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Exercise, PGC-1 α and metabolic adaptation in skeletal muscle

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Abstract

Endurance exercise promotes skeletal muscle adaptation, and exercise-induced peroxisome proliferator-activated receptor γ co-activator-1 α (*Pgc-1 α*) gene expression may play a pivotal role in the adaptive processes. Recent applications of mouse genetic models and *in vivo* imaging in exercise studies started to delineate the signaling-transcription pathways that are involved in the regulation of the *Pgc-1 α* gene. These studies revealed the importance of p38 mitogen-activated protein kinase (MAPK)/activating transcription factor 2 (ATF2) and protein kinase D (PKD)/histone deacetylase 5 (HDAC5) signaling transcription axes in exercise-induced *Pgc-1 α* transcription and metabolic adaptation in skeletal muscle. The signaling/transcription network that is responsible for exercise-induced skeletal muscle adaption remains to be fully elucidated.

Keywords

exercise; skeletal muscle; fiber type transformation; angiogenesis; mitochondrial biogenesis; signal transduction; transcription; p38 mitogen-activated protein kinase; peroxisome proliferator-activated receptor γ co-activator-1 α

Mammalian skeletal muscles are the source of power for locomotion and other activities essential for survival. Loss of contractile function is the major cause of falling, morbidity and mortality, especially in elderly populations (Roubenoff, 2000; Janssen *et al.*, 2002). More importantly, skeletal muscles participate in metabolism, disruption of which leads to and/or exacerbates many chronic diseases, such as coronary heart diseases, obesity and type 2 diabetes (Booth *et al.*, 2002; Saltin & Pilegaard, 2002). Regular exercise has significant positive impacts on most of these diseases with no or little side effects. Improved understanding of the molecular mechanisms of skeletal muscle adaptation will not only provides information to guide correct use of regular exercise, but also facilitate new drug discovery, to combat the diseases.

Endurance exercise induces skeletal adaptation, which includes transformation of type IIb to IIa myofibers (referred to fiber type transformation) (Fitzsimons *et al.*, 1990), and increased mitochondrial (Hoppeler *et al.*, 1973; Wallberg-Henriksson *et al.*, 1982) and capillary densities (referred to mitochondrial biogenesis and angiogenesis, respectively) (Svedenhag *et al.*, 1984), that are the fundamental basis for health benefits of regular exercise. It is believed that an orchestrated signal transduction-transcription coupling from neuromuscular activity to the gene regulatory machinery plays an essential role in the adaptation processes (Booth & Baldwin, 1996; Williams & Neufer, 1996; Sakamoto & Goodyear, 2002). Adding to this complexity is a temporally cumulative induction of gene expression that is required for the ultimate phenotypic change (Williams & Neufer, 1996).

PGC-1 α , a versatile transcription co-activator (Puigserver *et al.*, 1998), is involved in important cellular processes, such as adaptive thermogenesis, fatty acid oxidation, gluconeogenesis and mitochondrial biogenesis (Knutti & Kralli, 2001). Numerous findings support the view that PGC-1 α mediates and coordinates gene regulation during skeletal muscle adaptation. First, *Pgc-1 α* mRNA and protein are highly expressed in slow, oxidative fibers compared to fast, glycolytic fibers (Lin *et al.*, 2002; Wu *et al.*, 2002), consistent with the function of a gene involved in fiber type specialization. Secondly, there is a tight correlation of muscle contractile activity with increased *Pgc-1 α* gene expression. Endurance exercise induces *Pgc-1 α* mRNA and protein expression in rats and humans (Goto *et al.*, 2000; Baar *et al.*, 2002; Terada *et al.*, 2002; Irrcher *et al.*, 2003; Pilegaard *et al.*, 2003). Finally, *Pgc-1 α* gene overexpression is sufficient to enhance mitochondrial biogenesis and promote fast-to-slow fiber transformation in cultured myoblasts (Wu *et al.*, 1999) and in transgenic mice (Lin *et al.*, 2002), which leads to improved exercise performance (Calvo *et al.*, 2008).

Indeed, a global disruption of the *Pgc-1 α* gene in mice resulted in reduction of oxidative phenotype in skeletal muscle (Arany *et al.*, 2005; Leone *et al.*, 2005; Handschin *et al.*, 2007). Surprisingly, Leick *et al.* has recently shown in a global gene disruption mouse model that lack of the *Pgc-1 α* gene does not prevent exercise-induced muscle adaptive responses despite of reduced basal level expression of the genes that encode mitochondrial proteins (Leick *et al.*, 2008). They interpreted the findings as if PGC-1 α is not mandatory for exercise-induced adaptive gene expression in skeletal muscle. However, results from our laboratory using a skeletal muscle-specific gene targeting mouse model suggest that *Pgc-1 α* gene expression is required for exercise-induced mitochondrial biogenesis and angiogenesis, but not required for fiber type transformation (unpublished results). These findings genetically segregate the metabolic adaptations from contractile adaptation in skeletal muscle. The apparent differences between the two genetic models may suggest the complexity of the issue and justify a more vigorous delineation of the muscle adaptation processes.

Multiple signaling transduction pathways are activated in skeletal muscle during exercise, among which calcium signaling decodes neuromuscular activity to gene transcription for the adaptive processes. Calcineurin, a Ca²⁺/calmodulin-dependent phosphatase, has been shown to play a functional role in fiber transformation in both gain-of- and loss-of-function animal models (Chin *et al.*, 1998; Naya *et al.*, 2000; Parsons *et al.*, 2003); however, a direct involvement of calcineurin activity in exercise-induced *Pgc-1 α* gene regulation and enhanced mitochondrial biogenesis in skeletal muscle has not been established as pharmacological inhibition of calcineurin failed to inhibit exercise-induced *Pgc-1 α* gene expression and enhanced mitochondrial biogenesis (Garcia-Roves *et al.*, 2006). Some studies have suggested that Ca²⁺/calmodulin-dependent protein kinase 4 (CaMK4) plays an important role in skeletal muscle adaptation (Wu *et al.*, 2002; Zong *et al.*, 2002) with a possible link to the transcriptional control of the *Pgc-1 α* gene (Handschin *et al.*, 2003), whereas more recent studies have ruled out CaMK4 as the endogenous regulator of the *Pgc-1 α* gene since genetic disruption of the gene did not prevent exercise-induced skeletal muscle adaptation (Akimoto *et al.*, 2004a). It remain to be determined if other Ca²⁺/calmodulin-dependent protein kinase pathways play a role in the adaptive processes in skeletal muscle.

Endurance exercise training is associated with chronic metabolic stress and energy deprivation. AMP activated protein kinase (AMPK), a metabolic master switch in skeletal muscle, can be activated in the muscles of exercised animals and humans (Winder & Hardie, 1996; Fujii *et al.*, 2000; Wojtaszewski *et al.*, 2000). Pharmacological activation of AMPK increases *Pgc-1 α* gene expression and mitochondrial biogenesis in skeletal muscle (Winder

& Hardie, 1996; Zong *et al.*, 2002; Suwa *et al.*, 2006), and forced expression of a dominant-negative form of AMPK in skeletal muscle can block these adaptive processes (Zong *et al.*, 2002). However, genetic disruption of functional AMPK isoforms failed to block exercise-induced *Pgc-1 α* gene expression and enhanced mitochondrial biogenesis in skeletal muscle (Jorgensen *et al.*, 2005; Jorgensen *et al.*, 2006). The molecular link between AMPK activity and *Pgc-1 α* -mediated metabolic adaptation in skeletal muscle remain to be fully investigated.

The mitogen-activated protein kinase (MAPK) signaling molecules have also long been speculated to regulate gene transcription in skeletal muscle in response to various types of contractile activities. All three families of MAPK pathways, extracellular signal-regulated kinase (ERK), c-Jun NH(2)-terminal kinases (JNK) and p38, can be activated by increased contractile activity, and the p38 MAPK pathway appears to play a direct role in *Pgc-1 α* gene regulation (Akimoto *et al.*, 2005; Wright *et al.*, 2007). Interestingly, targeted disruption of the canonical upstream p38 MAPK kinases, MAPK kinase 3 (MKK3) and MKK6 (unpublished results). Therefore, the upstream activator and the p38 isoform(s) that are required for exercise training-induced *Pgc-1 α* gene transcription and enhanced mitochondrial biogenesis remain to be identified.

Finally, to investigate the transcriptional control of the *Pgc-1 α* gene in skeletal muscle *in vivo*, our laboratory has established a bioluminescence-based optical imaging system to analyze promoter activity in live animals. This unique *in vivo* imaging system in combination with electric pulse-mediated gene transfer allowed us to measure the *Pgc-1 α* gene activity in skeletal muscle in live mice. We have shown that contractile activity-induced *Pgc-1 α* gene transcription in skeletal muscle depends on both the myocyte enhancer factor 2 (MEF2) binding sites and the cyclic-AMP responsive element (CRE) consensus sequence on the *Pgc-1 α* promoter (Akimoto *et al.*, 2004b). Expanding this unique system by *in vivo* co-transfection of *Pgc-1 α* -luciferase reporter gene with genes encoding dominant negative forms of potential upstream regulatory factors, we have confirmed the essential role of activating transcription factor 2 (ATF2, binding to the CRE site) and histone deacetylase 5 (HDAC5, repressing MEF2 function), but not HDAC4, to contractile activity-induced *Pgc-1 α* transcription (Akimoto *et al.*, 2008). These findings provide *in vivo* information about *Pgc-1 α* transcriptional regulation in response to increased contractile activity in skeletal muscle. Future studies should define the causal relationships of the upstream signaling pathways to the *Pgc-1 α* gene that are responsible for neuromuscular activity-mediated skeletal muscle adaptation.

In summary, new finding support that *Pgc-1 α* gene expression plays a pivotal role in metabolic, but not contractile, adaptation in skeletal muscle adaptation. p38 MAPK/ATF2 and kinase D (PKD)/HDAC5/MEF2 signaling transcription axes mediate exercise-induced *Pgc-1 α* transcription and metabolic adaptation in skeletal muscle. The signaling/transcription network responsible for exercise-induced skeletal muscle adaptation remains to be fully elucidated.

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