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MINI REVIEW

Multi-regulatory network of ROS: the interconnection of ROS, PGC-1 alpha, and AMPK-SIRT1 during exercise

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Abstract Transcriptional factors are easily susceptible to any stimuli, including exercise. Exercise can significantly influence PGC-1 α and AMPK-SIRT1 pathway, as it is involved in the regulation of energy metabolism and mitochondrial biogenesis. Exercise is a major energy deprivation process by which many of transcription factors get tuned positively. However, how transcription factors help to boost the antioxidant defense system at cellular level is elusive. It is well known that physical exercise can induce reactive oxygen species, but how these reactive oxygen species can help to regulate multiple transcription factors during exercise is an important area to be discussed yet. This review mainly focuses on interconnecting role of PGC-1 α and AMPK-SIRT1 pathway during exercise and how these proteins are getting tuned by reactive oxygen species in exercise condition.

Keywords ROS · AMPK · Sirt1 · PGC-1 α · Muscle · Exercise

Abbreviations

AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate protein kinase
ATP	Adenosine triphosphate
CAT	Catalase
FoxO1	Forkhead box protein O1
H_2O_2	Hydrogen peroxide
iNOS	Inducible nitric oxide synthase
LKB1	Liver kinase B1
MEF	Myocyte enhancer factor
NRF-1	Nuclear respiratory factor 1
NRF-2	Nuclear respiratory factor 2
NAD^+	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide dehydrogenase
Nampt	Nicotinamide phosphoribosyl transferase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B
NoXs	NADPH oxidases
OH	Hydroxyl radicals
PGC-1 α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
ROS/RNS	Reactive oxygen species/reactive nitrogen species
SIRT1	Sirtuin
SOD	Superoxide dismutase
TNF-α	Tumor necrosis factor alpha
TFAM	Mitochondrial transcription factor A
UCP1	Uncoupling protein 1
UCP2	Uncoupling protein 2

Introduction

There are interconnections in every cellular network in order to adapt to the external stimuli, including exercise. These interconnected networks are involved in the regulation of energy metabolism, e.g., peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), adenosine monophosphate protein kinase (AMPK), and sirtuin (SIRT1) network. These networks respond to many stimuli, including

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physical exercise [12, 61]. Physical exercise is known to induce the metabolic adaptations in muscles via activating the associated transcription factors [9, 14]. However, molecular-based adaptation in response to exercise is unequivocal. Reactive oxygen species (ROS) production during exercise can induce many transcription coactivators and factors positively, but its coordinated mechanism is not well established. Among these transcription factors, PGC-1 α plays a central role in mitochondrial biogenesis and antioxidants boosting via several signaling kinases, including AMPK and p38. This review discusses the overview of PGC-1 α and AMPK-SIRT1 mechanisms by which how these proteins are getting regulated itself during exercise and how the ROS molecules interlink these proteins during exercise; we searched many articles published up to 2016 in PubMed, Medline, and Embase for addressing the role of ROS-mediated PGC-1 alpha and AMPK-SIRT1 during exercise.

ROS are a family of molecules that are continuously generated, transformed, and utilized for various pathophysiological processes in all aerobic living organisms [22]. These ROS induce oxidative stress and damage many cellular and subcellular systems. However, recent studies show that ROS serve as multi-connecting factors in the signaling mechanism particularly exercise-mediated mechanism, but increased ROS production can perturb the exercise-mediated signaling and thus lead to reduced muscle activity during exercise. Studies have shown that various organelles within the cell can generate ROS such as mitochondria, sarcoplasmic reticulum and peroxisomes in exercise condition [15, 21, 64]. In addition, various enzymatic systems, including oxidases and oxygenases produce ROS. However, the random production of ROS impedes to know the exact source during physical activity.

PGC-1 alpha is a transcriptional coactivator that interacts with many other transcription factors in different biological responses, including mitochondrial biogenesis and glucose/fatty acid metabolism [35]. PGC-1 alpha is a first member of PGC family expressed highly where mitochondria are abundant and oxidative metabolism is active, including brown adipose tissue, the heart, and skeletal muscle. PGC-1 alpha expression is also found in the brain, kidney, and at a very low level in white adipose tissue [62]. PGC-1 alpha is composed of an N-terminal region, a middle region, and a C-terminal region. The N-terminal region is key to control the interaction of PGC-1 alpha with other transcription factors such as nuclear respiratory factor 1 (NRF-1), myocyte enhancer factor-2C (MEF2C), and forkhead box protein O1 (FOXO1) [42, 63]. The C-terminal region controls the stability of PGC-1 alpha, as it possesses RNA recognition motifs.

AMPK is a fuel-sensing enzyme found in all mammals and unicellular organisms. Its activation is regulated by the ratio of adenosine monophosphate and adenosine triphosphate (AMP–ATP) due to stresses which deprive the consumption of ATP in relation with increased AMP (e.g., muscle contraction). The enzyme is a heterotrimeric structure composed of one catalytic (α) and two regulatory (β,γ) subunits. These subunits have further two or more isoforms, and their presence varies among different species and types of tissues, but their expression is necessary for full AMPK activity [12, 13, 26, 27]. Under lowered intracellular ATP levels, AMP binds to the γ subunit of AMPK and further causes the conformational changes in the heterotrimeric and phosphorylate the 172 threonine residue of the AMPK α subunit. This 172 threonine phosphorylation is required for catalytic activity. Recent evidence has found that liver kinase B1 (LKB1) is a major upstream enzyme that phosphorylates the 172 threonine residue of the AMPK α subunit in the skeletal muscle [40, 41].

Sirtuins have received significant interest for its regulatory role in the metabolism in response to physiological changes. Sirtuins family is composed of seven proteins (SIRT1–SIRT7), and they vary in source tissues, enzymatic activities, and targets. Sirt1 is the most studied member of the Sirtuins family, present mainly not only in nucleus but also in cytoplasm. It was initially found to deacetylate the histones, but later it was shown that Sirt1 deacetylates other proteins as well [29, 30, 45, 55]. Sirt1 is known to regulate more than 40 protein targets through its deacetylase activity and also is an important regulator of muscle differentiation and metabolism [28, 56]. It has been purported as a central regulator of the mitochondrial biogenesis in the skeletal muscle, as it deacetylates PGC-1 alpha.

Role of nitric oxide in exercise

In the recent decades, nitric oxide (NO) research has gained more importance in exercise physiology. This labile molecule plays an important role in regulating vasodilation, muscle contractility, and mitochondrial respiration. It is synthesized by nitric oxide synthase (NOS)-dependent mechanism in endogenous systems and also it can be increased by dietary supplements sources such as glycin propionyl-L-carnitine. In relation with exercise, NO is increased due to shear stress on vessel walls during exercise and thus improves the oxygen delivery and nutrients to muscles, resulting in increased muscle strength and recovery mechanism. Prolonged exercise increases the NO production, resulting in vasodilation in the heart and skeletal muscles. However, strenuous exercise increases the chances of superoxide production, thereby decreasing the bioavailability of NO, as superoxide combines with NO to produce peroxynitrite—a potent cellular damager. In this scenario, we mainly review about PGC-1 alpha and AMPK, and how NO can act with AMPK synergistically to upregulate the PGC-1 alpha. Lira et al. [48, 49] reported

that NO and AMPK cooperatively regulate the PGC-1 alpha and stimulate the mitochondrial biogenesis in the skeletal muscle cells. However, this mechanism is still illusive in exercise biology.

PGC-1 alpha role in exercise

The coordinated function of PGC-1 α with other transcriptional factors in the cellular process augments the interest to reveal its role in exercise biology. PGC-1 α is a key regulator of exercise-induced phenotype adaptation in the muscles [49].Overexpression of PGC-1 α increases the mitochondrial biogenesis, thus increasing the capacity of oxidative fiber in the muscles. PGC-1 α regulates many transcriptional factors, including mitochondrial transcription factor A (TFAM) and nuclear respiratory factors (NRF-1 and NRF-2) [18, 63]. Furthermore, PGC-1 α is a direct binding site for MEF2, which regulates the muscles fiber type, particularly slow type, resulting in increased endurance activity [18, 60]. A single bout of exercise can induce increased expression of PGC-1 α; however, its level reverts to normal when physical activity is stopped. However, chronic exercise alters the plasticity of muscle toward oxidative fiber type, resulting in increased expression of PGC-1 α [59]. Fiber-type switching toward the oxidative type by PGC-1 α is characterized by increased mitochondrial production, density, and oxidative metabolism [46]. Conversely, glycolytic fiber of muscles decreased the endurance activity [33]. Taken together, PGC-1 α is a key mediator of several cellular processes required for endurance capacity.

Role of ROS/RNS-dependent PGC-1 α and antioxidants in exercise

The prematurely donated electrons to oxygen in the electron transport chain become reactive oxygen (superoxide) anions in the mitochondria. These superoxide radicals are further dismutated into H_2O_2 by superoxide dismutase (SOD). Hydrogen peroxide can be reduced to water by catalase (CAT) and glutathione peroxidase (GPx); alternatively, it becomes OH radicals via Fenton reaction. These superoxide and OH radicals have a negative impact on cellular proteins and lipids through oxidation, resulting in cellular damage that is associated with a wide variety of diseases including degenerative disorders. However, ROS have been linked with several essential cellular signaling processes of growth regulation, differentiation, proliferation, and apoptosis. Mitochondrial biogenesis is an important process by which energy depletion can be saturated during exercise. ROS have been shown to regulate many transcriptional coactivators that are required for mitochondrial biogenesis, including PGC-1 α.

It is well known that endurance training can increase the activity of PGC-1 α in the skeletal muscle, but its activity depends, at least in part, on ROS mechanism [5, 67, 68]. For example, PGC-1 α is activated through phosphorylation by p38 MAPK along with nuclear factor kappa-light-chain-enhancer of activated B (NF-κB), but both are known to be activated by ROS in the muscles; also Ca^{2+} signaling may help to autoregulate PGC-1 α through MEF2, which is an important regulator of muscle cell differentiation and development [32, 39, 52], and in this case also ROS play a crucial role in the regulation of Ca^{2+} signaling. Although PGC-1 α represents the master regulator of mitochondrial biogenesis, it is an upstream activator of mitochondrial metabolism in the muscles, influencing the amount of ROS production. However, studies proposed that PGC-1 α expression is regulated by ROS and thereby a potential network between PGC-1 alpha and ROS [3, 25, 66–68]. For example, there is a reasonable chance to increase the ROS production during exercise in the skeletal muscles, as exercise increases the activity of PGC-1 α, but PGC-1 α can consequently activate several detoxifying enzymes. St-Pierre et al. [65] reported that ectopic expression of PGC-1 alpha in muscle cells increases the expression of SOD2 and GPx1, which remove superoxide and hydrogen peroxide, and their further studies confirmed that PGC-1 α regulated these detoxifying enzymes [66–68] particularly in the promoter sequence of MnSOD and glutathione system [10], and thus, antioxidants and PGC-1 alpha coordinately regulate the mitochondrial system in the skeletal muscles and remove the toxic derivatives in the muscles during exercise [23]. However, depletion of antioxidants can also alter the PGC-1 α expression. Aquilano et al. [1] found that glutathione decrement due to metabolic stress in exercised condition increases the expression of PGC-1 α via p53. PGC-1 alpha can also be involved in reducing the ROS generation by increasing the expression of uncoupling proteins UCP-1 and UCP-2 which dissipates the proton gradient and reduces the mitochondrial membrane potential [53]. Conversely, ROS are involved in the regulation of PGC-1 α. For example, H_2O_2 regulates the expression PGC-1 α via AMPK pathway and indirectly it is involved in upregulation of PGC-1 α by lactate, a by-product of glycolytic pathway [43, 44]. Therefore, it is a multi-dependent process of PGC-1 α, antioxidants, and ROS. Ample evidence supported that muscle contraction during exercise increased the production of ROS in the form of superoxide (O_2), hydrogen peroxide (H_2O_2), and hydroxyl (OH) radicals [10, 39, 65]. H_2O_2 is an important signaling molecule for muscle adaptation. However, ROS have been shown to increase the expression of PGC-1 α and metabolic adaptation in the muscles, but at what level the production of ROS could help regulate PGC-1 α during exercise needs more study. Additionally, reactive nitrogen species (RNS) play an important role in the regulation of PGC-1 α; particularly, NO increases the PGC-1 α expression via AMPK activation and Ca^{2+}/

calmodulin. Nitric oxide production is increased during physical exercise [2, 58]. Several studies have suggested the role of NO in the PGC-1 α regulation, mitochondrial biogenesis, and fiber type changes [48, 51].

Role of PGC-1 α in mitochondrial biogenesis of muscular adaptation

Muscular adaptation involves activation of many transcriptional factors and coactivators that regulate the mitochondrial biogenesis and muscle fiber type. It is believed that exercise induces the mitochondrial biogenesis by mimicking the activity of transcription factors [36, 38, 47]. This increased amount of mitochondria in the skeletal muscle can have many beneficial health effects including exercise endurance and oxidative capacity. Recent studies have proved that PGC-1 α is an important transcription coactivator that supports to activate other transcription factors (MEF), nuclear respiratory factors (NRF-1 and NRF-2) [46] and upregulate gene expression of mitochondrial biogenesis. Thus, it is a master regulator in mitochondrial biogenesis and also considered as a one of the important factors influencing muscle fiber type. Exercise like stimuli induces the PGC-1 α expression, which contributes the muscular contraction activity. This contraction activates the Ca^{2+} channels leading to increased amount of Ca^{2+} in the cytosol. This increased amount of Ca^{2+} stimulates the calcium/calmodulin-dependent protein kinase, which further phosphorylates the PGC-1 α. In another way, muscle contraction-mediated AMPK and p38 MAPK induces PGC-1 α expression. PGC-1 α can also regulate the homeostasis of oxidants and antioxidants by increasing the stimulation of superoxide dismutase-2, catalase, and GPx expression. Taken together, PGC-1 α plays a crucial role in response to external stimuli like exercise to increase the mitochondrial biogenesis by mimicking the many metabolic responses and transcription factors including NRF.

Interconnecting role of AMPK-SIRT1 and PGC-1 α during exercise

Significant understanding of AMPK-SIRT1 and PGC-alpha has been gained both animal and clinical models (Tables 1 and 2). AMPK regulates both anabolic and catabolic processes to balance the energy level. During exercise, AMPK is activated for energy-consuming process, as it regulates the glucose uptake and fatty acid oxidation. Several studies suggest that AMPK is involved in mitochondrial biogenesis, angiogenesis, and calorie restriction [19, 37, 70]. A single bout of exercise can activate AMPK, resulting in stimulation of many metabolic pathways and also its activation leads to mimic several signaling factors in response to muscle adaptation. Both physical exercise and physical inactivity can either activate or inactivate the AMPK pathway, but its complete activation depends on the intensity of exercise. For example, AMPK activation has been reported after an hour at 75% VO_{2max} until exhaustion [69] and also threonine 172 phosphorylation of AMPK α2 was increased at 45% VO_{2max} [70]. Likewise, Chen et al. [16] reported that the duration as well as the intensity and type of exercise can directly increase the AMPK activation in human muscles. In addition to physical exercise, other forms of stresses including hypoxia also increased the AMPK level in the skeletal and cultured muscles [54]. Although various signaling pathways are involved in regulating the antioxidant defense system for giving protection against ROS-mediated damage, AMPK–SIRT1 is a major signaling pathway involved in controlling different

Table 1 Experimental model of AMPK-Sirt1 and PGC-1 alpha in skeletal muscle

Experimental model	Possible mechanism of AMPK-Sirt1 and PGC-1 alpha	References
AMPK activation in the rat model	AMPK phosphorylation in the pancreatic islets and skeletal muscle in exercise condition.	[50]
Exercise in Wistar rats	Increases the insulin and leptin sensitivity for enhancing the AMPK through rapamycin pathway	[24]
Total AMPK knockout model	Interruption in the glucose transport, impaired glycogen resynthesis in the skeletal muscle. Impaired exercise induced gene expression in the skeletal muscle and increased muscle fatigue	[6–8]
Sirt1 expression in mice	Prevented high fat induced glucose intolerance and insulin resistance	[4]
Sirt1 over expression in mice model	Increased the mitochondrial content and increased the mitochondrial activity in the skeletal muscle	[61]
PGC-1 alpha transgenic mice	Muscle specific expression PGC-1 alpha improves the exercise performance due to enhanced mitochondrial function, mitochondrial expression, mitochondrial DNA and mitochondrial enzyme activity.	[11]

Table 2 Clinical model of AMPK-Sirt1 and PGC-1 alpha in skeletal muscle

Clinical model	Possible mechanism of AMPK-Sirt1 and PGC-1 alpha	References
AMPK in human skeletal muscle	AMPK is activated during cycling exercise particularly α2-AMPK is more prone to activation in the contraction/exercise	[17]
PGC-1 alpha expression in human skeletal muscle	PGC-1 alpha expression is a muscle specific type and its level is increased following physical activity	[34, 57]
Sirt1 activation in humans following exercise	Both acute and chronic exercise training activate the Sirt1 via NAMPT pathway (nicotinamide phosphoribosyltransferase) and also PGC-1 acetylation.	[20, 31]

transcription coactivators and factors like PGC-1 α, FOXO1, and NF-κB that are directly linked with ROS production in order to protect muscle cells from ROS-mediated damage and inflammatory mediators, and thus it becomes an important therapeutic target to unravel the physiological role of muscle and other tissues.

As noted earlier, LKB1 is an important enzyme present in muscles and its deacetylation or phosphorylation is crucial to

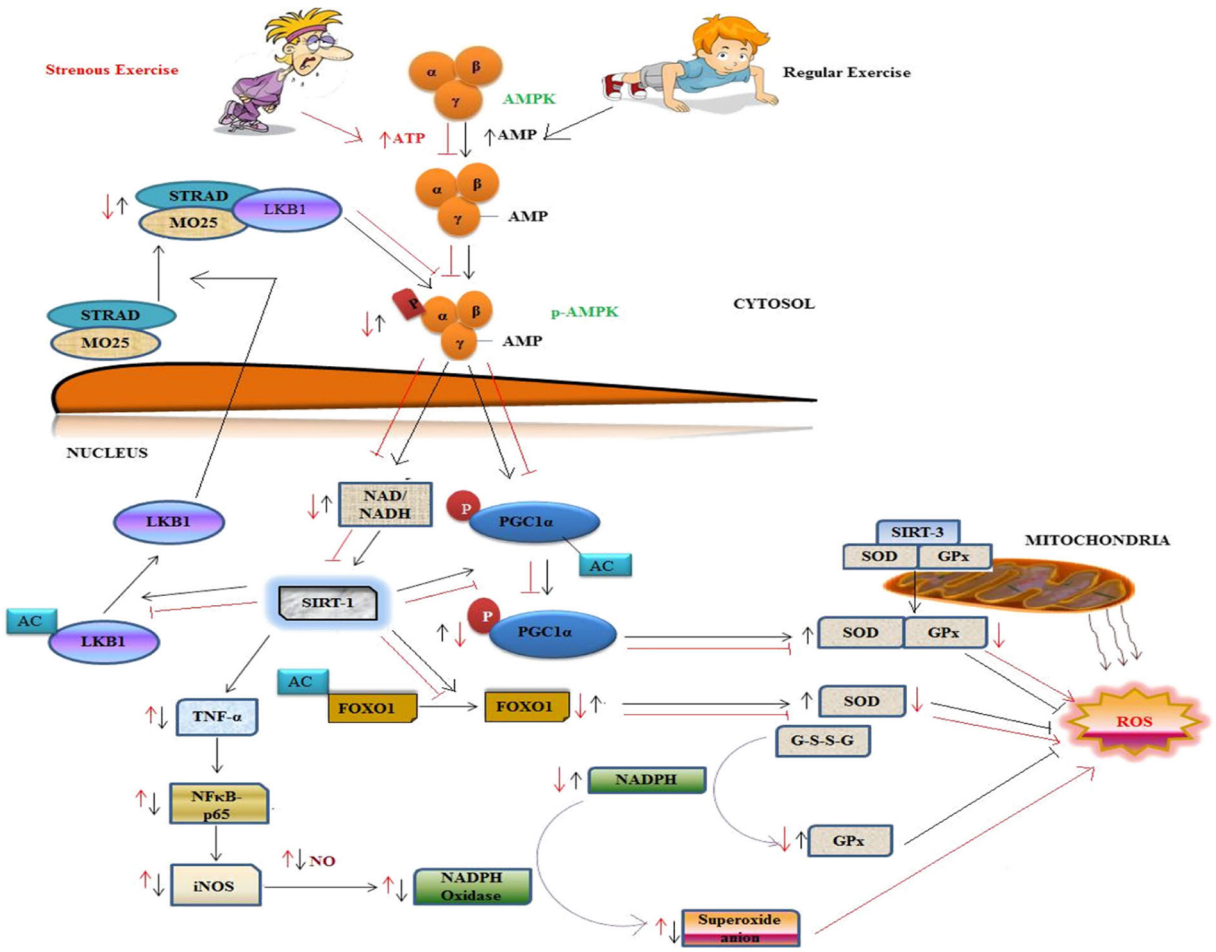

Fig. 1 Physical exercise (*black line*) alters AMP–ATP ratio, resulting in an increased amount of AMP, which binds to the γ subunit of AMPK. This binding causes conformational changes in the heterotrimeric structure and leads to activation of AMPK. SIRT1 regulates AMPK by deacetylation of LKB1. Likewise, AMPK regulates SIRT1 by inducing NAD^+. AMPK and SIRT1 activate PGC-1 α by phosphorylation and deacetylation which further activate the release of SOD and GPx. SIRT1 deacetylates FOXO1 and TNF-α. This deacetylated FOXO1 activates the SOD and GPx, and TNF-α deacetylation by SIRT1 leads to reduction in NFkB-p65 expression which further decreases the iNOS and NADPH oxidase. This decreased NADPH oxidase level increases the NADPH level, which further induces the SOD and Gpx release by these pathways, and it reduces the mitochondrial ROS-mediated muscle damage during exercise. The *red line* indicates the effect of vigorous exercise on AMPK-SIRT-1 pathway. Overtraining physical exercise increases the ATP to sustain the energy demand, and this causes decreased AMP level and reduces the AMPK activity, which further decreases the SOD and Gpx expression

activate the AMPK. Recent reports suggest that silent information regulator 1 (Sirt1) is a NAD^+-dependent histone/protein deacetylase, which may deacetylate the LKB1, and it leads to activate the AMPK [45]. Price et al. [61] showed that SIRT1 is required for AMPK activation in the resveratrol treatment. They reported that low-dose resveratrol induces the AMPK activation in a SIRT1-dependent manner. These collective reports suggested that AMPK activity relies on SIRT1 activity. In contrast, SIRT1 activity depends on AMPK activation but in different mechanism. For example, Fulco et al. [29] found that AMPK can activate SIRT1 in vitro through nicotinamide phosphoribosyl transferase (Nampt) which in turn activate NAD^+/NADH, the substrate for SIRT-1. Interestingly, AMPK and SIRT1 mediate the PGC-1 α expression in mitochondrial biogenesis and glucose metabolism. In a recent report, AMPK phosphorylates the PGC-1 α directly [35]. However, how this happens is still elusive. AMPK-mediated SIRT1 deacetylates the PGC-l α which in turn increased activity of PGC-1 α. Canto et al. [12] showed that AMPK-dependent PGC-1 alpha activation relies on SIRT1 activation. Nemoto et al. [55] have explained the complex relationship between SIRT1, PGC-1 α, and mitochondrial function in PC12 cells. Similarly, Gerhart-Hines et al. [30] showed that SIRT1 expression is regulated by PGC-1 as ectopic expression of PGC-1 α, and also these authors were the first to demonstrate the role of SIRT1 on mitochondrial adaptation in skeletal muscle. Altogether, SIRT1, AMPK, and PGC-1 α have an imperative role to increase the mitochondrial adaptation to exercise. From these collective reports, we speculate that abnormal or overexercise can increase the amount of ROS generation in muscles and that it further causes the oxidative environment in the muscle. This increased oxidative environment may impair AMPK, SIRT1, and PGC-1 α, mediated pathways. During vigorous exercise, ATP production is increased to sustain the energy demand in the muscle. This increased intracellular ATP level causes AMP depletion as a result of decreased activity of AMPK, and this further decreases the SIRT1 activity. Reduced activity of SIRT1 may fail to deacetylate the LKB1, PGC-1 α, FOXO1, and tumor necrosis factor alpha (TNF-α), which in turn reduces the endogenous antioxidants expression, and this condition may activate the NF-κB, iNOS, and NoXs, resulting in increased amount of ROS (Fig. 1). However, this linking mechanism needs to be established more clearly.

Conclusions and future aspects

A large number of studies reveal that the transcription factors and coactivators play an important role in the positive response of ROS during exercise. Although these transcription factors help to regulate the redox system during exercise, limited evidences persist regarding PGC-1 α and AMPK-SIRT1 connection on ROS regulation and how the ROS mediate these signaling processes in response to external stimuli including exercise. Even less is known about these PGC-1 α and AMPK-SIRT1 networks from a therapeutic aspect. However, different mechanisms are involved in response to exercise. Further quantitative studies will reveal the holistic benefits of these proteins, paving way for their therapeutic applications in muscle-related pathology, as well as determining proper exercises to prevent diseases associated with these proteins.

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