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PGC-1α: a key regulator of energy metabolism

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Liang, Huiyun, and Walter F. Ward. PGC-1α: a key regulator of energy metabolism. Adv Physiol Educ 30: 145–151, 2006; doi: 10.1152/advan.00052.2006.—Peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α is a member of a family of transcription coactivators that plays a central role in the regulation of cellular energy metabolism. It is strongly induced by cold exposure, linking this environmental stimulus to adaptive thermogenesis. PGC-1α stimulates mitochondrial biogenesis and promotes the remodeling of muscle tissue to a fiber-type composition that is metabolically more oxidative and less glycolytic in nature, and it participates in the regulation of both carbohydrate and lipid metabolism. It is highly likely that PGC-1α is intimately involved in disorders such as obesity, diabetes, and cardiomyopathy. In particular, its regulatory function in lipid metabolism makes it an inviting target for pharmacological intervention in the treatment of obesity and Type 2 diabetes.

adaptive thermogenesis; transcription coactivator; proliferator peroxisome-activated receptor; glucose metabolism; diabetes

PGC-1α and Adaptive Thermogenesis

PGC-1α was originally discovered as a cold-inducible transcription coactivator of adaptive thermogenesis, a physiological process through which energy is dissipated as heat in response to environmental conditions such as cold stress and overfeeding (8, 51). BAT and skeletal muscle are the two major organs involved in this process. While rats and mice have prominent brown fat depots, this isn’t the case in larger mammals, including humans, although there may be brown fat cells dispersed among the adipocytes of WAT (49). Thus, in larger mammals, skeletal muscle is generally thought to be the major thermogenic tissue. The primary physiological function of WAT is energy storage, whereas the primary function of BAT is energy dissipation, largely in the form of heat. In fact, BAT produces ~60% of the heat generated by nonshivering, adaptive thermogenesis. Spurred on in part by the prevalence of human obesity, interest in adaptive thermogenesis has increased because of the possibility that it may provide a physiological defense against obesity (68). This has also led to increased attention being directed toward the regulation of adipose tissue differentiation. It was known that the transcription factor PPAR-γ is an important regulator of adipocyte differentiation, but, surprisingly, it is unable, by itself, to induce brown fat differentiation (45). It was during the search for the solution to this puzzle that PGC-1α was discovered (49). PGC-1α binds to PPAR-γ and coactivates PPAR-γ to stimulate the transcription of genes involved in the brown adipocyte differentiation process (49).

The adaptive thermogenic program in both brown fat and skeletal muscle involves the stimulation of mitochondria biogenesis, increased fatty acid oxidation, and the uncoupling of oxidative phosphorylation. In response to cold exposure,
Table 1. Selected list of transcription factors for which PGC-1α functions as a coactivator

<table>
<thead>
<tr>
<th>Transcription Factor</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRF1</td>
<td>Mitochondria biogenesis</td>
<td>68</td>
</tr>
<tr>
<td>NRF2</td>
<td>Mitochondria biogenesis</td>
<td>36</td>
</tr>
<tr>
<td>ERR-α/β/γ</td>
<td>Mitochondria biogenesis</td>
<td>35</td>
</tr>
<tr>
<td>PPAR-α</td>
<td>Fatty acid oxidation</td>
<td>62</td>
</tr>
<tr>
<td>PPAR-δ</td>
<td>Fatty acid oxidation</td>
<td>64</td>
</tr>
<tr>
<td>TR-β</td>
<td>PTP-1 induction</td>
<td>67, 72</td>
</tr>
<tr>
<td>FXR</td>
<td>Triglyceride metabolism</td>
<td>71</td>
</tr>
<tr>
<td>LXR-α/β</td>
<td>Lipoprotein secretion</td>
<td>30</td>
</tr>
<tr>
<td>GR</td>
<td>Gluconeogenesis</td>
<td>23</td>
</tr>
<tr>
<td>HNF-4α</td>
<td>Gluconeogenesis</td>
<td>39</td>
</tr>
<tr>
<td>FOXO1</td>
<td>Gluconeogenesis</td>
<td>47</td>
</tr>
<tr>
<td>PPAR-γ</td>
<td>Brown adipocyte differentiation;</td>
<td>16, 20</td>
</tr>
<tr>
<td></td>
<td>UCP1 induction</td>
<td></td>
</tr>
</tbody>
</table>

PGC-1α expression is increased, with the induction being mediated through the sympathetic nervous system’s β1-adrenergic receptor/cAMP pathway (49). Increased PGC-1α induces the transcription of nuclear respiratory factor (NRF)1 and NRF2, leading to the increased expression of mitochondrial transcription factor A (mtTFA) (68) as well as other nuclear-encoded mitochondria subunits of the electron transport chain complex such as β-ATP synthase, cytochrome c, and cytochrome c oxidase IV (56, 57). mtTFA translocates to the mitochondrion, where it stimulates mitochondrial biogenesis as manifested by stimulation of mitochondrial DNA replication and mitochondria gene expression (14, 24). PGC-1α also interacts with other nuclear hormone receptors such as PPAR-α, retinoic acid receptor, and thyroid receptor in BAT to enhance the expression of brown fat-specific uncoupling protein 1 (UCP1) (6, 9, 58). UCP1 action leads to dissipation of the proton gradient and the uncoupling of oxidative phosphorylation, thereby increasing heat production. Under these conditions, there is a marked increase in the rate of energy metabolism. The essential role of PGC-1α in adaptive thermogenesis is convincingly demonstrated by the observation that the PGC-1α-deficient mice are unable to withstand a cold stress (4°C) for longer than 6 h due to a continuous decrease of core body temperature. Wild-type control mice, on the other hand, were able to tolerate the cold stress by keeping their core body temperature at ~36.5°C, after an initial drop of ~1.5°C (26, 29).

PGC-1α and Skeletal Muscle Fiber Conversion

Skeletal muscle fibers are classified into three types: type I, type IIa, and type IIb. Slow-twitch type I and fast-twitch type IIa fibers contain more mitochondria and exhibit relatively higher rates of oxidative metabolism. In contrast, type IIb fibers have fewer mitochondria and are metabolically glycolytic. It is now well established that PGC-1α induces a remodeling of skeletal muscle fiber composition. In general, the ratio of glycolytic type IIb fibers to the more oxidative type I and type IIa fibers decreases. The expression of PGC-1α in skeletal muscle is readily inducible by both short-term exercise and endurance training in rodent models and human subjects (5, 15, 41, 52). Our understanding of the biological role of PGC-1α in skeletal muscle structure and function has been greatly improved through the use of gain of function and loss of function mouse models. In a gain of function transgenic model, PGC-1α is overexpressed in a skeletal muscle-specific manner under the control of the muscle creatine kinase (MCK) promoter (28). PGC-1α overexpression results in the conversion of fast-twitch type IIb muscle fibers to type Ia and slow-twitch type I fibers by 20% and 10%, respectively, in plantaris muscle. In addition, there is an activation of genes involved in mitochondrial oxidative metabolism. The conversion to slow-twitch fibers is also evidenced by the redder muscle color and the expression of contractile proteins characteristic of slow-twitch fibers such as slow troponin I and myoglobin. As would be predicted, based on these alterations, muscles isolated from the MCK- PGCG-1α transgenic mouse show increased resistance to electrically stimulated fatigue (28). Consistent with this, Mortenson et al. (39) recently reported that overexpression of PGC-1α in primary rat skeletal muscle cells leads to enhanced levels of mRNA for the slow oxidative-associated myosin heavy chain (MHC) isoform (MHCib) and decreased mRNA levels for the fast glycolytic-associated MHC isoforms (MHCIIIX and MHCIIb) (39). In contrast, PGC-1α-deficient mice exhibit decreased mitochondrial number and decreased respiratory capacity in slow-twitch muscle as well as reduced exercise capacity and a reduced fatigue resistance index (26).

The upstream signaling involved in the activation of PGC-1α are unclear at present, but several pathways have been implicated, such as the calcineurin A and CaMK, p38 MAPK, and AMP-activated protein kinase pathways (1, 67, 73). Although the relative importance of these kinases in controlling PGC-1α is yet to be determined, there appears to be a considerable amount of evidence suggesting that the calcineurin and CaMK pathways play important roles in the regulation of PGC-1α expression. During exercise, the combination of increased neuromuscular input and increased contractile activity induces the expression of several transcription factors, e.g., myocyte-specific enhancer factor (MEF)2 and CREB (10, 17). These induction processes appear to be mediated by calcineurin and CaMK (67). Increased expression of MEF2 leads to increased MEF2 binding to the promoter region of the PGC-1α gene, increasing PGC-1α expression. PGC-1α can then bind directly to MEF2 to coactivate the transcription of those genes involved in the determination of slow-twitch fiber types and mitochondrial oxidative metabolism (10, 27). Finally, it should be pointed out that recent work from Holloszy’s laboratory (13) suggests that calcineurin may not be required for exercise-induced increases in PGC-1α and a range of mitochondrial proteins. Obviously, further work is needed to elucidate the roles of calcineurin and calcium signaling pathways in the regulation of PGC-1α.

PGC-1α and Heart Development

The heart, an organ with a very high and dynamic demand for ATP, derives most of the required ATP from fatty acid oxidation. In the developing mouse heart, as the energy source turns toward mitochondria fatty acid oxidation after birth, there is a large burst of mitochondria biogenesis and oxidative metabolism that is preceded by a dramatically increased expression of PGC-1α (25). Short-term fasting, another condition
that produces an increased reliance on mitochondrial fatty acid oxidation, also activates myocardial PGC-1α (25). Under in vitro conditions, ectopic expression of PGC-1α in cultured cardiac myocytes has been shown to drive mitochondrial biogenesis, and oxidative phosphorylation in these mitochondria is tightly coupled with ATP production (25). In contrast, in adipocyte and C2C12 mouse myoblast cell lines, PGC-1α expression leads to the uncoupling of oxidative phosphorylation, resulting in decreased ATP formation and increased heat production (68). When the heart undergoes hypertrophy in response to pressure overload or cyclin T1-induced activation of Cdk9, PGC-1α expression is markedly decreased, and this reduction of PGC-1α levels is associated with a conversion from fatty acid oxidation to glycolytic metabolism (54, 55, 55).

To further investigate the role of PGC-1α in the heart, two independent lines of PGC-1α-deficient mouse models have been established (26, 29). Although myocardial mitochondrial volume density didn’t change significantly in either PGC-1α knockout model, the expression of genes of oxidative phosphorylation was markedly blunted in the PGC-1α-deficient heart. This was accompanied with reduced mitochondrial enzymatic activities and decreased levels of ATP and phosphocreatine (2). The PGC-1α-deficient heart also exhibits a diminished response to exercise and β-adrenergic stimulation in vivo (26). Consistent with this, it has been reported that there is a decreased ability to increase both the heart rate and rate of change of pressure in response to chemical or electrical stimulation in a isolated perfused heart preparation of PGC-1α-deficient mice (2). In addition, starting from 7 to 8 mo of age, PGC-1α-deficient mice exhibit significant cardiac dysfunction (2). Consistent with this, it has been reported that PGC-1α-deficient mice underwent accelerated heart failure when challenged by transverse aortic constriction (3). These data indicate that PGC-1α is essential for the heart to be able to meet the increased demands for both ATP and work output in response to physiological stimuli. Surprisingly, the in vivo gain of function studies, carried out using two independent transgenic mouse models that overexpress PGC-1α specifically in the heart (MHC-PGC-1α mice and tet-on PGC-1α mice), revealed modest to dramatic mitochondria biogenesis associated with cardiomyopathy (25, 53). The development of this cardiomyopathy is thought to be associated with mitochondrial ultrastructural abnormalities and the disruption of sarcomere structure by overwhelmingly increased mitochondria biogenesis (25, 53).

PGC-1α and Glucose Metabolism

Maintenance of plasma glucose homeostasis is vital for the survival of mammalian organisms, and, as a result, glucose levels are tightly regulated in response to nutrient conditions and hormonal signals. Insulin suppresses plasma glucose level by the inhibition of glucose production in the liver and by promotion of glucose disposal into skeletal muscle and white fat tissue. Conversely, glucagon and glucocorticoids increase glucose levels through the activation of gluconeogenesis, in addition to the activation of glycogenolysis, in the liver and reduction of glucose utilization in skeletal muscle. Under normal, fed conditions, PGC-1α is expressed at very low levels in the liver (49). However, fasting produces a robust increase of PGC-1α expression, which, in turn, stimulates hepatic gluconeogenesis and fatty acid oxidative metabolism (19, 69). During fasting, the expression of PGC-1α is activated by glucagon and catecholamines via the stimulation of the cAMP pathway and the CREB transcription factor. PGC-1α then coactivates a variety of transcription factors such as hepatic nuclear factor-4α, glucocorticoid receptor, and forhead box O1 (FoxO1). These transcription factors bind to the promoter regions of those genes encoding key gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase).

Tissue culture studies have revealed that forced overexpression of PGC-1α in primary hepatocytes is sufficient to drive the expression of key gluconeogenic genes (69). In contrast, knockdown of PGC-1α expression by short interfering RNA in the mouse liver dramatically reduced the expression of PEPCK and G-6-Pase (22). The essential role of PGC-1α in the control of hepatic gluconeogenesis has been further reinforced by studies in the PGC-1α-deficient mouse model (26, 29). One strain of PGC-1α knockout mice exhibited fasting hypoglycemia in response to impaired gluconeogenic gene expression and hepatic glucose production (26, 29). Although the expression of PGC-1α target genes involved in gluconeogenesis was not altered in another strain of PGC-1α-deficient mice, the hepatic glucose production was reduced secondary to diminished fatty acid β-oxidation and tricarboxylic acid cycle flux (7). Interestingly, after short-term starvation, one line of PGC-1α-deficient mice developed hepatic steatosis due to a combination of reduced mitochondrial fatty acid oxidation capacity and an increased expression of lipogenic genes (26). Fasting also induces PPAR-α expression, which, when coactivated by PGC-1α, results in the expression of genes involved in hepatic fatty acid oxidation. The gene expression changes that have been described, under conditions of nutrient deprivation, cause a shift in fuel usage from glucose utilization to fatty acid oxidation, which contributes to the conservation of glucose for use by the central nervous system (19, 69).

Under fed conditions, skeletal muscle is a major site for glucose disposal. Skeletal muscle takes up glucose using glucose transporters (GLUTs) located in the cell membrane. There are two types of skeletal muscle GLUTs: constitutive, insulin-insensitive GLUT1 and GLUT3 and insulin-sensitive GLUT4. PGC-1α has been shown to increase the expression of GLUT4 in cultured muscle cells and skeletal muscle (5, 33, 33). Whereas MEF2C has been shown to mediate PGC-1α-induced GLUT4 expression in cultured muscle cells (33), the MEF2A isoform appears to be responsible for GLUT4 upregulation under other conditions (4, 37). Surprisingly, PGC-1α has not been shown to increase glucose uptake in skeletal muscle in vivo, although it induced an increased glucose uptake into skeletal muscle cells (33). In addition, it has been reported that GLUT4 expression is downregulated in a muscle-selective PGC-1α transgenic mouse model (34). Resolution of the role of PGC-1α in the regulation of skeletal muscle glucose uptake thus requires further investigation.

It is now well established that insulin also stimulates the recruitment of GLUT4 to the cell membrane of insulin-sensitive tissues. A very important area of future research is the elucidation of the interaction between insulin and PGC-1α in the regulation of glucose metabolism, an interaction about which there is very little known at the present time. There is some evidence suggesting that insulin has a suppressive effect on the expression of PGC-1α, i.e., PGC-1α promoter activity...
is inhibited by insulin (19). Consistent with this, hepatic PGC-1α expression levels have been reported to be increased in animal models exhibiting insulin deficiencies (69). On the other hand, there is evidence showing a suppressive effect of insulin downstream of PGC-1α. The mechanism for this effect may involve the transcription factor FOXO1. Activation of the insulin signaling pathway leads to phosphorylation of FOXO1, inhibiting its translocation to the nucleus and increasing its susceptibility to degradation. Because PGC-1α requires FOXO1 to bind to the promoter regions of gluconeogenic genes, this action of insulin could have a suppressive effect on PGC-1α action (47).

**PGC-1α and Type 2 Diabetes**

Type 2 diabetes is the most common metabolic disease in the world, reaching epidemic proportions. Although there are multiple complicated genetic elements involved in the pathogenesis of Type 2 diabetes, lifestyle and age seem to be the two major risk factors triggering the disease. A sedentary lifestyle and overeating can contribute to excessive weight gain and obesity, with the latter being closely associated with insulin resistance. Insulin resistance is considered to be present when the biological effects of insulin are less than expected for both glucose disposal in skeletal muscle and suppression of glucose production by the liver (11). When the insulin level is not sufficient to overcome this insulin-resistant state, Type 2 diabetes ensues. In this regard, there is increasing evidence suggesting that mitochondrial dysfunction plays a role in the pathogenesis of insulin resistance and Type 2 diabetes. For example, it has been reported that the activities of both mitochondrial oxidative enzymes and mitochondrial complex I are decreased in Type 2 diabetic patients (21, 63). In keeping with the observations that both obesity and mitochondrial dysfunction are risk factors for the development of insulin resistance, obese individuals have been reported to have smaller mitochondria that exhibit a compromised bioenergetic capacity (21). Insulin resistance also develops with age, and, in this case, a potentially important defect has been found in the mitochondrial fatty acid oxidation pathway. There appears to be a reduction in the rate of fatty acid oxidation, leading to the accumulation of intracellular triglycerides in elderly patients compared with matched young controls (43). Furthermore, the accumulation of triglycerides has been directly correlated with the development of insulin resistance in skeletal muscle and the liver. Thus, a specific type of mitochondrial dysfunction, i.e., decreased fatty acid oxidation, may play a significant role in the development of insulin resistance in both aging and obesity (43). It is interesting to note that triglycerides can also accumulate in pancreatic β-cells, resulting in decreased rates of insulin secretion, which would further exacerbate the problem of glucose disposal (32, 60). As noted above, the accumulation of intracellular triglycerides could be the result of a deficiency in fatty acid oxidation related to mitochondrial dysfunction. As a result, the cause of insulin resistance may well be due to mitochondrial dysfunction rather than the accumulation of triglycerides, a mechanistic concept that will be important to establish in gaining an understanding of the etiology of Type 2 diabetes.

It has been hypothesized that a close relationship exists among PGC-1α function, insulin sensitivity, and Type 2 diabetes, which is most likely related to the essential roles of PGC-1α in mitochondria biogenesis and glucose/fatty acid metabolism. Evidence supporting this hypothesis has been found in a number of studies. For example, it has been observed that expression of PGC-1α is downregulated in muscles of Type 2 diabetic subjects (36, 42, 44). In addition, a common polymorphism of the PGC-1α gene (Gly482Ser), expressing reduced PGC-1α activity, has been linked to an increased risk of Type 2 diabetes (18, 40). These observations would suggest that either reduced levels or compromised activity of PGC-1α can be associated with the development of insulin resistance and Type 2 diabetes (Fig. 1). In this context, it is interesting to note that TZDs, an important class of antidiabetic drugs, also act to increase insulin sensitivity coincident with the activation of PGC-1α (66). The effects of TZDs are likely mediated through the ability of PGC-1α to activate mitochondria biogenesis and increase mitochondrial function. As described above, PGC-1α stimulates the conversion of muscle fiber type toward more oxidative type I and IIa fibers, favoring fatty acid oxidative metabolism (28). The promotion of fatty acid oxidative metabolism would be expected to lead to a reduction of fat accumulation in muscle, which, in turn, could increase insulin sensitivity because there is a close relationship between triglyceride accumulation and insulin resistance (43). One manifestation of increased insulin sensitivity would be increased glucose uptake by insulin-sensitive tissues. PGC-1α has, as previously noted, been reported to activate the expression of insulin-sensitive GLUT4 in skeletal muscle (5, 33). Taken together, the evidence presented supports a role for PGC-1α in preventing insulin resistance and Type 2 diabetes mellitus.

However, it should be pointed out that PGC-1α expression has been reported to be increased in the liver of both Type 1 and Type 2 diabetic mouse models, in contrast to the reported decrease in PGC-1α expression observed in the muscle of human Type 2 diabetic subjects described above (48). Furthermore, PGC-1α has been shown to inhibit the insulin signaling pathway in the liver (22), inhibit glucose utilization in cultured myotubes (65), and suppress β-cell energy metabolism and insulin release in mice (70). Increased hepatic PGC-1α expression could be expected to stimulate hepatic glucose output,
and, when coupled with the reported inhibitory effect of PGC-1α on insulin signaling and secretion, the combined effects would be to contribute to the hyperglycemic state, a prodiabetes effect. This prodiabetic effect of PGC-1α has been further supported by the manifestation of improved insulin sensitivity in PGC-1α-deficient mouse models (22, 26, 29). Moreover, another recent report (38) has indicated that PGC-1α expression is normal in insulin-resistant subjects despite severe impairments in mitochondrial function. These apparently paradoxical actions of PGC-1α in different tissues are intriguing. The underlying mechanisms for the interactions between these tissues are currently unknown and deserve further intensive investigations.

Summary

As an inducible transcription coactivator, PGC-1α is enriched in metabolically active tissues. It is intimately involved in adaptive thermogenesis, skeletal muscle fiber type switching, glucose/fatty acid metabolism, and heart development. Among these varied biological responses, a common mechanism of action appears to be the promotion of oxidative metabolism accompanying the stimulation of mitochondria biogenesis. Furthermore, there is growing evidence that PGC-1α plays a role in disorders such as obesity, diabetes, and cardiomyopathy. Because of the involvement of PGC-1α in so many important biological processes, in conjunction with the rapid improvement in our understanding of its mechanisms of action, it has become an inviting target for the design of pharmacological interventions for treatment of these disorders.

REFERENCES


