation of estrogen receptor α compared with full-length PGC-1β (13, 62).

Alternatively, recruitment of specific coactivators by transcription factors can be regulated by particular DNA binding elements, as has been elegantly shown for nuclear factor κb (63). PGC-1α preferentially induces UCP-1 but not aP2, even though both are PPARγ target genes (5). In the liver, only a subset of HNF4α target genes are induced by PGC-1α, although PGC-1α is a very powerful coactivator of HNF4α (23). Finally, despite being potent transcriptional coactivators of the liver X receptor α, PGC-1α and PGC-1β are only recruited to the cytochrome P450 7A1 and the ATP-binding cassette A1 promoters but not to liver X receptor α binding to the sterol regulatory element-binding protein 1 (SREBP1) promoter (30). In the same context, PGC-1β coactivates SREBP1c in the transcriptional induction of fatty acid synthase but is not recruited to SREBP1c at the low-density lipoprotein receptor promoter (30). In a recent report, hepatic lipin 1 was found to selectively amplify the PGC-1α-PPARα axis but not other

PGC-1α target genes in the liver (64). Thus, additional components of the PGC-1 complexes might control PGC-1 specificity.

Elucidating the molecular mechanisms underlying the specification of PGC-1 in different tissues and contexts will be one of the biggest challenges and breakthroughs in dissecting the roles for these coactivators in the future. Knowledge of these mechanisms would allow researchers to specifically target certain functions of PGC-1 that might be beneficial in a disease state while avoiding detrimental properties.

III. PGC-1s in Health and Disease

Aberrant mitochondrial function has been associated with a vast number of human pathologies (65, 66). It is thus not surprising that dysregulated PGC-1 levels have been associated with many disease states in different tissues.

A. Brain

Several neurodegenerative diseases have been linked with impaired mitochondrial function and decreased expression of genes involved in mitochondrial OXPHOS, most prominently Parkinson's disease, Alzheimer's disease, and Huntington's disease (67). PGC-1α deficiency in knockout animal models result in behavioral changes and neurodegeneration (29, 68). One of the two published PGC-1α knockout mouse lines exhibits signs of increased anxiety (68), whereas the other mouse line is hyperactive (29). This hyperactivity and other behavioral peculiarities such as stimulus-induced myoclonus, exaggerated startling response, dystonic posturing, and frequent limb clasping are reminiscent of mouse models for Huntington's disease. Indeed, PGC-1α knockout mice have a striking spongiform lesion in the striatum, the brain region primarily affected in human Huntington's disease and which is important in the control of movement (29). However, sporadic lesions were also observed in the cortex of PGC-1α knockout mice, including the substantia nigra and hippocampus, two regions that are severely affected in Parkinson's and Alzheimer's, respectively (29).

B. Peripheral metabolic tissues

In recent years, strong evidence for mitochondrial dysregulation in type 2 diabetes has been found (69). In muscle biopsies of type 2 diabetic patients, OXPHOS gene expression is reduced (70, 71). These dysregulated OXPHOS genes are transcriptional targets for PGC-1α and PGC-1β and, accordingly, the relative levels of PGC-1α and PGC-1β are lower in skeletal muscle of type 2 diabetic patients (70, 71). Importantly, OXPHOS and PGC-1 dysregulation is also found in first-degree family members of type 2 diabetic patients (70) and individuals with impaired glucose tolerance (71), suggesting that aberrant expression of PGC-1 and OXPHOS is found early in the development of the disease. In a monozygotic twin study, PGC-1α expression has been found to correlate with insulin-stimulated glucose uptake and oxidation (72). In contrast, PGC-1β expression was found to be related to fat oxidation and nonoxidative glucose metabolism (72). Expression of both PGC-1α and PGC-1β decreases in age; this correlation might provide an explanation by which age influences the susceptibility to type 2 diabetes (72). Finally, a Gly482Ser polymorphism in PGC-1α has been associated with type 2 diabetes in several different populations (35). However, causality of PGC-1 dysregulation in the pathogenesis of type 2 diabetes has not been shown yet. Moreover, at least one other study failed to replicate the PGC-1 dysregulation in skeletal muscle of type 2 diabetic patients (73). Thus, the role for PGC-1α and PGC-1β dysregulation on type 2 diabetes in skeletal muscle warrants further studies.

PGC-1α expression is reduced in WAT of morbidly obese subjects (74) and in sc fat of insulin resistant individuals (75). Rosiglitazone treatment of obese mice boosts PGC-1α transcription in WAT concomitant with increased mitochondrial function and, more importantly, insulin sensitivity (76). Increasing PGC-1 levels in skeletal muscle and WAT would therefore be potentially beneficial in the treatment of type 2 diabetes. In contrast, PGC-1α is elevated in the liver and pancreas of rodent models of type 1 and type 2 diabetes (21, 77). In these tissues, increased PGC-1α levels can account for elevated gluconeogenesis and decreased insulin secretion in diabetes, respectively (21, 77). Moreover, PGC-1α promotes hepatic insulin resistance (26). To achieve a net beneficial effect of modulating PGC-1 levels, tissue-specific effects have to be taken into consideration. Interestingly, PGC-1α regulates OXPHOS genes in skeletal muscle by inducing and binding to ERRα and GABP (10, 11). Disruption of the PGC-1α and ERRα interaction in skeletal muscle provokes a type 2 diabetes-like phenotype without affecting gluconeogenesis in liver cells (10). Enhancing the coactivation of ERRα by PGC-1α might therefore be a valid approach to boost OXPHOS gene expression in skeletal muscle without detrimental effects on gluconeogenesis in the liver (78).

Regulation of PGC-1α in fasting and feeding has additional implications in patients suffering from hepatic porphyrias with inherited defects in heme biosynthesis. In susceptible individuals, fasting can trigger an acute, potentially life-threatening, porphyric attack (79). PGC-1α induces the first and rate-limiting step of heme biosynthesis, ALAS, by binding to NRF-1 and Foxo1 in the fasted liver (24). Indeed, liver-specific PGC-1α knockout animals have blunted induction of ALAS (24). Moreover, ectopic expression of PGC-1α can trigger an acute porphyric attack in mouse models with chemically induced porphyria, whereas liver-specific PGC-1α knockout animals are protected from fasting-induced acute attacks in chemical porphyria (24). These findings have implications both on the prevention as well as the treatment of acute porphyric attacks (80).

C. Heart

PGC-1α expression is reduced in a number of animal models of heart disease, often accompanied by a switch of substrate use from fatty acids to glucose (81, 82). Accordingly, hearts from PGC-1α knockout animals appear normal at baseline but are unable to increase their workload when stimulated by adrenergic agonists, suggesting an important role for PGC-1α in cardiac reserve (83). Moreover, PGC-1α knockout mice exhibit lower treadmill running times and

diminished cardiac function after exercise (68). Consistent with the reduced expression of PGC-1α in animal models of heart failure, transverse aortic constriction in PGC-1α knockout animals accelerates cardiac dysfunction and clinical signs of heart failure (84), suggesting that decreased PGC-1α expression in heart disease is maladaptive. On the other hand, superphysiological expression of PGC-1α in the heart leads to mitochondrial proliferation, myofibrillar displacement, and eventually, cardiac dilation and failure in mice (85, 86). Thus, therapeutic regulation of PGC-1α in heart failure should aim at achieving moderate induction of PGC-1α within a therapeutically beneficial window.

The first description of PGC-1α in 1998 and the numerous papers after that established the PGC-1 family of transcriptional coactivators as master regulators of mitochondrial function and oxidative metabolism. Thus, these proteins have great potential in the prevention and treatment of diseases associated with impaired mitochondrial biology. Moreover, the high transcriptional inducibility of PGC-1α suggests that regulation of this gene should be amenable to pharmacological interventions. However, it is clear that several challenges in understanding the role of dysregulation of the PGC-1s in human pathophysiology are still ahead. First, although we have a relatively good understanding of many functions of PGC-1α in different tissues, our knowledge about PGC-1β and especially PRC is still rudimentary. A mouse model that ectopically expresses PGC-1β in a number of tissues has increased oxidative capacity in muscle, increased energy expenditure, lower insulin levels, and resistance to obesity (62). However, the specific functions of PGC-1β in different tissues remain to be elucidated. Secondly, as mentioned above, we will have to understand the mechanisms controlling the specificity of the PGC-1-mediated coactivation in different contexts. Thirdly, because of the complex phenotype of the whole-body knockout of PGC-1α, the PGC-1s will have to be deleted in a tissue- and perhaps developmental stage-specific manner to dissect their functions in peripheral tissues. These studies should be combined with tissue-specific gain-of-function animal models to test potential therapeutic effects of elevated PGC-1 expression, with the caveat that superphysiological expression can itself lead to pathogenesis, as observed in the heart. Once we have a firmer grip on the actions and regulations of the PGC-1s in different tissues and contexts, this knowledge is likely to result in novel approaches in the therapy of diseases that have been associated with mitochondrial dysfunction.

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