Review

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Intercellular: local and systemic actions of skeletal muscle PGC-1s

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Physical exercise promotes complex adaptations in skeletal muscle that benefit various aspects of human health. Many of these adaptations are coordinated at the gene expression level by the concerted action of transcriptional regulators. Peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1 (PGC-1) proteins play a prominent role in skeletal muscle transcriptional reprogramming induced by numerous stimuli. PGC-1s are master coactivators that orchestrate broad gene programs to modulate fuel supply and mitochondrial function, thus improving cellular energy metabolism. Recent studies unveiled novel biological functions for PGC-1s that extend well beyond skeletal muscle bioenergetics. Here we review recent advances in our understanding of PGC-1 actions in skeletal muscle, with special focus on their systemic effects.

The growing family of PGC-1 coactivators

The founding member of the PGC-1 family of transcription coactivators, PGC-1α, was first identified in brown adipose tissue (BAT) as a regulator of genes involved in cold-induced thermogenesis [1]. From PGC-1α protein and DNA sequence homology searches, PGC-1β and PGC-1-related coactivator (PRC) joined the family soon after [2,3]. PGC-1s do not interact directly with DNA and rely on docking transcription factors and coactivator complexes to exert their biological activities. The protein domains that mediate these interactions, and the resulting biological activities, are shared between most PGC-1s, including several of the variants more recently identified (see Figure I in Box 1) [4–7]. For this reason, almost all identified PGC-1s exert effects on cellular bioenergetics, including enhancement of fuel handling, nutrient supply and transport, and mitochondrial respiratory capacity and biogenesis [4–6,8]. With all of the recent additions to the PGC-1 family, this system of transcriptional coactivators highlights the diversity of biological actions that can be controlled by only three genes (Figure 1). For clarity, here we use PGC-1α1 to refer to the original PGC-1α protein and PGC-1α to refer to the α proteins collectively, and we specify whenever possible the PGC-1 variant that we are reviewing.

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The activation of PGC-1s is a complex and tissue-specific process that includes regulation of gene expression, protein stabilization, subcellular localization, and a specific code of post-translational modifications (Box 2). PGC-1s have been shown to be important mediators of cellular adaptation to diverse stimuli in several tissues including BAT [1], liver [9], brain [10], heart [11], and, most notably, skeletal muscle (the subject of this review). In addition to regulating important cellular processes, local activation of the various PGC-1s is communicated to other tissues in the body, thus eliciting an integrated systemic response. Here we review recent developments in our understanding of skeletal muscle PGC-1 actions and their systemic consequences.

PGC-1 coactivators and skeletal muscle mass maintenance

Loss of skeletal muscle mass is a debilitating consequence of many diseases, including cancer, diabetes, and neuromuscular disorders, and of aging. This muscle wasting stems from an imbalance between protein synthesis and degradation, favoring the latter. Over time, a constantly growing body of evidence has highlighted the potential of PGC-1 coactivators as therapeutic targets in various pathophysiological settings of muscle atrophy [7,12–16]. Skeletal muscle PGC-1α expression is reduced in rodent models of muscle wasting-inducing diseases including diabetes, cancer, and chronic renal failure [12]. Disuse-induced muscle atrophy is also accompanied by decreased skeletal muscle PGC-1α mRNA levels in humans [17,18]. PCG-1α expression is impaired in aged murine [19] and human [20] skeletal muscle, suggesting a possible role in age-related sarcopenia. Although the reasons for reduced PGC-1α expression in atrophic skeletal muscle remain poorly understood, the tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK)–Fn14 pathway was recently established as a key regulator of skeletal muscle mass in various catabolic states [15,21]. Activation of TWEAK–Fn14 signaling induces muscle wasting and reduces PGC-1α expression in denervated skeletal muscle. Ectopic PGC-1α1 expression in skeletal muscle prevents TWEAK-induced loss of skeletal muscle mass, suggesting that TWEAK promotes muscle wasting by repressing PGC-1α1 transcription [15]. The antiatrophic properties of PGC-1α1 are ubiquitous to various settings of muscle wasting. Skeletal muscle-specific PGC-1α1 transgenic mice are resistant to denervation- and disuse-induced skeletal muscle atrophy, defending not only their skeletal muscle mass but also mitochondrial function better than

Box 1. The 101 on PGC-1

The PGC-1 family has three founding members: PGC-1α, PGC-1β, and PRC [1–3]. These proteins have similar modular structures and partly overlapping functions. PGC-1α has several variants and isoforms with different biological activities that result from alternative promoter use and/or alternative splicing. These include PGC-1α-b, and c [4], NT-PGC-1α-a, b, and c [6,75,76], and PGC-1α2, 3, and 4 [7] (Figure I).

PGC-1 proteins possess no known intrinsic enzymatic activity and rely on interactions with DNA-bound transcription factors and other coactivator complexes to exert their biological activity. The most common biological activity of PGC-1 proteins, and the least tissue specific, is the regulation of cellular bioenergetics through the regulation of genes involved in mitochondrial biogenesis, oxidative metabolism, and lipid oxidation [1,4,6,24,76–78]. Specifically in skeletal muscle, PGC-1s induce a fiber switch toward a more oxidative fiber type [8].

PGC-1α is the most studied member of the family. It is highly regulated by several mechanisms including gene expression, protein stability, and post-translational modifications that modulate its biological activity. Individual inhibition of PGC-1α or PGC-1β has a mild effect on mitochondrial gene expression while simultaneous inhibition leads to a massive reduction in mitochondrial gene expression [79].

PRC is the least known member of the family, largely due to the embryonic lethal phenotype of PRC knockout mice [80]. So far PRC has been described as a mitochondrial biogenesis regulator [24] and has been implicated in the control of inflammatory programs [61,62]. Silencing PRC in proliferating cells leads to aberrant mitochondrial biogenesis and consequently inhibition of cell cycle progression [81].

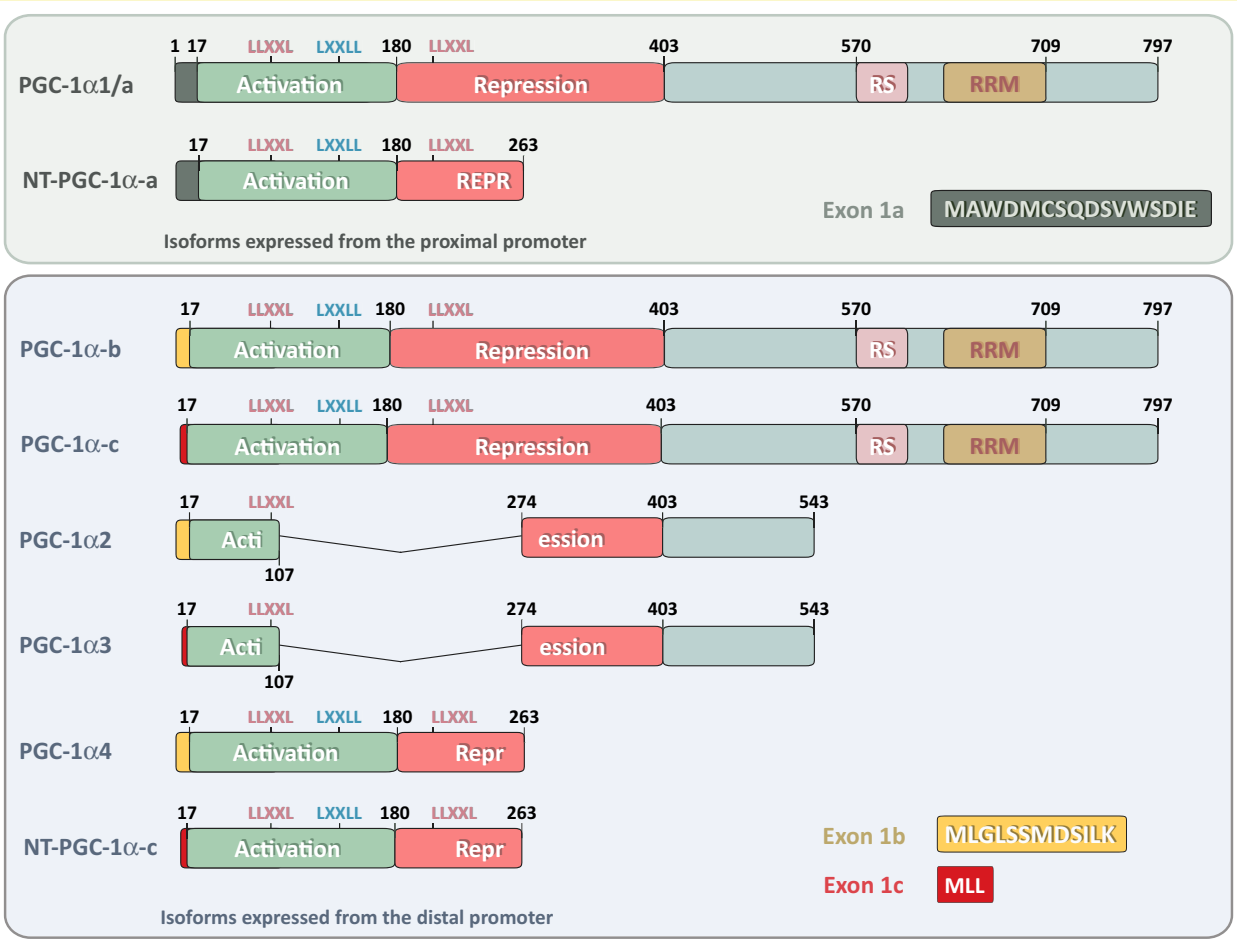

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Figure I. Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) isoforms. Schematic representation of protein domain conservation between the different PGC-1α variants. PGC-1α1 (also named PGC-1α-a) and NT-PGC-1α-a are expressed under the control of a proximal PGC-1α gene promoter (top panel). The remaining PGC-1α variants (bottom panel) are expressed from a distal promoter located approximately 14 kb upstream of the proximal transcription start site. LXXLL motifs mediate PGC-1α interaction with transcription factors and other coactivator complexes. The distinct N termini and respective amino acid sequences are depicted in green, yellow, and red. Amino acid numbers refer to mouse PGC-1α1. The RS (Arg/Ser-rich) and RRM (RNA recognition motif) domains are characteristic of proteins involved in RNA splicing. Despite the marked differences in structure, most known PGC-1α isoforms have partially overlapping activities linked to oxidative metabolism. The exceptions are PGC-1α4, which regulates muscle hypertrophy, and PGC-1α2 and α3, whose functions remain unknown.

wild type controls [12,16]. Likewise, skeletal muscle-specific PGC-1α1 expression restrains loss of muscle mass in aged mice [13]. The antiatrophic effects of PGC-1α1 in all of these conditions converge in a common molecular mechanism. TWEAK–Fn14 signaling, disuse, denervation, and aging markedly induce protein degradation via the ubiquitin–proteasome pathway. This is mainly through Forkhead box O3 (FoxO3)-dependent transcriptional activation of genes encoding the E3 ubiquitin ligases muscle RING-finger protein-1 (MuRF-1) and Atrogin-1. PGC-1α1 suppresses FoxO3 transcriptional activity, thus reducing MuRF-1/Atrogin-1 expression and consequently protein degradation [12,13,15,16]. In addition, PGC-1α1 expression limits autophagy activation in atrophic skeletal muscle [13,16].

Despite the antiatrophic effects of PGC-1α1, skeletal muscle-specific PGC-1α ablation does not render mice more susceptible to denervation-induced muscle atrophy