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New insights in the regulation of skeletal muscle PGC-1α by exercise and metabolic diseases

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Abstract

Skeletal muscle energy metabolism is severely impaired in insulin resistant and type 2 diabetic patients. In particular, deregulated transcription of oxidative metabolism genes has been linked to the development of non-communicable metabolic diseases. The peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) is a key molecule in the regulation of oxidative metabolism in different tissues, including skeletal muscle. In this tissue, physical exercise is one of the most dominant physiological stimuli to induce PGC-1α. In addition, exercise training efficiently prevents the development of metabolic diseases. Hence, better knowledge about the regulation of PGC-1α by exercise would significantly help to design effective treatments for these diseases.

Introduction

Physical inactivity is nowadays considered as a pandemic, representing an important etiological factor in the development of non-communicable diseases and a major cause of premature death worldwide [1,2]. The detrimental effects of a sedentary life style are largely associated with the impairment of skeletal muscle metabolic fitness, which is mainly characterized by a lower oxidative metabolism [3,4]. Even though causality of mitochondrial dysfunction in the development of insulin resistance remains controversial, insulin-resistant and type 2 diabetic patients often present an impairment of skeletal muscle oxidative metabolism [5]. Is important to note that a pathological decrease in skeletal muscle insulin sensitivity is sufficient to promote the development of the metabolic syndrome [6,7]. Therefore, the metabolic remodeling of skeletal muscle cells plays a central role in the pathogenesis of metabolic diseases like type 2 diabetes.

The development of obesity and type 2 diabetes largely depends on different environmental factors, including the balance between physical activity and inactivity [8-10]. At the transcriptional level, the peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) plays a key role in exercise-linked mitochondrial remodeling [11,12]. This coactivator regulates a specific transcriptional network, in which the estrogen related receptors (ERRs), nuclear respiratory factors (NRFs) and PPARδ are the principal transcription factors involved in the enhancement of oxidative metabolism [11]. Consistent with its metabolic function, impairment of PGC-1α expression and activity have been identified as potential pathogenic factors in the development of insulin resistance and type 2 diabetes [5,13,14]. The expression of PGC-1α is sensitive to muscle contraction with high levels in trained subjects and a strong down-regulation in muscle from people with spinal cord injury [15]. Here, we review the specific mechanism by which different types of physical exercise regulate skeletal muscle PGC-1α and how this process is affected by non-communicable metabolic diseases.

Regulation of PGC-1α expression and activity by skeletal muscle contraction

Muscle contraction modulates different signal pathways that trigger the activation or repression of a very specific subset of genes, such as the slow-oxidative or fast-glycolytic gene program observed in type 1 and 2 skeletal muscle fibers, respectively [16]. PGC-1α specifically controls the expression of the slow-oxidative gene program, while the expression and activity of this coactivator is regulated by several protein kinases/phosphatases, transcription factors and coregulators in response to muscle contraction [12].

Transcriptional regulation of PGC-1α in skeletal muscle

The human and mouse PGC-1α promoters contain a number of binding sites for different transcription factors, including PPARs, myocyte enhancer factor 2 (MEF2), activating transcription factor 2 (ATF2), forkhead box O1 (FOXO1), p53 and others [17-19]. Primarily however, muscle contraction mediates the activation of this promoter via the MEF2 binding sites and the cAMP response element (CRE) [20]. The transcriptional activity of MEF2 can be increased by PGC-1α or repressed by the histone deacetylase 5 (HDAC5) [18,21]. Muscle contraction can decrease the inhibitory effect of HDAC5 through its phosphorylation by protein kinase D (PKD), 5'AMP-activated protein kinase (AMPK) and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [22-24], representing an essential process in the activation of the PGC-1α promoter [22]. In contrast, PGC-1α is strongly induced by exercise (see below) and its positive effect on MEF2 has been suggested to activate a positive feedback loop, thus increasing its own transcription [18]. CRE binding protein (CREB) and ATF2 are the main transcription factors recruited to the CRE site in the PGC-1α promoter in response to muscle contraction [22]. Interestingly, both MEF2 and ATF2 are activated by p38 mitogen-activated protein kinase (MAPK) [25,26], indicating that this protein kinase is intimately involved in the regulation of PGC-1α transcription. Consistently, Pogozelski et al. [27] demonstrated that muscle-specific deletion of p38γ MAPK completely blocked the up-regulation of PGC-1α induced by exercise. Accordingly, activation of p38 MAPK by reactive oxygen species (ROS) in response to exercise training is indeed an important mechanism regulating PGC-1α expression in skeletal muscle [28,29]. Similarly, PKD activation is required for the activation of the PGC-1α promoter since the expression of a catalytic inactive form of PKD can fully prevent the effects of muscle contraction on PGC-1α expression [22]. In contrast to p38 MAPK and PKD, the relevance of AMPK and CaMKII in the regulation of PGC-1α expression by exercise has been more difficult to elucidate. For instance, muscle-specific deletion of the β1 and β2 subunits of AMPK significantly decreases the expression and activity of different mitochondrial enzymes during basal conditions, though it paradoxically results in higher levels of PGC-1α mRNA [30] while, to our knowledge, no studies exist that investigated the requirement for CaMKII for exercise-mediated regulation of PGC-1α expression. Interestingly, endurance exercise induces the activation p53 [31], suggesting that it could promote the activation of the PGC-1α promoter. Moreover, a single bout of low-intensity endurance exercise results in higher mRNA levels of the transcription factors PPARδ and FOXO1 [32], both of which have been described to bind to the PGC-1α promoter [17,19]. In particular, PPARδ in complex with RXRα can bind the PPAR response elements (PPRE) of the PGC-1α promoter and increase its transcriptional activity [19]. Considering that PGC-1α co-activates PPARδ [33], this could represent another positive feedback loop in the transcriptional regulation of this coactivator, but is currently unknown whether PPARδ plays a significant role during endurance exercise.

More recently, novel mechanisms involving epigenetic modifications of the DNA and post-transcriptional regulation by microRNAs have been proposed to modulate PGC-1α transcription in response to exercise and pathological conditions. Interestingly, Barrès et al. [34] demonstrated that the DNA methyltransferase 3B (DNMT3B) could repress PGC-1α expression through non-CpG dinucleotide methylation of its promoter in human skeletal muscle. Importantly, the PGC-1α promoter was found to be hyper-methylated in skeletal muscle from impaired glucose-tolerant and type 2 diabetic patients, showing a negative correlation with PGC-1α mRNA levels and a decreased expression of several mitochondrial enzymes [34]. Inversely, acute exercise in human skeletal muscle and ex-vivo electrical stimulation of mouse skeletal muscle induce a significant decrease in the methylation levels of the PGC-1α promoter, which precede the increase in its transcript levels [35].

Finally, physical activity and inactivity induce the down- and up-regulation of the microRNA miR-696, respectively, which negatively regulates PGC-1α expression in skeletal muscle [36]. Thus, overall, the PGC-1α promoter contains a high number of different transcription factor binding sites that control PGC-1α expression while the activation of additional signal pathways represent a potential mechanism by which PGC-1α transcript levels are further fine-tuned (Fig. 1A).

Post-translational regulation of PGC-1α in skeletal muscle

In skeletal muscle, PGC-1α is a direct target of both AMPK and p38 MAPK, which both phosphorylate it at distinct sites and hereby induce its activation [37,38]. Interestingly, it has been suggested that p38 MAPK-mediated phosphorylation and thereby stabilization of the PGC-1α protein precede transcriptional induction of PGC-1α gene expression in contracting muscle [39]. The balance between the acetylation and deacetylation of PGC-1α is controlled by the deacetylase sirtuin 1 (SIRT1) and the acetyl transferase general control of amino-acid synthesis 5 (GCN5), respectively [40,41]. SIRT1-mediated deacetylation activates PGC-1α whereas GCN5 activity reverses this effect [40,41]. Interestingly, activation of AMPK is a prerequisite for SIRT1-controlled deacetylation of PGC-1α in response to exercise [42]. Recently however, the relevance of SIRT1 for the modulation of muscle PGC-1α acetylation by exercise has been questioned since the skeletal muscle-specific genetic inactivation of SIRT1 did not affect deacetylation of PGC-1α and subsequent induction of its target genes in mouse skeletal muscle after acute and chronic exercise [43]. In this study, reduced interaction with GCN5 has been proposed as the main mechanism controlling the acetylation status of PGC-1α [43]. Interestingly, AMPKγ3 knockout mice exhibit impaired decrease of PGC-1α acetylation levels induced by exercise [42], suggesting a potential role of AMPK in the regulation of PGC-1α acetylation by GCN5 rather than its deacetylation by SIRT1.

Effects of low- vs. high-intensity exercise on PGC-1α

Endurance exercise

Physical activity represents one of the strongest physiological stimuli to promote skeletal muscle oxidative metabolism and stimulate PGC-1α expression. Initially, studies performed in rat skeletal muscle showed that 3 to 7 days of low-intensity swimming training could efficiently induce a ~2 fold increase in PGC-1α mRNA and protein content [44,45]. Acutely, the completion of a total of 6 hours of low-intensity swimming or running resulted in a significant 2 to 7 fold increase in PGC-1α transcript and protein levels [45-47]. Similar to rodents, a single bout of endurance exercise also results in a 4 to 12 fold increase of PGC-1α mRNA in human skeletal muscle, an effect that is observed immediately after exercise up to 3 to 8 hours. Later, PGC-1α expression returns to basal levels within 4 to 24 hours post-exercise [31,32,48-51]. The magnitude by which acute endurance exercise modulate human skeletal muscle PGC-1α protein content is not well known, with some studies showing no increase 3 hours post-exercise [31,49] and others reporting a slight increase after endurance exercise to exhaustion [51], indicating that the intensity at which exercise is performed could be an important factor. However, in humans, endurance training over a period of 6 weeks induces a significant ~2 fold increase of both mRNA and protein levels of muscle PGC-1α [52]. Interestingly, the activation of an alternative promoter of PGC-1α leads to the expression of different splice variant of this coactivator (PGC-1α-a, PGC-1α-b and PGC-1α-c) in skeletal muscle [53,54]. Of these three transcript variants, PGC-1α-b exhibits a higher sensitivity to exercise and was indeed strongly up-regulated by endurance exercise in mouse skeletal muscle [53,54].

Furthermore, there is some evidence implying cytoplasmic-nuclear translocation to contribute to the regulation of PGC-1α, however this concept remains controversial. Interestingly, a splice variant called novel truncated PGC-1α (NT-PGC-1α), which lacks key domains in nuclear localization, is thought to shuttle between cytoplasm and the nucleus [55]. Other studies imply that in rat skeletal muscle, low-intensity swimming significantly increased the nuclear abundance of "normal" PGC-1α immediately after exercise [39]. In human skeletal muscle, a similar effect was reported, in which a ~54% increase in nuclear PGC-1α has been detected immediately after a single bout of endurance exercise [56]. In these studies, PGC-1α nuclear translocation after endurance exercise correlates with an increase in the phosphorylation levels p38 MAPK and its substrate ATF2 [39,56]. Interestingly, whereas McGee & Hargreaves [57] did not detect PGC-1α nuclear translocation after a single bout of endurance exercise, they found a decrease and increase in the interaction between HDAC5 and PGC-1α with MEF2, respectively. Moreover, the exchange between HDAC5 and PGC-1α was also associated with an increase in p38 MAPK and MEF2 phosphorylation [57]. Furthermore, endurance exercise has been recently described to also increase PGC-1α levels in the mitochondrial matrix immediately after and 3 hours post-exercise [58]. Specifically, PGC-1α was detected in complex with the mitochondrial transcription factor A (TFAM) at the D-loop region of the mitochondrial DNA in the mitochondrial matrix and this interaction was further enhanced by endurance exercise [58]. Therefore, endurance exercise activates a broad spectrum of proteins involved in the expression, activation and maybe also the cellular localization of PGC-1α.

Low-volume high-intensity interval training

During the last years, low-volume, high-intensity interval training (HIT) has been proposed as a time-efficient alternative to traditional endurance training to improve whole body and skeletal muscle oxidative metabolism [59]. For example, 6 weeks of low-volume HIT result in a higher VO_{2peak}, lower respiratory exchange ratio during exercise and increased activity of different mitochondrial enzymes (e.g. citrate synthase) in skeletal muscle [60]. Interestingly, the coactivator PGC-1α has also been considered as a potential mediator of the adaptations of energy metabolism to this kind of exercise training [59]. Accordingly, similar to low-intensity swimming, a single bout of high-intensity swimming in rats also induces a robust increase in skeletal muscle PGC-1α protein levels [61]. Importantly, in humans, a single bout of low-volume HIT has been showed to promote a 2 to 10 fold increase in skeletal muscle PGC-1α mRNA 3 to 4 hours post-exercise [31,62-64]. It seems that the transient increase in PGC-1α mRNA after HIT precedes the subsequent increase of its protein levels 24 hours post-exercise [63,64]. In fact, 3 hours after acute HIT, no increase in PGC-1α protein is detected [31,62,64], further suggesting that mRNA levels need to be elevated before an increase at the protein level can be observed. In the long term, cycling low-volume HIT over a period of 2 to 6 weeks can induce a significant ~2 fold increase in total and nuclear muscle PGC-1α protein levels in recreationally active and sedentary subjects, thus to a similar extent as classical endurance training [60,65,66]. Even though HIT and endurance exercise result in similar effects on PGC-1α expression [60], the fact that the training volume during HIT is substantially lower strongly suggests that PGC-1α is highly sensitive to exercise intensity. Recent published data from rodents and humans studies further support this idea showing that PGC-1α mRNA is increased to a higher extent by high-intensity compared to low-intensity exercise [53,67,68].

Both chronic and acute low-volume HIT have been claimed to stimulate the translocation of PGC-1α from the cytosol to the nucleus, but different to endurance exercise, the acute effect is only detected

3 hours post-exercise in HIT [64,66]. The translocation of PGC-1α induced by HIT is associated with higher p38 MAPK phosphorylation levels [64]. Interestingly, besides p38 MAPK, acute HIT also increases AMPK, CaMKII and p53 phosphorylation in skeletal muscle [31,62,64,69]. Therefore, acute and chronic HIT activate the same signal pathways as endurance exercise (Fig. 1A), but it has been proposed that exercise at high intensity results in stronger effects overall. In fact, Egan et al. [68] compared cycling exercise trials at 40 and 80% of the VO_{2peak} and showed that only high-intensity exercise induced a significant increase in AMPK, CaMKII, ATF2 and HDAC5 phosphorylation in skeletal muscle. Moreover, though both low- and high-intensity cycling increased PGC-1α mRNA, the effects of cycling at 80% of the VO_{2peak} were significantly higher than that at 40% of the VO_{2peak} [68]. Interestingly, HIT elevates SIRT1 expression in skeletal muscle [66], suggesting that this kind of training modulates PGC-1α acetylation. Also similar to endurance training, HIT upregulates PPARδ in skeletal muscle [63]. Finally, high-intensity exercise is more efficient in decreasing the methylation levels of the PGC-1α promoter [35]. These data suggest that the activation of additional signal pathways in response to high-intensity compared to low-intensity exercise would promote a higher increase of PGC-1α activity and expression, representing thus a more efficient strategy in terms of time and potency compared to traditional endurance training.

Impairment of exercise effects on PGC-1α in metabolic diseases

Low expression levels of skeletal muscle PGC-1α are characteristic of physically inactive people and type 2 diabetes patients [3,14,15,70]. Accordingly, modulation of the PGC-1α axis in skeletal muscle in metabolic diseases has been proposed to be impaired at different levels. De Filippis et al. [71] demonstrated that insulin resistant skeletal muscle is also "exercise resistant", since insulin resistant people exhibit diminished and delayed increase of PGC-1α expression in skeletal muscle after acute high-intensity exercise. However, endurance exercise at 40% or 70% of the VO_{2max} results in a normal increase in PGC-1α mRNA in human skeletal muscle from obese and type 2 diabetes patients [72]. Interestingly, only 7 days of bed rest completely blunt the induction of PGC-1α by acute exercise in human skeletal muscle [73]. In animals, an attenuated or abolished up-regulation of PGC-1α mRNA and its target genes after chronic exercise has been reported in skeletal muscle from both mouse and rat models suffering from the metabolic syndrome [74,75]. The mechanism behind this response has been linked to impaired activation of AMPK by exercise, for example in acutely exercised mice fed a high fat diet [76]. In humans however, diminished induction of PGC-1α by high-intensity exercise was associated with normal activation of AMPK in insulin resistant subjects [71], while normal induction of PGC-1α by low-intensity exercise was associated with impaired activation of AMPK in obese and type 2 diabetes patients [72]. Interestingly though, skeletal muscle from *ob*/*ob* mice shows no increase in AMPK phosphorylation, SIRT1 protein and PGC-1α mRNA levels after chronic exercise [75]. Furthermore, the decrease of PGC-1α acetylation induced by endurance training was impaired in *ob*/*ob* mice skeletal muscle [75]. In *ob*/*ob* mice skeletal muscle, ex vivo muscle contraction induces a slightly attenuated increase of p38 MAPK phosphorylation even though the effect was not significant compared to that observed in wild type animals [77]. However, despite of the lower levels of PGC-1α expression in type 2 diabetes patients [14], p38 MAPK phosphorylation seems to be elevated [78]. Altogether it appears that the effects of physical exercise on PGC-1α are negatively affected by metabolic diseases, affecting the expression and activation of this coactivator (Fig. 1A).

Conclusions

Low- and high-intensity exercise positively modulates PGC-1α activity and expression through different signal pathways, in which p38 MAPK seems to play a central role (Fig. 1A). This response to exercise seems to be impaired by physical inactivity and metabolic diseases (Fig. 1A). Upon activation, PGC-1α not only enhance oxidative metabolism, but it also prevent muscle atrophy and improves ROS detoxification among other effects (Fig. 1B). Hence, the modulation of this coactivator in muscle cells is an attractive approach for the treatment of metabolic diseases [79], but it should be noted that as part of exercise-induced muscle plasticity, PGC-1α also enhances anabolic process such as de novo lipogenesis [80] (Fig. 1B). Accordingly, elevation of muscle PGC-1α in sedentary, high fat-fed mice accelerates the development of insulin resistance [81]. Importantly however, when combined with bona fide exercise, PGC-1α over-expression seems to be an efficient strategy to improve metabolic fitness under pathological conditions [82,83]. Importantly, HIT appears to be a more efficient approach to induce PGC-1α in skeletal muscle and improve whole body energy metabolism [59]. In fact, low-volume HIT efficiently reduces blood glucose levels in type 2 diabetic patients [84], further supporting its therapeutic effect. Therefore, the design of new therapies aiming to potentiate the effects of exercise on PGC-1α represents a potential path to combat non-communicable metabolic diseases.

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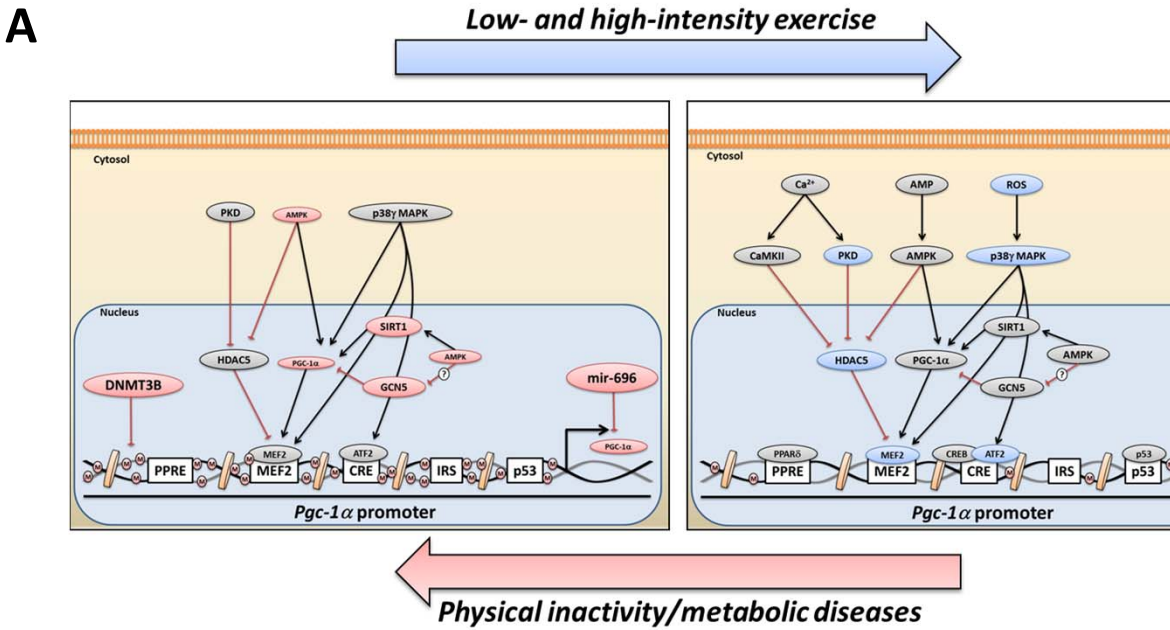
Figure Legends

Figure 1. Schematic representation of the signal pathways regulating PGC-1α expression and activity in skeletal muscle cells. (A) Under pathological conditions such as a sedentary life style and obesity, PGC-1α expression is impaired due to aberrant activity and expression of negative and positive regulators (red circles) of this coactivator. In contrast, skeletal muscle contraction during low- and high-intensity exercise lead to the activation and inhibition of a subset of essential (blue circles) and accessory (grey circles) molecules involved in the control of the PGC-1α promoter activity, in addition to its post-translational modifications and thus protein activity. Consequently, physical activity results in the activation and up-regulation of this coactivator, thereby promoting an improvement of skeletal muscle metabolic fitness. Black and red arrows show activation and inhibition, respectively. (B) PGC-1α drives the activation of different putative transcription factors (TF), regulating thus different aspects of muscle physiology. In this figure, some of the most relevant effects of PGC-1α on skeletal muscle are shown (for more details, see ref. [85]). Abbreviations: ERRα, estrogen-related receptor α; NRF1/2, nuclear respiratory factor 1 and 2; FoxO1/3, forkhead box O1/3; TFAM, mitochondrial transcription factor A; MEF2, myocyte enhancer factor 2; PPAR, peroxisome proliferator-activated receptor; RORα/γ, retinoic acid receptor-related orphan receptor α/γ; LXRα, liver X receptor α; Nuclear factor-kappaB, NFκB; RE, TF response elements.


A
Low- and high-intensity exercise
Cytosol
PKD
AMPK
p38γ MAPK
Nucleus
SIRT1
HDAC5
PGC-1α
AMPK
DNMT3B
GCN5
mir-696
MEF2
ATF2
PPRE
MEF2
CRE
IRS
p53
PGC-1α
Pgc-1α promoter
Cytosol
Ca2+
AMP
ROS
CaMKII
PKD
AMPK
p38γ MAPK
Nucleus
SIRT1
HDAC5
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AMPK
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CRE
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p53
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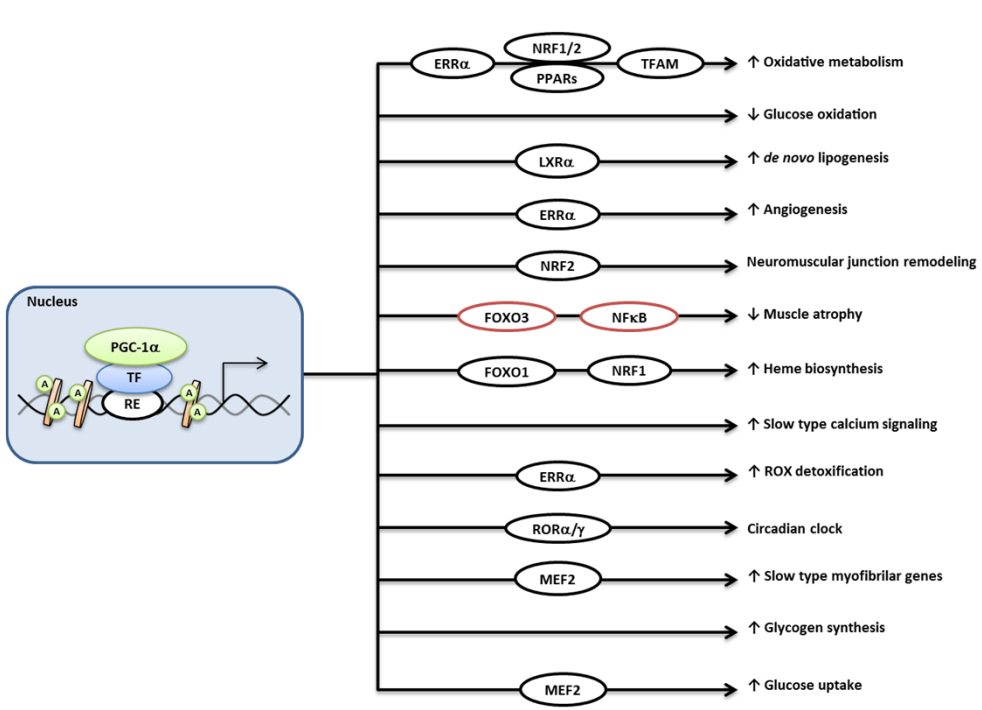
PGC-1α
Pgc-1α promoter
Physical inactivity/metabolic diseases


B
Nucleus
PGC-1α
TF
RE
NRF1/2
ERRα
TFAM
PPARs
↑ Oxidative metabolism
↓ Glucose oxidation
LXRα
↑ de novo lipogenesis
ERRα
↑ Angiogenesis
NRF2
Neuromuscular junction remodeling
FOXO3
NFκB
↓ Muscle atrophy
FOXO1
NRF1
↑ Heme biosynthesis
↑ Slow type calcium signaling
ERRα
↑ ROX detoxification
RORα/γ
Circadian clock
MEF2
↑ Slow type myofibrilar genes
↑ Glycogen synthesis
MEF2
↑ Glucose uptake