ATVB in Focus
Oxygen Sensing

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Regulation of Hypoxia-Inducible Genes by PGC-1α

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Abstract*—**Atmospheric oxygen appeared approximately 2.3 billion years ago and sustains most complex life on earth. As mitochondria evolved to harness the energy in oxygen, systems developed to sense and respond to local oxygen concentrations and metabolic conditions. For more than a decade, research has focused on hypoxia-inducible factor 1 (HIF1), a key component of the eukaryotic oxygen-response system. Recently, evidence for other systems has also surfaced. One of these systems involves the PGC-1α coactivator, a powerful transcriptional regulator of mitochondria and oxidative metabolic programs. This brief review will focus on this burgeoning role for PGC-1α and will highlight the many questions that remain unanswered. (Arterioscler Thromb Vasc Biol*. 2010;30:662-666.)**

Key Words: angiogenesis ■ hypoxia ■ ischemia ■ PGC-1 ■ PGC-1α

PGC-1 Transcriptional Coactivators

Transcriptional coactivators are proteins that bind to transcription factors on chromatin and modify gene expression, without themselves recognizing specific DNA sequences.[1] It is likely that all transcription factors require coactivators and corepressors for normal function. During the past two decades, it has become clear that certain transcriptional coactivators play key roles in how physiological signals affect gene expression. PGC-1α is the best-studied such coactivator.

PGC-1α was identified 10 years ago, by 2-hybrid screening using the nuclear receptor peroxisome proliferator-activated receptor (PPAR)-γ as bait, and shown to be able to confer on white fat some of the properties of brown fat.[2] Since then it has become clear that PGC-1α can bind to and coactivate most nuclear receptors as well as many other transcription factors.[3–5] PGC-1α interacts directly with the basal transcriptional machinery, including the mediator complex, to activate transcription. PGC-1α also recruits chromatin-modifying enzymes, such as the histone acetylase p300, to open the chromatin and facilitate transcription. In addition, PGC-1α interacts with the splicing machinery, thereby coordinating transcription with posttranscriptional events. The outcome is robust activation of targeted gene expression. PGC-1β and a more distant cousin, PGC-1-related coactivator (PRC), were identified by gene homology and are presumed to function in similar ways, although their biochemistry has been studied less extensively.

PGC-1α powerfully regulates oxidative and mitochondrial metabolism in a number of tissues, along with various ancillary programs specific to each tissue. As previously noted, PGC-1α confers on white fat some of the attributes of brown fat, including high mitochondrial content and the induction of the mitochondrial uncoupler uncoupling protein (UCP)-1. In the liver, in response to fasting, PGC-1α induces genes involved in gluconeogenesis and fatty acid oxidation.[6,7] In muscle, transgenic expression of PGC-1α powerfully induces mitochondrial biogenesis, leading to a pronounced switch in fuel consumption to fatty acids and marked increases in exercise performance.[8–10] Loss of PGC-1α in knockout mice leads to important defects in cardiac mitochondria and energetics, predisposing the animals to heart failure.[11–13] These pronounced effects on oxidative and mitochondrial variables are mediated by coactivation of specific sets of transcription factors, including nuclear respiratory factors 1 and 2 and estrogen-related receptor (ERR) α.

Given the dominant role that PGC-1α plays in critical metabolic pathways, it is not surprising that PGC-1α is highly regulated at multiple levels, including hormonal inputs and bioenergetic state. In the liver, the PGC-1α gene is induced by glucagon, via activation of the adenosine 3′-5′-cyclic monophosphate cascade and the cAMP response element binding (CREB) and transducer of regulated CREB-binding proteins transcriptional regulators.[6,7,14] Cold temperature dramatically induces PGC-1α expression in brown fat, again via the adenosine 3′-5′-cyclic monophosphate cascade and the p38 stress-activated mitogen-activated protein kinase, leading to mitochondrial uncoupling and heat generation.[2,15] In muscle, exercise strongly induces PGC-1α gene expression,[16–18] likely contributing to mitochondrial biogenesis and changes in fuel use that accompany endurance exercise.

In addition to regulation at the level of gene expression, PGC-1α is also highly modified posttranscriptionally. The

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p38 stress-activated mitogen-activated protein kinase phosphorylates PGC-1α on at least 3 sites, likely contributing to signal transduction in brown fat in response to cold challenge.[15,19–21] AMP-dependent kinase also phosphorylates PGC-1α on a number of sites, leading to increased PGC-1α activity.[22] Conversely, PGC-1α activity is inhibited by AKT and thus by insulin signaling, contributing to the inhibition of a gluconeogenic program in the liver after feeding.[23] The nicotinamide-adenine dinucleotide (NAD)–dependent deacetylase sirtuin 1 (SIRT1), homolog of the aging-associated sir2 in yeast and other organisms, activates PGC-1α directly by removing acetylation groups on 13 lysines, providing another important homeostatic mechanism for sensing metabolic state.[24,25] Evidence also exists for methylation of PGC-1α.[26]

PGC-1α and Metabolism in Ischemia

Mitochondria, metabolism, and oxygen are inextricably intertwined. The respiratory chain absolutely requires free oxygen as an electron acceptor. Given the prominent role of PGC-1α in mitochondrial biology it is therefore not surprising that PGC-1α be involved in the cellular response to ischemia. Indeed, PGC-1α gene expression is induced in cultured skeletal myotubes by ischemia-like conditions.[27] Similarly, hypobaric hypoxia induces PGC-1α and mitochondrial biogenesis in the mouse cerebral subcortex.[28] Also, PGC-1 expression in skeletal muscle is induced by hibernation, a known hypoxic state.[29]

If PGC-1α is induced in ischemic states, what role does it play? PGC-1α strongly induces mitochondrial biogenesis, but to do so seems counterintuitive in the face of ischemia, as mitochondria are energetically expensive machines to upkeep, with no clear benefit in the absence of oxygen. Indeed, in cultured myotubes, ischemialike conditions repress, rather than induce, mitochondrial genes (unpublished data). What prevents the activation of mitochondrial genes by the strong induction of PGC-1α in these conditions is not clear. In contrast to this finding in cultured myotubes, cerebral hypoxia/ischemia injury in rat neonates does induce mitochondrial biogenesis.[30] PGC-1 messenger RNA levels were not increased in this model; however, resveratrol, an activator of SIRT1 and PGC-1α activity,[31] is protective in the same model,[32] suggesting that PGC-1α may be posttranslationally activated under these conditions. Why mitochondrial biogenesis should be activated in cerebral ischemia remains unclear, but may relate to protection against oxidative damage (see below).

A second pathway, clearly induced by PGC-1α in response to ischemia, is angiogenesis.[27] Tissues respond to ischemia by orchestrating the secretion of numerous angiogenic factors, including vascular endothelial growth factor (VEGF), in an effort to recruit new blood vessels. PGC-1α strongly induces, both in cell culture and in intact animals, a broad angiogenic program, which includes VEGF. Transgenic expression of PGC-1α in skeletal muscle markedly induces capillary density. PGC-1$\alpha^{-/-}$ mice have significantly delayed recovery of blood flow in a well-established model of hind limb ischemia. Conversely, overexpression of PGC-1α in skeletal muscle accelerates recovery of blood flow in the same model. Thus, PGC-1α plays a critical role in the angiogenic response to ischemia in skeletal muscle.[27]

Endurance exercise is also a powerful stimulus for angiogenesis in skeletal muscle. It is generally believed that local ischemic conditions, caused by prolonged exercise, are responsible for the transcriptional reprogramming that leads to angiogenesis; however, the specific factors involved are not known. Deletion of HIF-1α specifically in skeletal muscle leads to constitutively increased, rather than decreased, capillarization, suggesting that it is not responsible for exercise-induced angiogenesis.[33] PGC-1α is strongly induced by exercise.[16] In light of its powerful angiogenic capacity in skeletal muscle, PGC-1α may, therefore, mediate exercise-induced angiogenesis, thereby coordinating mitochondrial biogenesis (oxygen and nutrient consumption) with angiogenesis (oxygen and nutrient delivery).

In addition to angiogenic factors, a number of other genes known to be induced by hypoxia and ischemia are regulated by PGC-1α, including glucose transporter 1 (GLUT1) and genes of glycolysis.[27,34] Increasing glycolytic flux under hypoxic conditions is a common homeostatic response, because fatty acid consumption absolutely requires mitochondria and the consumption of oxygen. Paradoxically, expression of PGC-1α typically favors the consumption of fatty acids over glucose. All studies demonstrating this fact, however, have been performed under conditions of normoxia and nutritional excess. PGC-1α induces genes of fatty acid consumption by coactivating the nuclear receptor PPAR-α,[35] and hypoxia has been shown to inhibit PPAR-α activity.[36] Therefore, it may be that under hypoxic conditions, PGC-1α is able to activate certain pathways, whereas other pathways are independently blocked. However, whether PGC-1α contributes to reprogramming of fuel consumption under ischemic conditions remains to be tested.

Finally, PGC-1α may also be involved in regulating the production and extinction of reactive oxygen species (ROS). Mitochondria are the main cellular producers of ROS. Low levels of oxygen, such as those caused by ischemia, reduce the efficiency of the respiratory chain and predispose to the generation of ROS.[37] This remains somewhat controversial, and likely depends on oxygen concentration; certainly, in the complete absence of oxygen, no ROS can be formed. ROS, in turn, can profoundly modify, and even damage, mitochondrial function. PGC-1α expression is induced by ROS, and PGC-1α has been shown to limit the accumulation of ROS and be protective against oxidative damage, in part via the induction of a number of genes involved in both limiting ROS production and increasing ROS scavenging.[38–40] Thus, PGC-1α is involved in many pathways that are critical to the cellular and organismal response to oxygen and nutrient insufficiency. PGC-1$\alpha^{-/-}$ mice have complex phenotypes, including marked metabolic derangements, pronounced central nervous system lesions, and a propensity to heart failure.[11,12,41,42] Improper responses to physiological ischemic cues may contribute to a number of these defects.

Regulation of Hypoxia-Inducible Genes by PGC-1α

The mechanisms by which genes are regulated by hypoxia have been studied extensively for decades. The best-studied

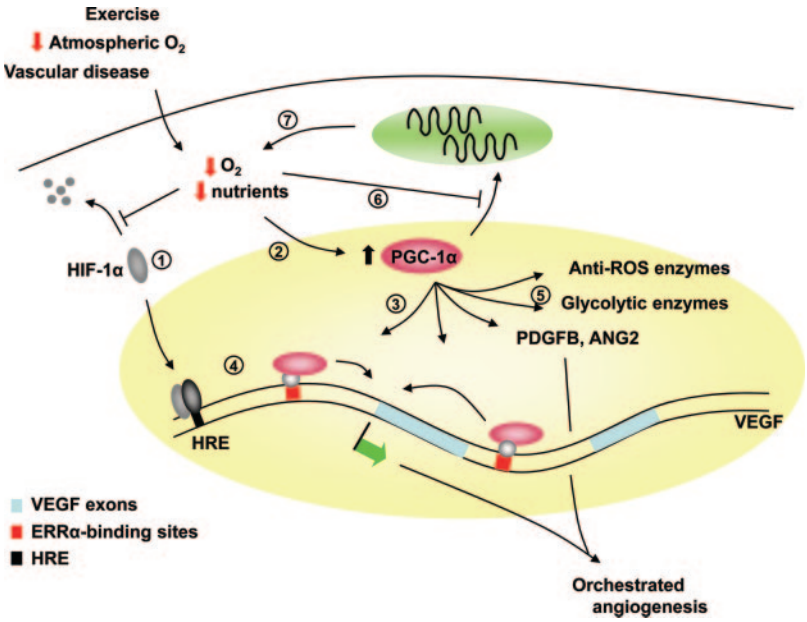

Figure. Tissue hypoxia and nutrient deprivation, stemming from vascular disease and other insults, blocks the degradation of HIF-1 (1), leading to activation of the HRE and induction of VEGF. Independently of HIF, PGC-1 is also induced (2), by mechanisms still unclear. PGC-1 then binds to ERR on the promoter and a novel enhancer in the first intron of the VEGF gene, leading to robust gene activation (3). The relationship between HIF-1 and PGC-1/ERR, if any, remains incompletely defined (4). Other genes are also activated by PGC-1 (5), contributing to the response to ischemia. The normal ability of PGC-1 to induce mitochondrial proliferation is blocked in ischemia, by unclear means (6). It is also possible that in some contexts, mitochondrial biogenesis does occur, and that excess mitochondrial activity leads to local hypoxia (7), in turn indirectly leading to HIF activation.

pathway involves the HIF-1α transcription factor.[43,44] In the presence of oxygen, HIF-1α is hydroxylated on two prolines, leading to its ubiquitination, targeting to the proteosome, and constitutive degradation. Oxygen deprivation halts these events, and HIF-1α translocates to the nucleus, binds its obligate heterodimer aryl hydrocarbon receptor nuclear translocator (ARNT), and induces a panoply of genes involved in hypoxic homeostasis, including VEGF and genes of anaerobic glycolysis. In light of this, and the fact that PGC-1α is a potent transcriptional coactivator, it was tempting to speculate that PGC-1α might coactivate HIF-1α during hypoxia or ischemia to induce VEGF and other target genes. This, however, appears not to be the case.[27] Efforts at demonstrating binding of PGC-1α to HIF-1α were fruitless. Moreover, PGC-1α induced VEGF gene expression even in the absence of ARNT, demonstrating that HIF activity was not needed. Instead, PGC-1α coactivates the transcription factor ERR-α on a number of sites found both in the promoter and a novel conserved enhancer located in the first intron of the VEGF gene. Chromatin immunoprecipitation demonstrated the presence of PGC-1α on these sites, and PGC-1α failed to induce VEGF in ERR-$\alpha^{-/-}$ myocytes enhancing factor (MEFs). Hence, the PGC-1α/ERR-α axis represents a novel, HIF-independent, pathway for the regulation of VEGF and angiogenesis.

Whether hypoxic genes other than VEGF are also regulated via coactivation of ERR-α remains uncertain. The induction of platelet derived growth factor B (PDGF-B) and GLUT1 by PGC-1α in skeletal muscle cells requires ERR-α,[27] but these genes lack conserved consensus ERR-α binding sites (unpublished observation). Other pathways may be at play. For example, PGC-1α may, in some circumstances, act via HIF-dependent mechanisms, perhaps by increasing mitochondrial respiration sufficiently to decrease local oxygen concentrations and activate HIF-1α.[34] By the same token, PGC-1α–mediated increased mitochondrial biogenesis may increase ROS production, and ROS has been shown to stabilize and activate HIF-1α.[45–47] Alternatively, PGC-1α may simply coactivate other transcription factors yet to be identified. Finally, only a subset of known PGC-1α–regulated genes appear to be targeted during hypoxia. The many upstream pathways converging on PGC-1α during hypoxia and nutrient deprivation (see below) likely contribute to this specificity.

Upstream Regulation of PGC-1α

How PGC-1α is induced by ischemia is not at all clear. Ischemia is a highly complex state marked by oxygen insufficiency, nutrient deprivation, and the inability to clear metabolic by-products, including profound extracellular acidification from the accumulation of lactic acid. Many of these by-products may contribute to PGC-1α activation. In cultured myotubes, for example, PGC-1α gene expression is induced by either hypoxia or nutrient deprivation alone; however, the combination has a synergistic effect.[27] The induction of PGC-1α by hypoxia does not appear to require HIF-1 activity: activation of HIF-1 by a variety of methods fails to induce PGC-1α and, conversely, PGC-1α is induced by hypoxia even in cells lacking ARNT. In fact, the induction is likely independent of upstream prolyl hydroxylases as well, because small molecule inhibitors of these enzymes have no effect on PGC-1α expression.[27] Again, the PGC-1α pathway appears to be independent of HIF-1.

If not HIF, what regulates PGC-1α under hypoxic and ischemic conditions? A number of candidate pathways exist. Nitric oxide is a potent bioactive gas, known to be produced, and to be protective, in various ischemic conditions. Nitric oxide induces PGC-1α and mitochondrial biogenesis in fibroblasts and adipocytes,[48] suggesting that the same might be true in other tissues. Reactive oxygen species are also well-known products of hypoxic conditions, and ROS can also induce PGC-1α expression.[38] Hypoxia and/or nutrient deprivation may also affect PGC-1α indirectly by changing the metabolic state of the cell. As previously noted, PGC-1α

activity is increased by the NAD-dependent SIRT1. Hypoxia increases the reduced nicotinamide–adenine dinucleotide (NADH)/NAD ratios,[49] leading to activation of an NADH-dependent hypermethylated in cancer 1: C-terminal binding protein (HIC1-CtBP) corepressor complex and subsequent repression of SIRT1 messenger RNA expression.[50] In addition, a high NADH/NAD ratio might be expected to decrease SIRT1 activity itself (though this is not certain, because NAD is in vast excess to NADH and its levels likely do not change appreciably even during hypoxia[50]). These redox-dependent effects of hypoxia would be predicted to inhibit PGC-1α activity. AMPK is also activated by hypoxia[51] and can both activate PGC-1α directly and induce its expression.[22] Similarly, the p38 mitogen-activated protein kinase, well-known to be activated by hypoxia,[52,53] can phosphorylate and stabilize PGC-1α.[19] Forced adenosine-5′-triphosphate depletion has also been shown to induce PGC-1α in cell culture, likely in part through aberrant calcium ion transients.[54] In short, it remains unclear how hypoxia and/or nutrient deprivation induces PGC-1α expression, and it is likely that PGC-1α is affected at both the transcriptional and posttranslational level.

Concluding Remarks and Outstanding Questions

The observation that PGC-1α regulates blood vessel growth in response to ischemia provides a new and exciting link between angiogenesis and metabolism.[55,56] As with any new field, quite a few questions remain. How, for example, is specificity conferred on the PGC-1α complex under hypoxic conditions, such that angiogenic genes are induced but mitochondrial genes are not induced? What are the upstream oxygen/nutrient-sensing pathways involved? The precise relationship between the PGC-1α/ERR-α and HIF-1α pathways also needs further clarification; as previously noted, PGC-1α may indirectly activate HIF-1α, and evidence exists to suggest that HIF-1α activity requires ERR-α under some circumstances.[57] Do other pathways also activate PGC-1α–mediated angiogenesis, such as endurance exercise in skeletal muscle? Is the powerful angiogenic capacity of PGC-1α in skeletal muscle true in other tissues as well, such as in cerebral ischemia, tumor growth, or retinal pathologies? From a translational point of view, can PGC-1α stimulate angiogenesis in adult skeletal muscle, or is it limited to developmental windows? Are the vessels created by PGC-1α mature? What is the role of PGC-1β, if any? In short, more questions remain unanswered than not in this exciting new field.

Disclosures

None.

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