Metabolic Control Through the PGC-1 Family of Transcription Coactivators

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Published in Cell Metab. 2005 Jun;1(6):361-70. PMID: 16054085. DOI: 10.1016/j.cmet.2005.05.004

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Abstract

Many complex biological programs are controlled at the level of gene transcription by DNA-binding transcription factors. Recent studies have revealed a novel mode of regulation by coactivator proteins, best illustrated by the PGC-1 family of coactivators. These factors are highly responsive to a variety of environmental cues, from temperature to nutritional status to physical activities, and they coordinately regulate metabolic pathways and biological processes in a tissue-specific manner. Notably, the PGC-1 coactivators play a critical role in the maintenance of glucose, lipid and energy homeostasis, and are likely involved in the pathogenesis of diseases including obesity, diabetes, neurodegeneration, and cardiomyopathy. These actions also raise new opportunities for the development of novel therapeutics.

Transcription factors function through the docking of specific coactivator or corepressor proteins. While transcription factors bind to DNA in a sequence-specific fashion, they generally lack the enzymatic activities necessary to modify chromatin, unwind DNA and recruit RNA polymerase II. These biochemical activities are the job of coregulators, which usually exist as multiprotein complexes in the nucleus, and can be recruited to transcription factors in response to cellular signals. Until recently, most studies of biological processes controlled at the transcriptional level have focused on changes in the amounts or activities of transcription factors. While this is undoubtedly a major mode of regulation, it has become very clear that transcriptional coactivator proteins can be highly regulated and can, in fact, be the *primary* targets of hormonal control and signal transduction pathways (Spiegelman and Heinrich, 2004). Perhaps the best examples of this are the PGC-1 (PPARγ Coactivator-1) coactivators. While these proteins were not the first coactivators shown to be highly regulated, their regulation and biological function have been studied in greatest detail. In fact, the PGC-1 family of coactivators is emerging as major players that integrate signaling pathways in the control of cellular and systemic metabolism. The role of PGC-1 in the regulation of mitochondrial oxidative metabolism and the maintenance of glucose, lipid and energy homeostasis will be discussed further in this review.

The first member of the PGC-1 family was identified as a PPARγ-interacting protein from brown fat, and is now termed PGC-1α (Puigserver et al., 1998). PGC-1β is the closest homolog of PGC-1α and shares extensive sequence

identity (Kressler et al., 2002; Lin et al., 2002a), clustered in several distinct domains (Figure 1A), including an N-terminal activation domain (40%), a central regulatory domain (35%) and a C-terminal RNA binding domain (48%). PGC-related coactivator (PRC) has more limited homology (Andersson and Scarpulla, 2001), including the activation domain and RNA-binding domain. Sequence analysis reveals that the PGC-1 family of coactivators is conserved in many chordate species, including primates, rodents, ruminants, birds, amphibians and fishes (Figure 2). These coactivators have similar domain structure and several signature motifs, most notably TPPTTPP and DHDYCQ, that are present in all family members. To date, no clear PGC-1 homolog has been found in lower eukaryotes including worm, fly and yeast.

The PGC-1 coactivators have powerful transcriptional activity when covalently linked to a heterologous DNA binding domain (Knutti et al., 2000; Lin et al., 2002a; Puigserver et al., 1998), or when they dock on a transcription factor. While they have not been found to encode any histone acetyltransferase (HAT) activities in their primary sequence, they bind several powerful HAT-containing proteins at their N-terminal regions, including CBP, p300 and SRC-1 (Puigserver et al., 1999). These proteins acetylate histones and remodel chromatin structure to allow access of additional factors for gene activation (Figure 1B). In addition, several proteins encompassing the mediator complex (also known as the TRAP/DRIP complex) dock in the C-terminal region of PGC-1α (Wallberg et al., 2003). These proteins recruit RNA polymerase II and may have other activities as well. The C-terminal region also harbors a Ser/Arg-rich

domain and an RNA-binding domain, and has been shown to couple pre-mRNA splicing with transcription (Monsalve et al., 2000). Several studies have shown that the PGC-1α transcriptional activator complex is able to displace repressor proteins, such as histone deacetylase and small heterodimer partner (SHP), on its target promoters, leading to augmented gene transcription (Borgius et al., 2002; Guan et al., 2005).

A critical aspect of the PGC-1 coactivators is that they are highly versatile and have the ability to interact with many different transcription factors (Table 1); in doing so, they activate distinct biological programs in different tissues. PGC-1α, for example, can bind to and coactivate most members of the nuclear receptor family – often in a ligand-dependent manner (such as the ER) but sometimes without the addition of a ligand, such as with PPARγ (Puigserver and Spiegelman, 2003). Table 1 summarizes transcription factor targets of PGC-1α and β, and their respective roles in mediating certain aspects of PGC-1 function. Many of these proteins dock in a central region between the N-terminal activation domain and the C-terminal SR and RNA-binding domains. In addition, PGC-1α has three functional LXXLL motifs that are used for the binding of many nuclear receptors (Knutti et al., 2000; Puigserver et al., 1998). The fact that PGC-1α and β contain distinct binding sites for different transcription factors raises the interesting possibility that alleles can be made experimentally, or may exist naturally, that can carry out only a subset of functions that the full-length proteins can stimulate. In fact, both PGC-1α and β mRNAs are alternatively spliced to generate multiple isoforms, though the functional significance of this

remains unknown (Baar et al., 2002; Kamei et al., 2003; Meirhaeghe et al., 2003).

Regulation of mitochondrial oxidative metabolism by the PGC-1

Of the transcription factors that PGC-1α and β coactivate, one subset draws special attention; this includes NRF-1, NRF-2, and the nuclear hormone receptors, such as PPARα, PPARδ, ERRα and TR (Table 1). All of these transcription factors directly regulate the expression of certain nuclear-encoded mitochondrial genes, and were discussed in greater details in two recent reviews (Kelly and Scarpulla, 2004; Puigserver and Spiegelman, 2003). NRF-1 and 2 are themselves targets of PGC-1α (Wu et al., 1999), and are able to stimulate the expression of mitochondrial transcription factor A (Tfam), a mitochondrial matrix protein essential for the replication and transcription of mitochondrial DNA (Clayton, 1991; Parisi and Clayton, 1991; Virbasius and Scarpulla, 1994). The simultaneous stimulation of mitochondrial genes encoded by the two genomes by PGC-1α and β leads to increased enzymatic capacity for fatty acid β-oxidation, Krebs cycle and oxidative phosphorylation (OXPHOS). Importantly, PGC-1α and β also induce the expression of genes involved in heme biosynthesis, ion transport, mitochondrial translation, and protein import, and can stimulate mitochondrial biogenesis and increased respiratory function (St-Pierre et al., 2003; Wu et al., 1999). These two coactivators stimulate the biogenesis of mitochondria with different metabolic characteristics, reflecting the fact that they regulate the expression of overlapping but distinct sets of mitochondrial genes. For example, respiration stimulated by PGC-1β is more highly coupled than that

induced by PGC-1α, when they are expressed in differentiated C2C12 myotubes (St-Pierre et al., 2003). Thus, modulating the relative activity of PGC-1α and β within the cell may lead to fine-tuning of mitochondrial function in response to specific metabolic needs.

Recent studies in PGC-1α-deficient mice reveal that although this coactivator is dispensable for mitochondrial biogenesis *per se*, it is absolutely required for the normal expression of a large number of mitochondrial genes (Leone et al., 2005; Lin et al., 2004). The mRNA level of these genes is quantitatively reduced in all tissues examined to date, including skeletal muscle, heart, liver, brown fat and brain. Interestingly, although PGC-1β shares many of its target genes with PGC-1α in gain of function analysis, it is unable to completely compensate for the loss of PGC-1α in the normal transcription of these genes. PGC-1β mRNA levels remain unaltered in several tissues from PGC-1α-null mice. The loss of PGC-1α leads to significant functional deficits in oxidative metabolism in multiple tissues and renders mice exercise-intolerant (Leone et al., 2005). Notably, AMP-dependent kinase is constitutively activated in skeletal muscle lacking PGC-1α, presumably reflecting a state of energy deficit (Lin et al., 2004). These results underscore a critical role of PGC-1α in the control of mitochondrial OXPHOS and cellular energy homeostasis. Whether a switch of energy production through enhanced glycolysis occurs in PGC-1α-null mice remains to be determined.

Tissue-specific metabolic actions of the PGC-1 coactivators

As summarized in Figure 3A, PGC-1α has been shown to regulate adaptive thermogenesis in brown fat (Puigserver et al., 1998; Tiraby et al., 2003), hepatic gluconeogenesis and ketogenesis (Herzig et al., 2001; Rhee et al., 2003; Yoon et al., 2001), and the specification of slow-twitch muscle fibers (Lin et al., 2002b). In contrast, PGC-1β controls hepatic lipid synthesis and lipoprotein production (Lin et al., 2005). It is evident that a major feature of PGC-1 function is their ability to stimulate the program of mitochondrial biogenesis while simultaneously modulating biological processes commonly associated with increased oxidative capacity for a particular tissue. The following sections review PGC-1 function in brown fat, liver, skeletal and cardiac muscle and brain, based on gain- and loss-of-function analysis in cultured cells and *in vivo*.

Brown fat

PGC-1α was discovered as a molecular switch that turns on several key components of the adaptive thermogenic program in brown fat (Puigserver et al., 1998), including stimulation of fuel intake, mitochondrial fatty acid oxidation and heat production through expression of uncoupling protein-1 (UCP1). The expression of PGC-1α is rapidly and strongly induced by cold exposure. Ectopic expression of PGC-1α is sufficient to promote differentiation toward the brown fat lineage, as shown by activation of UCP1 expression (Puigserver et al., 1998), even in human cells (Tiraby et al., 2003). Notably, mice deficient in PGC-1α are extremely cold-sensitive (Leone et al., 2005; Lin et al., 2004). This is due to defective thermogenesis, likely caused by impaired mitochondrial programs for fatty acid β-oxidation and electron transport, accompanied by reduced induction

of UCP1 and deiodinase 2 in brown fat. Despite this, PGC-1α appears to be dispensable for brown adipocyte differentiation *per se*. One possibility is that PGC-1β, which is induced during brown fat cell differentiation (Lin et al., 2002a), may play a fundamental role in the development of brown adipocytes.

Liver

The expression of PGC-1α and β is induced in the liver at birth and in the adult liver following a short period of fasting (Lin et al., 2003; Yoon et al., 2001). The transition from fed to fasted states involves drastic metabolic changes in the liver to facilitate the adaptation of organisms to nutrient deprivation; these changes include activation of gluconeogenesis, fatty acid β-oxidation and the synthesis and secretion of ketone bodies. A shift in fuel usage from glucose to fats and ketone bodies by peripheral tissues is critical for the maintenance of systemic glucose homeostasis and survival of organisms in the period of food shortage. Studies in cultured hepatocytes and *in vivo* have demonstrated that PGC-1α is sufficient to activate nearly all aspects of the hepatic fasting response, including gluconeogenesis, fatty acid β-oxidation, and ketogenesis. It does so by coactivating key hepatic transcription factors, such as HNF4α, PPARα, GR and FOXO1, and directly stimulating transcription from their target promoters (Puigserver et al., 2003; Rhee et al., 2003; Yoon et al., 2001). In contrast to PGC-1α, PGC-1β has a minimal effect on the expression of gluconeogenic genes, though this factor also potently enhances the expression of genes involved in fatty acid oxidation and ketogenesis (Lin et al., 2003). The required role of PGC-1α in the control of hepatic gluconeogenesis has been revealed by

RNAi knockdown experiments *in vivo* and in genetic studies using PGC-1α knockout mice (Koo et al., 2004; Lin et al., 2004). PGC-1α deficiency clearly impairs gluconeogenic gene expression and hepatic glucose production, and leads to fasting hypoglycemia. In addition, mice lacking PGC-1α develop hepatic steatosis upon fasting (Leone et al., 2005). The physiological role of PGC-1β in the regulation of the hepatic fasting response remains under investigation.

Recent studies have implicated PGC-1β as a key regulator of hepatic lipogenesis and lipoprotein secretion in response to dietary intake of saturated fats (Lin et al., 2005). Here, the expression of PGC-1β is strongly induced by dietary fats in the liver, likely through direct regulation by fatty acids in hepatocytes. PGC-1β docks and coactivates the SREBP and LXR families of transcription factors, coupling triglyceride and cholesterol synthesis, lipoprotein transport and VLDL secretion. SREBPs are key transcription factors that control the expression of many genes that regulate fatty acid, triglyceride (Kim and Spiegelman, 1996; Tontonoz et al., 1993), and cholesterol biosynthesis (Brown and Goldstein, 1997), while LXRs are important in the control of lipoprotein secretion. The crucial role of PGC-1β in mediating the link between hyperlipidemia and saturated fat intake was demonstrated by RNAi knockdown studies in the livers of mice. Thus, the PGC-1β signaling pathway provides a plausible link between consumption of saturated and trans fats, and hyperlipidemia, including hypercholesterolemia.

Although the induction of PGC-1β by dietary fats is robust, the expression of most of its mitochondrial target genes is not elevated in response to fat intake.

These results raise the interesting possibility that the activities of PGC-1β in the regulation of hepatic metabolism is strongly influenced by nutritional status, perhaps as a result of hormonal milieu under different physiological conditions. Similarly, although PGC-1α has been demonstrated to coactivate a large number of transcription factors in various cell types, it is highly unlikely that these pathways are simultaneously active in the presence of PGC-1α. The molecular basis of this specificity in gene activation remains poorly understood. It is possible that the availability of ligands and posttranslational modification of transcription factors and/or the PGC-1 themselves may contribute to the promoter selectivity. This is a very important avenue for further inquiry.

Skeletal muscle

The ability of PGC-1α to control multiple pathways in a complex biological program is also illustrated in skeletal muscle. In this case, PGC-1α functions as a sensitive “rheostat” that responds to neuromuscular input and the ensuing contractile activity. The expression of PGC-1α is readily inducible by exercise training in rodents and humans (Baar et al., 2002; Goto et al., 2000; Norrbom et al., 2004). The subsequent activation of calcium signaling pathways appears to play a major role in the stimulation of PGC-1α transcription through calcium-dependent protein kinases (Wu et al., 2002), which culminate in the activation of several transcription factors, such as CREB and MEF2, in a feed forward loop (Figure 3B) (Handschin et al., 2003). Although AMPK has been shown to be required for exercise-induced PGC-1α expression (Zong et al., 2002), the transcriptional targets of AMPK action on the PGC-1α promoter are still not clear.

Ectopic expression of PGC-1α in myotubes stimulates GLUT4 expression and mitochondrial oxidative metabolism (Michael et al., 2001). Importantly, transgenic expression of PGC-1α in fast-twitch muscle fibers at or near physiological levels leads to activation of genetic programs characteristic of slow-twitch muscle fibers (Lin et al., 2002b). The skeletal muscle of these transgenic mice is resistant to contraction-induced fatigue, indicating a functional switch of muscle fiber types by PGC-1α. Consistent with these gain-of-function studies, PGC-1α deficient skeletal muscle is prone to contraction-induced fatigue and the knockout mice are exercise-intolerant (Leone et al., 2005). Again, PGC-1α is able to couple the metabolic and contractile arms of muscle fiber specification and functionally transforms fast-twitch fibers into more oxidative slow-twitch fibers. It is highly likely that similar regulatory mechanisms also occur in other tissues where related cell types acquire different oxidative capacities as they undergo terminal differentiation.

Transgenic expression of PGC-1β under the control of β-actin promoter leads to mitochondrial biogenesis in skeletal muscle and systemic resistance to diet-induced obesity (Kamei et al., 2003). However, the role of PGC-1β in the control of metabolic and contractile phenotype of skeletal muscle fibers remains to be ascertained.

Heart

Both PGC-1α and β are expressed very abundantly in the heart (Lin et al., 2002a; Puigserver et al., 1998), an organ with an extremely high and dynamic demand for ATP. Much of this supply comes from the oxidation of fatty acids,

though glucose can also be a substrate for mitochondrial oxidation. To date, the role of PGC-1β in cardiac energy metabolism is less well studied, but several studies have implicated PGC-1α as 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 fuel oxidation in cardiac muscle (Lehman et al., 2000). Forced expression of PGC-1α in cultured neonatal cardiomyocytes and *in vivo* powerfully stimulates mitochondrial gene expression and biogenesis (Lehman et al., 2000). In fact, very high transgenic expression of PGC-1α in mouse heart leads to such robust mitochondrial biogenesis that the contractile apparatus is displaced, and dilated cardiomyopathy ensues. Interestingly, PGC-1α-null mice develop early symptoms of heart failure, such as activation of a fetal program of cardiac gene expression and significant increase in circulating levels of atrial natriuretic peptide, a hallmark of cardiac dysfunction (Arany et al., 2005). Defects in cardiac function are most clearly seen when the intact hearts were studied *in isolated perfusion chambers*. Here, the PGC-1α deficient heart shows a significantly lower cardiac reserve in response to electrical or chemical stimulation (Arany et al., 2005), and is thus less able to perform work in response to increased demand. Abnormal heart rate and impaired left ventricular function were also observed in PGC-1α deficient mice following exercise (Leone et al., 2005).

Brain

PGC-1α deficiency leads to certain behavioral abnormalities, including profound hyperactivity (Leone et al., 2005; Lin et al., 2004). These behavioral

changes are associated with axonal degeneration in the brain, especially in the striatum (Lin et al., 2004), a region known to be very important in the control of movement. The molecular basis of this axonal degeneration is not completely understood. Though impaired energy homeostasis and ROS metabolism due to defects in mitochondrial function are the most likely causes. Neurons consume large amounts of ATP to maintain their membrane ionic gradient and axonal transport, and rely almost exclusively on oxidative metabolism to derive energy for this function. In fact, the most common symptoms of patients with genetic mutations of mitochondrial genes are neurological-related, reflecting an extremely low tolerance for perturbing OXPHOS in the brain (Schon and Manfredi, 2003). It cannot be ruled out, however, that PGC-1α also regulates pathways critical for neuronal function. In fact, the expression of several neurofilament proteins and α2 subunit of sodium pumps is reduced in the PGC-1α-null brain (Lin et al., 2004). It is not yet clear whether this represents the cause or the effect of the obvious brain lesions in the knockout mice.

PGC-1 and the metabolism of reactive oxygen species

The mitochondrial electron transport chain is a major site of reactive oxygen species (ROS) production in the cell (Lenaz et al., 2002; Lowell and Shulman, 2005). Under normal conditions, the balance between ROS generation and detoxification is controlled by a set of cellular enzymes including superoxide dismutase (SOD), catalase and those involved in glutathione metabolism. As PGC-1 stimulate mitochondrial-based respiration, they also increase the expression of SOD and glutathione peroxidase, as well as enzymes responsible

for glutathione biosynthesis (St-Pierre et al., 2003). Thus, certain components of the ROS scavenging pathway are linked by the PGC-1 to mitochondrial oxidative metabolism, apparently enabling cells to maintain normal redox status in response to changing oxidative capacity. In addition, PGC-1α and β stimulate the expression of UCP2 and UCP3 (Puigserver et al., 2001; St-Pierre et al., 2003; Wu et al., 1999), which dissipate the proton gradient and lower mitochondrial membrane potential, a process thought to greatly reduce ROS production by mitochondria (Miwa and Brand, 2003). Hence, the PGC-1 coactivators apparently have two related but distinct mechanisms to regulate ROS metabolism in cells.

Reactive oxygen and nitrogen species are capable of transducing cellular signals under certain conditions (Soberman, 2003). However, excess free radical production leads to oxidative stress, which causes DNA damage, lipid peroxidation and oxidative protein modifications. It is now clear that ROS generation is greatly elevated following certain metabolic perturbation, such as ischemia reperfusion of the heart, stroke in the brain, as well as in a wide range of disorders including neurodegenerative diseases (Ischiropoulos and Beckman, 2003). Given the abnormality seen in the brain and heart of PGC-1α knockout mice (Leone et al., 2005; Lin et al., 2004), it is highly likely that the PGC-1 are important regulators of ROS metabolism in normal physiological conditions and under certain states of oxidative stress.

Regulation of PGC-1 activity

The diverse and potent effects of PGC-1α and β on cellular energy metabolism necessitate that their activities are under tight control. This, in theory, can be achieved at the transcriptional and posttranscriptional levels. In fact, PGC-1α protein has a very short half-life (~2.3 hours) and is greatly stabilized following phosphorylation at three sites (T262, S265, and T298) by p38 MAP kinase (Puigserver et al., 2001). These modifications also enhance the transcriptional activity of PGC-1α by displacing p160 myb-binding protein ($p160^{MBP}$), a strong transcriptional suppressor (Fan et al., 2004). The binding of p160 may largely account for the suppressive activity residing in the central domain of PGC-1α.

Another protein that has been shown to modulate PGC-1α activity is SirT1, the mammalian homolog of the yeast Sir2. SirT1 associates with PGC-1α in the central regulatory region between amino acids 200-400 and deacetylates PGC-1α, leading to enhanced transcriptional activity in a NAD^+-dependent way (Rodgers et al., 2005). This is particularly interesting because Sir2 regulates aging in yeast and other organisms (Blander and Guarente, 2004); aging is a process that is affected by metabolic parameters, especially caloric restriction, in many species. The ability of SirT1 to bind to PGC-1α and activate it makes a direct molecular connection between the pathways that impact organismal aging and metabolic regulation. An important question is whether SirT1 also modulates the transcriptional activity of PGC-1β and PRC.

In addition to post-translational mechanisms, many studies have clearly demonstrated that the PGC-1 coactivators are regulated at the transcriptional

level in response to a variety of nutritional and environmental stimuli (Figure 3A). PGC-1α and β are abundantly expressed in tissues with high energetic need, including brown fat, cardiac and skeletal muscle and the central nervous system (Kressler et al., 2002; Lin et al., 2002a; Puigserver et al., 1998). In addition, their mRNA levels are subject to substantial regulation by physiological signals within these tissues. For example, PGC-1α mRNA levels are rapidly induced in brown fat following cold exposure (Puigserver et al., 1998), and in skeletal muscle in response to bouts of exercise (Baar et al., 2002; Goto et al., 2000); PGC-1β expression remains unchanged under these conditions (Lin et al., 2002a). In contrast, hepatic expression of PGC-1β, is stimulated by dietary fat intake and thyroid hormone to a much greater extent than PGC-1α (Lin et al., 2005; Weitzel et al., 2003). The expression of both of these coactivators is increased in the neonatal liver and heart, correlating with a dramatic expansion of oxidative capacity in these tissues during early postnatal development (Lehman et al., 2000; Lin et al., 2003). PGC-1α and β mRNA levels are relatively low in adult liver in the fed state, however, they are readily inducible upon brief fasting (Lin et al., 2002a; Lin et al., 2003; Yoon et al., 2001).

Although the expression of PGC-1β is not regulated by cold exposure, its mRNA level is increased during differentiation of cultured brown and white adipocytes (Kamei et al., 2003; Lin et al., 2002a). While the role of PGC-1α in adaptive thermogenesis has been firmly established, the function of PGC-1β in the regulation of development and function of adipocytes remains unexplored. Interestingly, the expression of PRC in cultured fibroblasts is inducible by serum

treatments and is regulated in a cell-cycle dependent manner that peaks during the G_0-to-G_1 transition (Andersson and Scarpulla, 2001). Thus, it is now clear that the expression of this entire family of coactivators is under control by distinct extracellular signals, consistent with the fact that they modulate different aspects of metabolism and other biological processes in the cell.

Activation of the cAMP signaling pathway is a major mechanism underlying the induction of PGC-1α in several different cell types. In fact, the proximal promoter of PGC-1α contains a functional CREB binding site that is required for cAMP response (Herzig et al., 2001). CREB integrates multiple signaling pathways in various cell types, including glucagon action in the fasted liver (Herzig et al., 2001), calcium signaling through calcium/calmodulin-dependent protein kinase IV and calcineurin A in exercised skeletal muscle (Handschin et al., 2003; Ojuka et al., 2003) and adaptive thermogenesis in brown fat (Puigserver et al., 1998). Stimulation of activating transcription factor 2 (ATF2) by p38 MAP kinase has also been shown to modulate the induction of PGC-1α in brown fat by cold (Cao et al., 2004). In states of low energy, PGC-1α can also be induced by the AMP-dependent protein kinase (AMPK) in skeletal muscle and subsequently increase energy levels by boosting oxidative metabolism (Irrcher et al., 2003; Suwa et al., 2003; Terada et al., 2002; Zong et al., 2002). In contrast, cyclin-dependent kinase 9 suppresses the expression of PGC-1α and mitochondrial function in the heart, leading to the development of cardiomyopathy (Sano et al., 2004).

Intriguingly, some transcription factors that are coactivated by PGC-1α can simultaneously serve as regulators of PGC-1α transcription. This is best illustrated by the regulation of PGC-1α expression by MEF2 in skeletal muscle (Czubryt et al., 2003; Handschin et al., 2003). The presence of such autoregulatory loops provides a molecular mechanism to sustain PGC-1α expression following physiological stimuli, as in the case of endurance exercise (Figure 3). It seems likely that similar mode of regulation also occurs for the thyroid hormone receptor in muscle and liver (Irrcher et al., 2003) and glucocorticoid receptor in liver (Yoon et al., 2001).

PGC-1 and metabolic diseases

It is apparent now that the PGC-1 family of coactivators is highly responsive to environmental stimuli and nutritional states of an organism. These coactivators transduce physiological and/or environmental signals and modulate programs of gene expression in a tissue-specific manner. The major activities of PGC-1α and β studied to date have been in the modulation of glucose, lipid and energy metabolism, enabling the organisms to adapt to their fluctuating nutritional status and environmental conditions. This adaptation to a variety of environmental challenges, from temperature to nutritional changes, to alterations in physical activity, seems to be a *raison d'etre* for the PGC-1 coactivators. Abnormal PGC-1 activities might alter metabolic properties of tissues and lead to various diseases with underlying dysregulation of metabolism, or alternatively,

allow certain cells to thrive in their unique tissue environment, such as during the progression of cancer.

Since the PGC-1 coactivators regulate multiple aspects of glucose, lipid and energy metabolism, it is not surprising that dysregulation of these proteins has been observed in several pathological conditions. PGC-1α mRNA levels are elevated in the liver of rodents of both type 1 and type 2 diabetes; this is likely due to alterations of the insulin/glucagons axis and hepatic insulin resistance, respectively (Herzig et al., 2001; Yoon et al., 2001). Increased PGC-1α activity clearly contributes to elevated hepatic glucose output and the development of hyperglycemia. In fact, acute knockdown of PGC-1α in liver improves hepatic insulin sensitivity and glucose tolerance in db/db mice (Koo et al., 2004). Thus, modulating PGC-1α activity in the liver may have important implication for systemic glucose homeostasis. PGC-1α stimulates gluconeogenic gene expression through coactivation of GR, FOXO1, and HNF4α. It is tempting to speculate that chemical compounds that selectively disrupt the docking of PGC-1α to these gluconeogenic transcription factors may provide a novel therapeutic modality for the treatment of hyperglycemia (Barthel and Schmoll, 2003). Similarly, disruption of PGC-1β docking on SREBP and LXR may specifically lead to suppression of the lipogenic and hyperlipidemic activities of PGC-1β in liver. This has been demonstrated as a proof of principle that compounds can be developed to target the interaction between GR and PGC-1α, but not its interaction with other coactivators such as GR-interacting protein (Coghlan et al., 2003).

Insulin resistance is a major pathogenic factor for the development of type 2 diabetes. Recent evidence clearly points to a strong association between insulin resistance and mitochondrial dysfunction in skeletal muscle (Lowell and Shulman, 2005). The expression of a large set of OXPHOS genes is quantitatively reduced in skeletal muscle from type 2 diabetic patients and insulin-resistant prediabetic individuals (Mootha et al., 2003; Patti et al., 2003). This is accompanied by a significant decrease in the mRNA levels of PGC-1α, PGC-1β and NRF1 (Patti et al., 2003), and abnormal mitochondrial morphology (Kelley et al., 2002). Importantly, a single nucleotide polymorphism (Gly482Ser) in human PGC-1α has been associated with insulin resistance and susceptibility to type 2 diabetes in some populations (Ek et al., 2001; Hara et al., 2002; Lacquemant et al., 2002; Muller et al., 2003). Impairment of mitochondrial oxidative metabolism has also been observed in age-related insulin resistance (Petersen et al., 2003). Despite these strong associations, it is not clear whether reduced PGC-1 expression and impaired mitochondrial OXPHOS is a *causal* factor in the development of insulin resistance and type 2 diabetes. It is interesting to note that the expression of PGC-1α and β is induced in skeletal muscle in response to insulin (Ling et al., 2004). Hence insulin resistance *per se* may lead to reduced PGC-1 expression and mitochondrial dysfunction, which may in turn aggravate insulin resistance, resulting in a deleterious spiral. It is tempting to speculate that elevating the activity of PGC-1 in skeletal muscle might provide beneficial effects on muscle metabolism and insulin sensitivity. Toward this end, compounds targeting the expression of PGC-1 and/or docking

of PGC-1 on certain transcription factors, such as ERRα, PPAR and NRF, should be developed and tested.

The regulation of PGC-1α expression in the heart suggests a role for this protein in the control of fuel utilization, particularly the switch from glucose to fatty acid oxidation in neonatal development and under physiological stresses, such as fasting (Huss and Kelly, 2004). PGC-1α mRNA levels are elevated in the myocardium of streptozotocin-treated and *db*/*db* mice (Finck et al., 2002), suggesting that this coactivator may play a role in the development of diabetic cardiomyopathy. Recent studies indicate that PGC-1α deficient heart has impaired oxidative energy generation and decreased contractile function, suggesting that PGC-1α is required for energy homeostasis in cardiac muscle. The expression of PGC-1α is reduced in animal models of heart failure caused by pressure overload or ischemia, along with PPARα and genes involved in fatty acid oxidation. These results would argue that the decrease of PGC-1α mRNA in heart may represent a maladaptive response that eventually leads to energetic failure and cardiac dysfunction. Similar to the situation in skeletal muscle, enhancing PGC-1 activity in cardiac muscle may boost cellular oxidative metabolism and improve contractile function of heart. In addition, PGC-1α has been shown to protect cardiomyocytes from apoptosis (Sano et al., 2004), suggesting that there may be additional therapeutic benefit for activating the PGC-1 pathway in various forms of cardiomyopathy and congestive heart failure.

Clearly, abnormal PGC-1 activity is likely to play an important role in the pathogenesis of hyperglycemia, insulin resistance, and cardiomyopathy. It

remains to be determined whether dysregulation of the PGC-1 is also present in other disorders associated with impaired mitochondrial OXPHOS and increased oxidative stress, most notably, in various forms of neurodegenerative disease. More importantly, the PGC-1 pathways offer novel targets for potential therapeutic intervention. It can be expected that the modulation of coactivator docking on their specific binding partners will provide opportunities to selectively stimulate or suppress certain pathways, hence obtaining desirable physiological effects. The development of ligands for nuclear receptors which can selectively recruit certain coactivators has already been demonstrated (Coghlan et al., 2003). Thus, new classes of valuable drugs may be in the offing.

Acknowledgements

We thank Drs. Pere Puigserver and Bradford Lowell for critical reading of the manuscript. This work was supported by grants from the N.I.H., DK065584 (J.L.), DK54477 and DK61562 (B.M.S.), and the Muscular Dystrophy Association (C.H.).

(Huss et al., 2002)

(Huss et al., 2004)

Figure Legends

Figure 1. Structure and function of the PGC-1 family coactivators.

(A) Sequence homology of PGC-1α, PGC-1β and PRC. Note that activation domain (red), Arg/Ser-rich domain (yellow), and RNA-binding domain (purple) are present in all three PGC-1 family members. PGC-1α and PGC-1β share an additional domain of similarity in the central region.

(B) Protein complexes associated with PGC-1α. PGC-1α binds to the HAT and TRAP/DRIP/Mediator complexes at the amino and carboxyl termini, respectively. SirT1 and p160 bind to the repression domain, which also contains three p38 MAP kinase phosphorylation sites. LXXLL and LLXXL denote nuclear receptor binding sites.

Figure 2. Conservation of the PGC-1 family of coactivators in vertebrates.

Amino acid sequences of the PGC-1 family of coactivators currently available in the GenBank database are aligned using the Clustal program. The relative distance represents the degree of sequence identity among different members. Note that the absence of certain members in some species is likely due to the lack of full-length cDNA sequences in available databases.

Figure 3. Biological activity and regulation of PGC-1α.

(A) Tissue-specific function of PGC-1α and β. PGC-1α regulates adaptive thermogenesis in brown fat, muscle fiber specification, and hepatic fasting response, while PGC-1β coordinates lipogenesis and lipoprotein secretion in liver in response to dietary fats.

(B) Regulation of PGC-1α expression in skeletal muscle and mechanisms by which PGC-1α stimulates mitochondrial gene expression. Coactivation of MEF2 by PGC-1α provides a positive feed-forward signal to rapidly induce PGC-1α expression following muscle contraction. PGC-1α induces the expression of ERRα, which activates the expression of NRF1, NRF2 and ERRα itself. These molecular events lead to the stimulation of nuclear-encoded mitochondrial genes. PGC-1α also simultaneously regulates the expression of slow-twitch muscle fiber genes through coactivation of MEF2.

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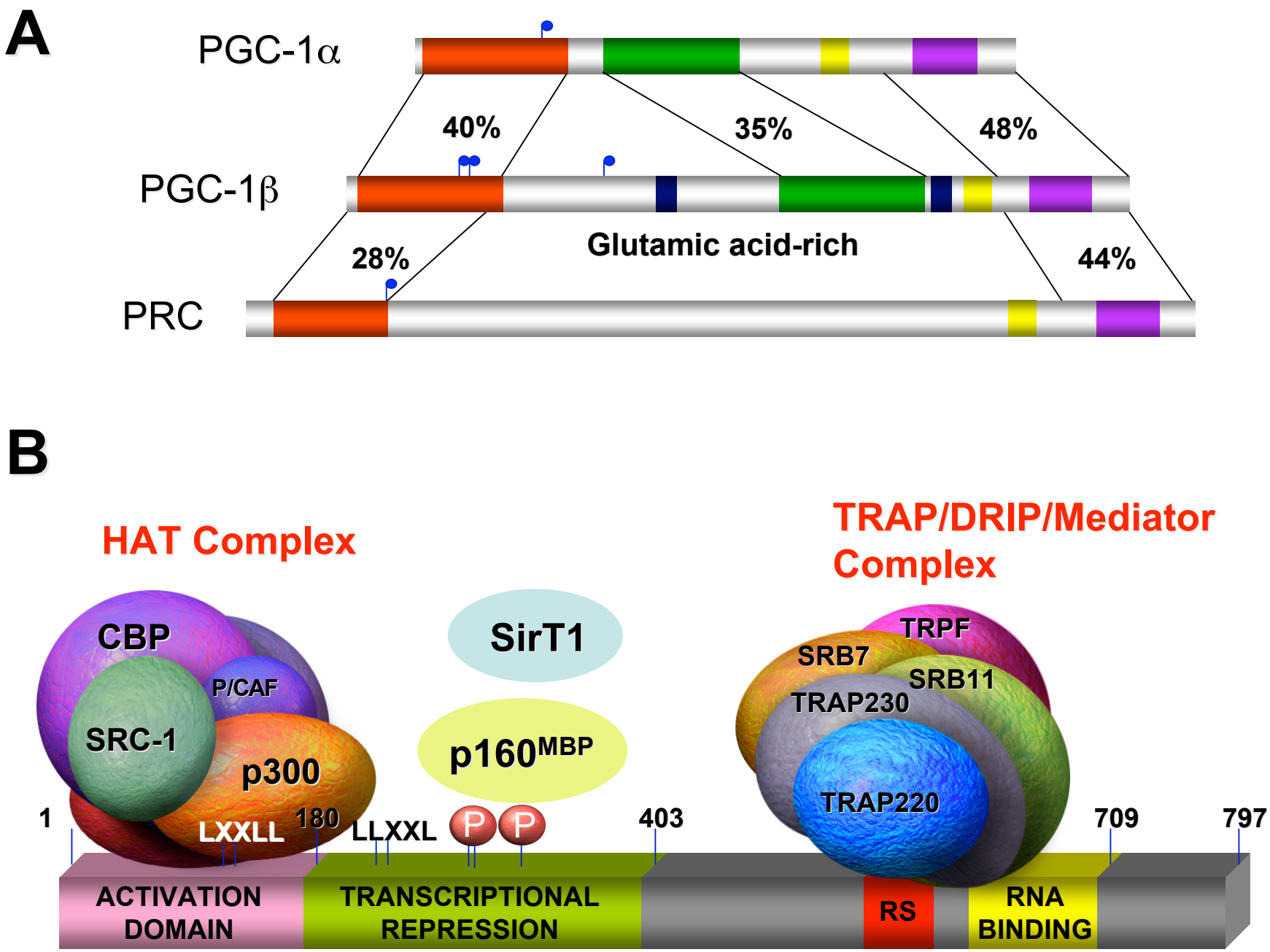
Table 1. Transcription factor targets of the PGC-1 family of coactivators.

Transcription factor	PGC-1α	PGC-1β	Function	References
NRF1	+	+	mitochondrial genes	Wu et al., 1999
NRF2	+	ND	mitochondrial genes	Mootha et al., 2004
PPARα	+	+	fatty acid oxidation	Vega et al., 2000
PPARβ/δ	+	ND	fatty acid oxidation	Wang et al., 2003
PPARγ	+	+	UCP1/GyK induction	Guan et al., 2005; Puigserver et al., 1998
ERRα,β,γ	+	+	mitochondrial genes	Kamei et al., 2003; Mootha et al., 2004; Schreiber et al., 2004
TRβ	+	+	cpt1 induction	Wu et al., 2002; Zhang et al., 2004b
LXRα,β	+	+	lipoprotein secretion	Lin et al., 2005; Oberkofler et al., 2003
FXR	+	ND	triglyceride metabolism	Zhang et al., 2004a
GR	+	−	gluconeogenesis	Kressler et al., 2002; Yoon et al., 2001
ERα,β	+	+	unknown	Kressler et al., 2002
PXR	+	ND	unknown	Bhalla et al., 2004
Sox9	+	ND	chondrogenesis	Kawakami et al., 2005
MEF2	+	ND	slow fiber genes	Lin et al., 2002b; Michael et al., 2001
FOXO1	+	−	gluconeogenesis	Puigserver et al., 2003
HNF4α	+	+/−	gluconeogenesis	Lin et al., 2002a; Yoon et al., 2001
SREBP1a, 1c, 2	−	+	lipogenesis/ lipoprotein secretion	Lin et al., 2005

Figure 1


A
PGC-1α
40%
35%
48%
PGC-1β
28%
Glutamic acid-rich
44%
PRC
B
HAT Complex
TRAP/DRIP/Mediator Complex
CBP
P/CAF
SRC-1
p300
SirT1
p160MBP
TRPF
SRB7
SRB11
TRAP230
TRAP220
1
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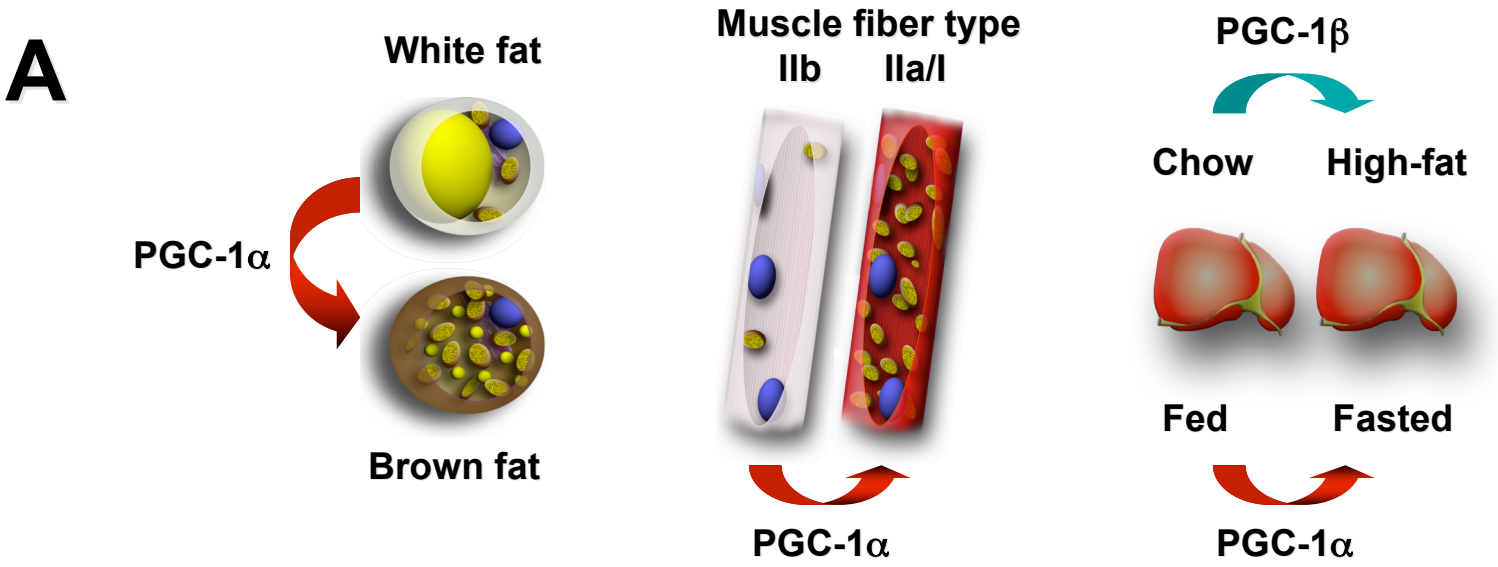
ACTIVATION DOMAIN
TRANSCRIPTIONAL REPRESSION
RS
RNA BINDING

Figure 2


A
White fat
PGC-1α
Brown fat
Muscle fiber type
IIb
IIa/I
PGC-1α
PGC-1β
Chow
High-fat
Fed
Fasted
PGC-1α

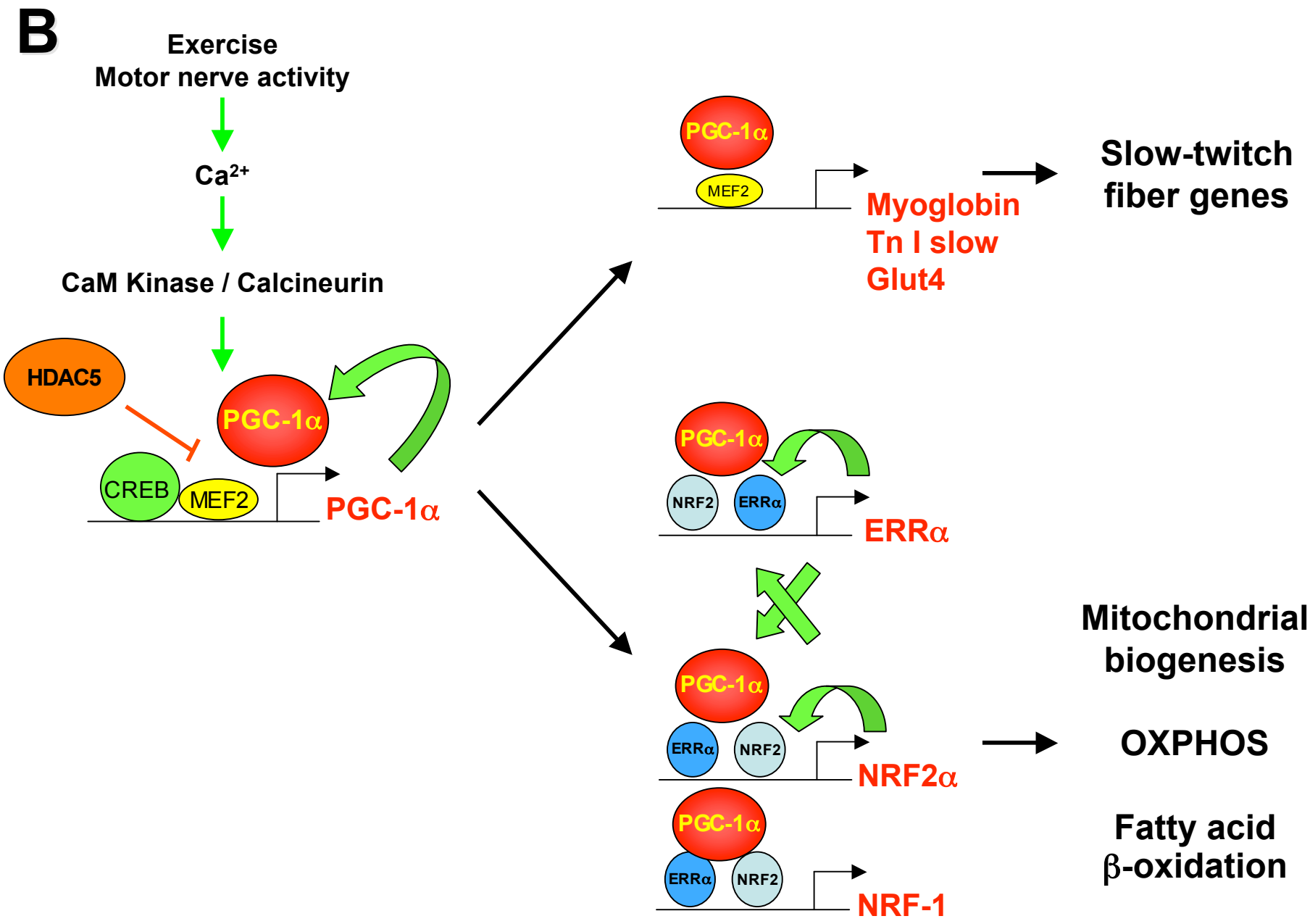
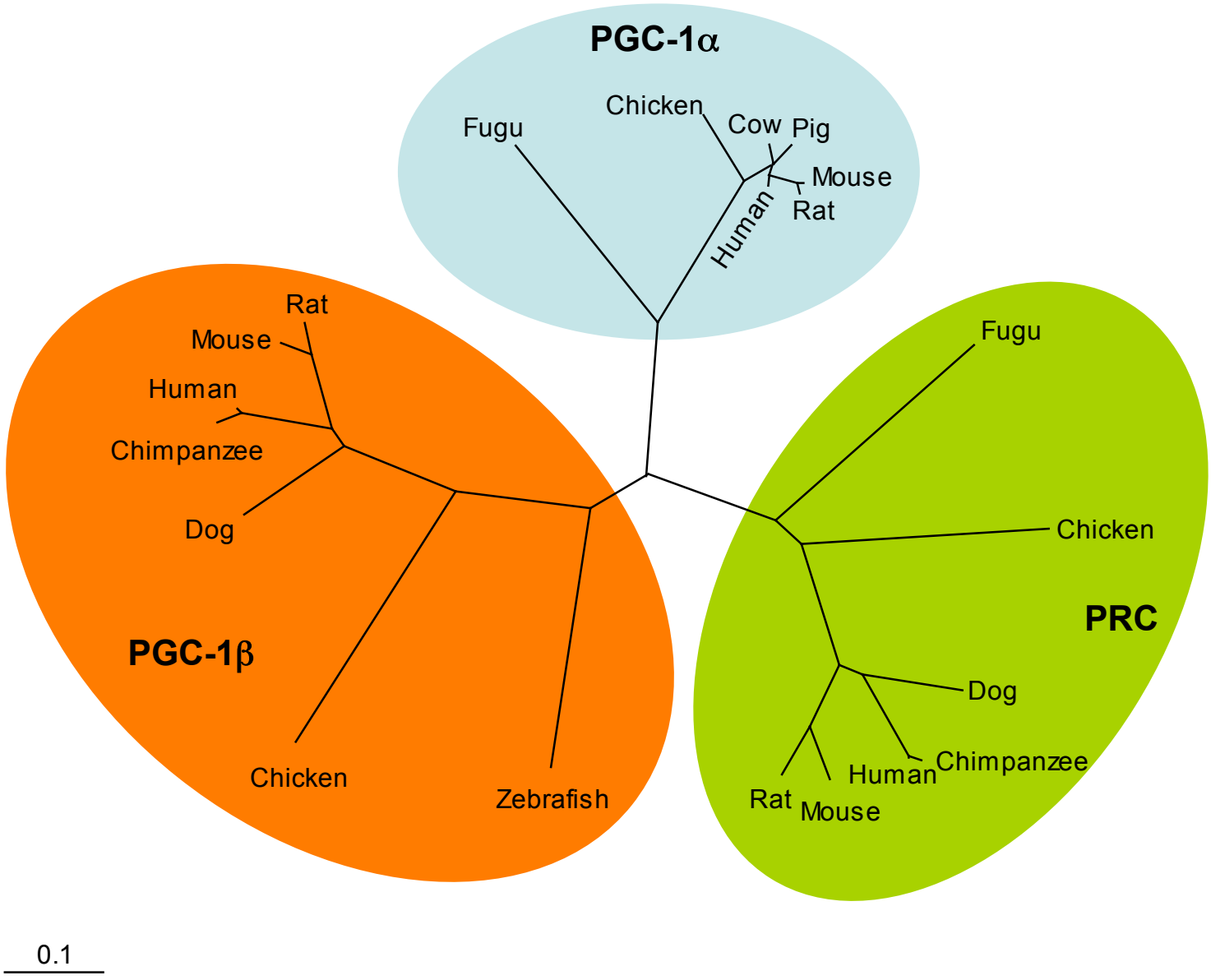

B
Exercise
Motor nerve activity
Ca2+
CaM Kinase / Calcineurin
HDAC5
CREB
MEF2
PGC-1α
PGC-1α
PGC-1α
MEF2
Myoglobin
Tn I slow
Glut4
Slow-twitch
fiber genes
PGC-1α
NRF2
ERRα
ERRα
PGC-1α
ERRα
NRF2
NRF2α
PGC-1α
ERRα
NRF2
NRF-1
Mitochondrial
biogenesis
OXPHOS
Fatty acid
β-oxidation

Figure 3


PGC-1α
Fugu
Chicken
Cow
Pig
Mouse
Rat
Human
PGC-1β
Rat
Mouse
Human
Chimpanzee
Dog
Chicken
Zebrafish
PRC
Fugu
Chicken
Dog
Chimpanzee
Human
Rat
Mouse
0.1