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Regulation of skeletal muscle cell plasticity by the peroxisome proliferator-activated receptor \( \gamma \) coactivator 1\( \alpha \)

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Abstract

Exercise triggers a pleiotropic response in skeletal muscle, which results in a profound remodeling of this tissue. Physical activity-dependent muscle fiber plasticity is regulated by a number of distinct signaling pathways. Even though most of these pathways are activated by different stimuli and in a temporally and spatially separated manner during exercise, many of the major signal transduction events converge on the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) by posttranslationally modifying the PGC-1α protein, modulating PGC-1α gene expression or both. In turn, depending on the cellular context, PGC-1α regulates specific gene programs. Ultimately, PGC-1α modulates many of the transcriptional adaptations of skeletal muscle to exercise. In this review, the regulation and function of this pivotal transcriptional coactivator in muscle are discussed.
Background

Skeletal muscle is an extremely versatile tissue that can respond to a variety of external stimuli, including changes in the levels of physical activity, temperature, oxygen, nutrient supply and composition (1-3). Plasticity of this organ is facilitated by different muscle fiber types within muscle beds. Oxidative, fatigue resistant type I and type IIa muscle fibers enable high endurance activities whereas glycolytic, fast twitch type IIx and type IIb fibers allow explosive movements with maximal peak force generation (4, 5). Before, during and after exercise bouts, neuronal, hormonal, mechanical and metabolic parameters affect contracting muscle fibers and trigger appropriate adaptations for subsequent muscle loading events. An inability of muscle to properly function or respond to external stimuli has drastic health consequences, as observed in many muscular dystrophies. Similarly, a voluntary or forced relative physical inactivity is a severe and independent risk factor for many chronic diseases, thereby compromising quality of life and reducing life expectancy (2, 3, 6-8).

Despite the obvious consequences of physical activity on human health, surprisingly little is known about the molecular mechanisms that regulate skeletal muscle plasticity in the active and inactive muscle fiber, respectively. While individual signaling pathways have been identified, the coordination of the complex response, that even in a single bout of endurance exercise comprises a change in the expression of more than 900 genes (9), remains enigmatic. In recent years, the increasing use of molecular biology and transgenic techniques revealed candidate factors that contribute to the exercise response in muscle. In particular, the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), a transcriptional
coactivator protein, emerged as a central regulator in exercise-induced muscle fiber plasticity (6, 7, 10-12).

**PGC-1α: a master regulator of mitochondrial biogenesis and function**

Similar to the different fiber types in muscle, fat also consists of two tissue subtypes that vary dramatically in their oxidative capacity, brown and white adipose tissue, respectively (13). Pere Puigserver, Zhidan Wu, Bruce Spiegelman and colleagues used these two types of fat to search for factors that determine an oxidative phenotype and thereby established PGC-1α as a master regulator of mitochondrial biogenesis and activity (14, 15). According to this core function, PGC-1α is expressed in every oxidative tissue with a high energy turnover, including brain, heart, muscle, liver, kidney, brown adipose tissue, and pancreas (6, 10, 11, 16). Importantly, in addition to promote mitochondrial function and oxidative metabolism, PGC-1α regulates many tissue-specific processes, such as fasting-induced hepatic gluconeogenesis, glucose-stimulated pancreatic insulin secretion and cold-mediated adaptive thermogenesis in brown adipose tissue.

PGC-1α is a transcriptional coactivator and therefore relies on interactions with DNA-binding transcription factors in order to be recruited to target gene promoters (16, 17). Such interactions are formed with various members of the nuclear receptor superfamily, but also many non-nuclear receptor-type transcription factors. The functional domains that mediate the binding of PGC-1α to transcription factors are located throughout the PGC-1α protein: nuclear receptors predominantly bind to LXXLL and LLXXL domains at the N-terminus whereas other factors such as FoxO1
or the myocyte enhancer factors 2 (MEF2) interact more C-terminally (16, 17). Once bound to a transcription factor, PGC-1α serves as a protein docking platform and assembles histone acetyl-transferase (HAT), TRAP/DRIP/Mediator and SWI/SNF complexes (18-20). As a consequence, transcription of PGC-1α target genes is greatly increased.

The PGC-1α protein can vary depending on alternative splicing of its transcript (21), usage of two different promoters separated by 13kb in the mouse genome (22), and posttranslational modifications. So far, phosphorylation by the AMP-dependent protein kinase (AMPK) (23), p38 mitogen-activated protein kinase (p38 MAPK) (24, 25) and protein kinase B (PKB/Akt) (26) at different serine and threonine residues, lysine acetylation and deacetylation by GCN5 and SIRT1, respectively (27, 28), arginine methylation by PRMT1 (29), ubiquitination (30), lysine sumoylation (31) and serine O-linked β-N-acetylglucosamination (32) have been described to alter the stability, activity or specificity of the PGC-1α protein or modulate the interaction with binding partners such as the repressor p160 myb (33). Combinatorially, these differences in splicing, promoter usage and protein modifications enable a huge repertoire of PGC-1α protein species and thereby provide the base for an extremely fine-tuned and specific regulation of PGC-1α level and function (10). Together with the ability to bind to many different transcription factors, this variability of the PGC-1α protein confers significant advantages to this transcriptional coactivator over any individual transcription factors to regulate complex biological programs (34-36). In a similar fashion, transcriptional regulators form large protein complexes, sometimes even including RNA-based coregulators, to control the expression of gene families in other tissues (37). Some of these coregulators, for example the nuclear receptor
coregulator (NRC), are multifunctional and involved in the regulation of many different cellular processes (38).

Expression and regulation of PGC-1α in skeletal muscle

In skeletal muscle, PGC-1α exhibits a fiber type-specific expression pattern with higher levels in oxidative type I and IIa compared to glycolytic type IIx and IIb fibers (39). Analogous to the metabolic and external stimuli that induce PGC-1α in other tissues, such as fasting in the liver or cold in brown adipose tissue, physical activity is the major driver that alters PGC-1α gene expression in muscle (21). PGC-1α is acutely induced during an endurance exercise bout, and the levels revert to those observed pre-exercise within a couple of hours (40). Concomitant with a fiber type shift towards oxidative fibers, chronic endurance exercise increases the basal expression of PGC-1α while retaining the pulsatile regulation during each individual exercise bout (40, 41). In contrast, muscular inactivity results in a rapid decline in PGC-1α levels (42).

Motor neuron-induced muscle fiber contractions are mediated by a transient rise in intramyocellular calcium (43). Calcium signaling is also involved in increasing the transcription of PGC-1α via activation of the calcium/calmodulin-dependent protein kinase (CaMK) and the protein phosphatase calcineurin A (CnA) (44, 45). Subsequently, the altered phosphorylation status of MEF2C/D and the cyclic AMP-responsive element binding protein (CREB) result in an activation of these transcription factors, binding to the PGC-1α promoter and induction of PGC-1α transcription (45, 46). Interestingly, the PGC-1α protein competes with histone
deacetylases (HDAC) for binding to MEF2C/D and thereby controls its own transcription in a positive autoregulatory loop (45, 47).

In addition to the regulation of PGC-1α gene expression by motor neuron activity, many of the other major signaling pathways that are induced in a contracting muscle fiber also converge on this coactivator by either activating PGC-1α transcription, modifying the PGC-1α protein, or both (Fig. 1). Even preceding transcriptional induction of the PGC-1α gene, the mechanical stress of fiber contraction activates the p38 MAPK, which then phosphorylates and stabilizes the PGC-1α protein (24, 48). Contractile stress-mediated generation of reactive oxygen species (ROS) triggers an adaptive response by inducing PGC-1α gene expression and subsequently elevating ROS detoxifying enzyme levels (49). The metabolic demand of exercise results in a shift of the ratio of AMP to ATP and of NAD+ to NADH. AMPK is an important energy sensor in muscle, which promotes metabolic pathways that favor ATP synthesis (50). Once activated by rising AMP levels, AMPK phosphorylates the PGC-1α protein and induces PGC-1α gene expression (23). PGC-1α in turn regulates some, but not all of the AMPK target genes (23). Similarly, augmented NAD+ activates the protein deacetylase SIRT1, which deacetylates and activates PGC-1α (51, 52). The increased muscle tone during exercise results in vascular occlusion in this tissue. In combination with increased oxygen consumption, hypoxic conditions occur as a consequence in working muscle (53). Subsequent compensatory mechanisms trigger exercise hyperemia that in turn leads to microvascular shear stress (54). Both the hypoxic signaling and the endothelial released nitric oxide boost PGC-1α transcription (55, 56). The hormonal milieu peri- and post-exercise is characterized by fight-or-flight signals and anti-inflammatory stimuli in the repair
phase, respectively. Activators of β2-adrenergic receptors, thyroid hormone and corticosteroids all induce PGC-1α gene expression in muscle fibers (57-59). Finally, in the vicinity of the neuromuscular junction, paracrine factors released from the motor neuron such as the neurotrophic factor neuregulin promote phosphorylation of the PGC-1α protein (60).

At the moment, it is unclear how the effects of these different signaling pathways on PGC-1α are integrated. However, it is evident that a temporal and spatial coordination exist. As mentioned, rapid stabilization of the PGC-1α protein by p38 MAPK phosphorylation precedes transcriptional induction of the gene (48), ultimately followed by ubiquitination and degradation of the protein (30). Furthermore, all the signaling pathways in the contracting muscle fiber that converge on PGC-1α are activated in specific cellular contexts. Accordingly, PGC-1α function is controlled by posttranslational modifications to react to these defined situations (Fig. 2). For example, only PGC-1α protein in subsynaptic nuclei will be modified by neurotrophic factor signaling (60). Thereby, induction of gene expression of post-synaptic neuromuscular junction genes in these nuclei is achieved, but not in other, non-subsynaptic nuclei where expression of these genes is not required. Activation of AMPK and SIRT1 reflects an energy crisis of the muscle fiber. The posttranslational modifications of PGC-1α by this protein kinase and deacetylase, respectively, primarily increase the expression of PGC-1α target genes that are involved in substrate oxidation and ATP synthesis (23, 51). In contrast, many of the other PGC-1α-controlled gene families are not regulated in this context and thereby, further breakdown of ATP is avoided.
PGC-1α regulates many of the adaptations of skeletal muscle to endurance exercise

Moderate ectopic expression of PGC-1α in skeletal muscle that mimics the increase in PGC-1α levels after chronic exercise induces pleiotropic changes in muscle fibers (39, 61). Most importantly, muscle-specific PGC-1α transgenic mice have muscle fibers with an increased fatigue resistance and exhibit an improved endurance exercise performance (39, 62). Whether PGC-1α indeed controls the complete exercise-regulated muscle cell plasticity remains to be shown. However, ectopic elevation of PGC-1α in muscle is sufficient to trigger all of the adaptations of skeletal muscle that are important for increased endurance (Fig. 3). Glucose uptake and glycogen synthesis are increased by PGC-1α in muscle whereas glycolysis is inhibited (61, 63). In endurance trained muscle, lipids are the preferred substrate for ATP synthesis. Accordingly, PGC-1α strongly induces mitochondrial biogenesis and function in muscle by promoting gene expression of nuclear-encoded mitochondrial genes, the mitochondrial transcription factor A that is required for replication of mitochondrial DNA (15, 39, 64-68) and of mitofusin 2, a protein involved in mitochondrial fission and fusion that regulates morphology and distribution of mitochondria (69). In particular, mitochondrial fatty acid β oxidation, the Krebs cycle and oxidative phosphorylation are augmented by PGC-1α (61, 70-72). Interestingly, PGC-1α boosts both total as well as uncoupled mitochondrial respiration, most likely by inducing the expression of the uncoupling protein 2 (UCP-2) in muscle (49, 64). Mitochondrial uncoupling might be part of the broader, PGC-1α-regulated detoxification system against reactive oxygen species (ROS) that are generated in contracting muscle fibers (49, 73). Many of the mitochondrial proteins that are
PGC-1α elevated by PGC-1α contain heme as the prosthetic group (74). To meet the increased demand for heme, PGC-1α induces the expression of the first and rate-limiting enzyme of heme biosynthesis, the housekeeping δ-aminolevulinate synthase 1 (ALAS-1) (66, 75). Adequate oxygen levels for the oxidative metabolism are provided by PGC-1α-controlled angiogenesis and increase in myoglobin levels (39, 55, 76). As a consequence of these adaptations, a steady supply of ATP is generated that can be used by myofibrillar proteins that are prototypical of oxidative muscle fibers, including troponin I slow and the myosin heavy chains I and IIa, which also are directly regulated by PGC-1α (39, 65). PGC-1α-driven gene expression of postsynaptic neuromuscular junction genes provides a feedback for the tonic motor neuron input in endurance exercise by remodeling the neuromuscular junction (60). In addition, inhibition of FoxO3 by PGC-1α reduces the expression of ubiquitine ligases that mediate protein degradation and fiber atrophy in inactive fibers (42). Moreover, muscle cell apoptosis and autophagy are reduced by PGC-1α (77). Finally, muscle performance differs with the time of the day, usually being higher in the afternoon than in the morning (78). Accordingly, PGC-1α expression in muscle exhibits circadian variations (79). However, circadian peak muscle performance can be entrained by repeated muscle activity because muscle contraction is one of the major time cues, or zeitgeber, for the peripheral circadian clock in skeletal muscle (78). PGC-1α coactivates the retinoic acid receptor-related orphan nuclear receptors α and γ (RORα and RORγ) and thereby regulates the expression of clock genes that control the circadian rhythm in muscle (79). Therefore, PGC-1α might link physical activity to muscle-cell autonomous clock function in exercise-mediated entrainment of the circadian rhythm.
Pathological consequences of PGC-1α dysregulation in muscle and therapeutic potential

Reduced levels of PGC-1α in skeletal muscle have been reported in different disease contexts, including type 2 diabetic patients, aging and pathologically inactive muscle (42, 80-82). In human patients, it is unclear whether the decrease in PGC-1α levels in muscle is cause or consequence of these pathologies. However, animal models with a muscle-specific knockout of one or both PGC-1α alleles offer important insights into the health consequences of reduced PGC-1α. In many ways, muscle-specific PGC-1α knockout mice are a phenotypical mirror image of muscle-specific PGC-1α transgenic animals. Mitochondrial biogenesis and function are reduced in PGC-1α muscle knockouts and the proportion of glycolytic relative to oxidative fibers is increased (65, 66). Moreover, these mice exhibit reduced voluntary physical activity as well as a dramatically impaired endurance capacity when exercised (65). Surprisingly, muscle fiber damage and serum creatine kinase are increased in muscle-specific PGC-1α knockout animals (65). This fiber damage is further exacerbated by physical activity indicating a role for PGC-1α in the maintenance of muscle fiber integrity (65). Furthermore, the expression of several pro-inflammatory genes is augmented in these animals (66). Interestingly, increased circulating levels of the pro-inflammatory cytokines interleukin 6 (IL-6) and, at least after exercise, of the tumor necrosis factor α (TNFα) are found in muscle-specific PGC-1α knockouts (66). Related to this change in circulating factors, a muscle-specific ablation of the PGC-1α gene results in systemic changes that affect distal organs, for example pancreatic islets that exhibit an abnormal morphology and impaired insulin secretion in vivo (66). Thus, like a sedentary lifestyle that is associated with an increased risk for many
chronic diseases and a reduced life expectancy, PGC-1α dysregulation in muscle elicits profound systemic effects and could be the molecular event that links inactivity, inflammation and chronic diseases (7, 8).

Inversely, therapeutic elevation of PGC-1α in muscle has the potential to ameliorate many different diseases (6). In animal models, a high efficacy of ectopically expressed PGC-1α in muscle has been shown in muscle wasting diseases. For example, fiber damage, serological markers of muscle wasting and exercise intolerance of a mouse model for Duchenne muscular dystrophy are significantly reduced by increased PGC-1α in muscle (60). Similarly, in a mouse line with ablation of the Cox10 gene that recapitulates the pathologies of a mitochondrial myopathy, life expectancy is increased by several months concomitant with an amelioration of ATP generation and exercise capacity when crossed with muscle-specific PGC-1α transgenic animals (83). In a severe model of fiber atrophy, mice with denervated hind legs, ectopic expression of PGC-1α almost completely prevents the normally occurring muscle fiber atrophy (42). Thus, even in the absence of a functional motor neuron, preventing the drop of PGC-1α that accompanies muscle inactivity is sufficient to retain an active muscle phenotype. Furthermore, muscle morphology disruption by drugs of the statin class can be prevented by PGC-1α in a zebrafish model (84). Finally, muscle-specific PGC-1α transgenic mice are resistant against age-associated muscle wasting, so-called sarcopenia (77). Importantly, regardless of the pathological context, increased PGC-1α expression rectifies muscle wasting, fiber damage and atrophy in these diseases with completely different etiologies. It is thus conceivable that the ability of PGC-1α to induce an endurance trained-like phenotype
enables a broad therapeutic spectrum of PGC-1α-based interventions against many muscle diseases (6, 7).

Finally, exercise reduces the risk for developing many chronic diseases by affecting almost every organ in the body (3). Similarly, modulation of PGC-1α in skeletal muscle has systemic consequences: loss-of-function is associated with increased inflammation (65, 66), gain-of-function in mice improves many parameters of aging and most importantly, significantly extends the life span of muscle-specific PGC-1α transgenic mice (77). Therefore, therapeutic modulation of PGC-1α in muscle might extend beyond isolated effects on this tissue and, like exercise, improve health, life quality and life expectancy in general.

Conclusion and outlook

In recent years, tremendous progress has been made in understanding the molecular mechanisms that regulate skeletal muscle cell plasticity in health and disease. Of particular interest is the discovery of the transcriptional coactivator PGC-1α as a key factor in the adaptation of muscle to endurance exercise. Despite these breakthroughs, many unknowns in this complex biological program still exist. For example, the coordination and integration of the numerous signaling pathways in a contracting muscle fiber that converge on PGC-1α remain enigmatic. Likewise, the cellular functions that are triggered by PGC-1α and that mediate the therapeutically beneficial effects of augmented levels of this coactivator on different muscle pathologies are mysterious. Furthermore, the distinct roles and functional overlap between the three members of the PGC-1 family, PGC-1α, PGC-1β and the PGC-1-related coactivator
PRC, have not been studied in muscle. Then, despite screening efforts, safe pharmacological interventions that chronically induce PGC-1α within a therapeutically desired window specifically in skeletal muscle are unknown (59, 85). Such drugs are essential to avoid detrimental effects of excessive PGC-1α in muscle or other tissues (6, 39, 86, 87) and of unwanted side effects of PGC-1α induction in distal organs, for example elevation of hepatic gluconeogenesis (6, 88). Finally, while ectopic expression of PGC-1α in muscle is sufficient to induce a trained phenotype (39), it is currently unclear whether PGC-1α is also necessary for training adaptation of muscle. Global PGC-1α knockout animals exhibit an almost normal training response to endurance exercise in young mice (89) but an impaired training-induced prevention of a decline in mitochondrial function in aging (90), despite or maybe because of their complex and confounding phenotype (67). However, the phenotype of these global PGC-1α knockout mice can be diametrically opposite to that of tissue-specific PGC-1α knockout mice. For example, hepatic gluconeogenesis is constitutively elevated in global PGC-1α knockout mice (67) whereas liver-specific PGC-1α knockout animals exhibit reduced fasting-induced glucose production in the liver (75), as expected from previous gain-of-function studies (91). In muscle, an unaltered fiber type distribution and activated AMPK were observed in global PGC-1α knockout animals (92) in contrast to the fiber type switch towards glycolytic fibers and normal AMPK activity in muscle-specific PGC-1α knockout mice (65, 66). Indeed, preliminary exercise studies with muscle-specific PGC-1α knockout animals indicate that this coactivator is indispensable for at least some of the endurance training adaptations, including muscle tissue vascularization and mitochondrial
biogenesis (76, 93). However, more comprehensive experiments are needed to further address this controversy.

The surprising finding that a coactivator, not a transcription factor, seems to be the nexus of muscle adaptation to exercise indicates that exciting years are yet to come for the study of muscle cell plasticity. Although many big gaps in our basic understanding of the molecular events up- and downstream of PGC-1α have to be filled, experiments with PGC-1α in different disease models are promising for the development of novel therapeutic avenues to treat muscular dystrophies, muscle wasting, and maybe even diseases that are associated with other organs. However, while the search for pharmaceutical entities for the modulation of PGC-1α in muscle goes on, exercise and a balanced diet remain the best interventions to ensure a long and healthy life.
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Declaration of interest statement

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Figure Legends

Fig. 1. Major exercise-induced signaling pathways converge on PGC-1α in skeletal muscle. The neuronal input, hormonal milieu, fiber contraction, mechanical stress and metabolic demand result in the activation of various signal transduction pathways. As a consequence, these signals lead to posttranslational modifications of the PGC-1α protein, alterations of PGC-1α gene expression, or both.

Fig. 2. Posttranslational modifications of the PGC-1α protein specify the transcriptional response. Many signal transduction pathways result in posttranslational modifications of PGC-1α. As a result of some of these modifications, the expression of specific PGC-1α target genes is modulated. For examples, neurotrophic signaling leads to transcriptional induction of neuromuscular junction genes by PGC-1α in nuclei close to the neuron-muscle interface. Phosphorylation of PGC-1α by the AMP-dependent protein kinase (AMPK) primarily affects PGC-1α target genes that are used to generate ATP and thereby rectify the energy crisis. In contrast, general elevation of PGC-1α in muscle results in the transcriptional regulation of a number of different gene families.

Fig. 3. PGC-1α regulates a pleiotropic response to exercise in skeletal muscle.

Known effects of PGC-1α in skeletal muscle and putative transcription factor binding partners involved in these functions are listed. Abbreviations: ERRα, estrogen-related receptor α; GABP/NRF2, GA-binding protein/nuclear respiratory factor 2; FoxO1/3, forkhead box O1/3; MEF2, myocyte enhancer factor 2; NRF1, nuclear respiratory
factor 1; OXPHOX, oxidative phosphorylation; PPARα, peroxisome proliferator-activated receptor α; RORα/γ, retinoic acid receptor-related orphan receptor α/γ; TFAM, mitochondrial transcription factor A.
Acetylcholine-induced calcium signaling
Paracrine factors

AMP

ATP

↑

↓

AMPK

NAD

NADH

↑

↓

SIRT1

Metabolic demand

Mechanical stress

Reactive oxygen species

p38 MAPK

Ca++

Endocrine signaling

β2-Adrenoreceptor activation
Thyroid hormone
Corticosteroids

Fiber contraction

PGC-1α

Hypoxia
Nitric oxide

Neuronal input

Ca++

Paracrine factors

PGC-1α

PGC-1α

AMP

ATP

↑

↓

AMPK

NAD'

NADH

↓

SIRT1
Erk, Jnk, others...

Neuromuscular junction genes

Metabolic genes

Myofibrillar genes

ROS detoxification

Vascularization

AMPK

PGC-1α

AMP↑

ATP↓

Metabolic genes for ATP synthesis

Metabolic genes

Myofibrillar genes

ROS detoxification

Vascularization

...