**Coregulator-mediated control of skeletal muscle plasticity – a mini-review**

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**Abstract**

Skeletal muscle plasticity is a complex process entailing massive transcriptional programs. These changes are mediated by the action of nuclear receptors and other transcription factors. In addition, coregulator proteins have emerged as important players in this process by linking transcription factors to the RNA polymerase II complex and inducing changes in the chromatic structure. An accumulating body of work highlights the pleiotropic functions of coregulator proteins in the control of tissue-specific and whole body metabolism. In skeletal muscle, several coregulators have been identified as potent regulators of metabolic and myofibrillar plasticity. In this mini-review, we will discuss the regulation, function and physiological significance of these coregulators in skeletal muscle biology.

**Abbreviations**

| | |
|---|---|
| AMPK | AMP-activated protein kinase |
| BAT | Brown adipose tissue |
| CACT | Carnitine/acyl-carnitine translocase |
| ERRα | Estrogen-related receptor α |
| GLUT4 | Glucose transporter 4 |
| Gys1 | Glycogen synthase 1 |
| HDAC | Histone deacetylase |
| HFD | High fat diet |
| KO | Knockout |
| MEF | Myocyte enhancer factor |
| MyHC | Myosin heavy chain |
| NCOR1 | Nuclear corepressor 1 |
| NR | Nuclear receptor |
| Pgam2 | Muscle phosphoglycerate mutase 2 |
| PGC-1 | Peroxisome proliferator-activated receptor γ coactivator-1 |
| PKB | Protein kinase B/Akt |
| PPARγ | Peroxisome proliferator-activated receptor γ |
| PRC | PGC-related coactivator |
| PRMT4 | Protein arginine methyltransferase 4 |
| Pygm | Muscle glycogen phosphorylase |
| RAR | Retinoic acid receptor |
| RER | Respiratory exchange ratio |
| RID1 | Receptor interacting domain 1 |
| RIP140 | Receptor interacting protein 140 |
| SMRT | Silencing mediator of retinoid and thyroid hormone receptor |
| SRC | Steroid receptor coactivator |
| TF | Transcription factor |
| TR | Thyroid hormone receptor |
| UCP-1 | Uncoupling protein 1 |
| WAT | White adipose tissue |

**Keywords**

Coregulators; metabolism; skeletal muscle; PGC-1

**Highlights**

- Coregulators are important signaling integrators and coordinate transcription
- Complex transcriptional networks control the plasticity of skeletal muscle tissue.
- In this review, we discuss the regulation and function of coregulators in muscle physiology.

## 1. Introduction

Maintenance of cellular metabolic homeostasis requires the precise integration of internal and external cues in a highly regulated manner. Transcriptional programs are central to many plastic changes, and often involve the action of numerous nuclear receptors (NRs) and other transcription factors (TF). Importantly, coregulator proteins provide an additional layer of control, and vastly expand the repertoire of specificity and fine-tuning of transcription [1, 2]. In many cases, coregulators are metabolic sensor and effector proteins and thereby directly link the cellular environment to the transcriptional output [3]. Coregulator proteins lack an intrinsic DNA binding domain and therefore require a direct or indirect interaction with TFs to be recruited to target gene enhancer and promoter elements. Direct binding partners of TFs are referred to as coregulators, while other members of the coregulatory complex are called secondary coregulators or co-coregulators [4]. Importantly, such complexes often encompass 10 or even more individual proteins, the composition of which can change in a highly dynamic manner. Moreover, coregulator complexes exist in three hierarchical layers with the stable core modules at the center, escalating to a more dynamic core complex formation between such modules and ultimately network-forming complex-complex interactions that are highly context-dependent [5]. Coregulators can be broadly categorized into coactivators and corepressors that induce or inhibit gene expression, respectively, even though some members of this protein family can act as both, depending on the local state of chromatin, TF activation or conformation [1]. While some coregulators primarily serve as scaffold for the assembly of complexes, others harbor intrinsic enzymatic activity, mainly targeted at the modification of histones and thereby affecting chromatin structure. Importantly, alternative splicing of the transcripts and post-translational modifications of coregulator proteins collectively allow a fine-tuned and specific assessment of homeostatic conditions, followed by a rapid, efficient and reversible transcriptional control to initiate the appropriate physiological response [1, 2]. Since the discovery of the first coregulator, SRC-1, two decades ago [6], more than 450 coregulator proteins, and hundreds of co-coregulators, have been identified and implicated in the general control of transcription or the regulation of tissue-specific programs [5]. Skeletal muscle tissue is one of the best examples of an organ that exhibits enormous plasticity upon various challenges, including specific and well-controlled short- and long-term adaptations. Even though the integration, regulation and coordination of numerous signaling pathways and the ensuing transcriptional programs are still poorly understood, several TFs and coregulators have been implicated in the regulation of this complex system. Skeletal muscle accounts for around 40-50% of total body mass and is one of the most active metabolic organs. This tissue is one of the main energy storage sites, generates force, maintains posture, is essential for shivering thermogenesis, acts as an endocrine organ and can detoxify excessive endogenous metabolites. However, the adaptation of skeletal muscle to exercise and inactivity are of particular physiological and pathological importance. Training can substantially improve metabolic and contractile functions of the muscle while inactivity has the opposite effect. This review will summarize the advances in understanding the role of coregulators in skeletal muscle plasticity.

**2.1 Steroid receptor coactivators (SRCs)**

SRCs have been the first coactivator proteins identified [6] consisting of 3 homologous family members termed SRC-1 (also known as NCoA1), -2 (also known as NCoA2, GRIP1 and TIF1) and -3 (also known as NCoA3, ACTR, AIB1, p/CIP, RAC3 and TRAM-1). SRCs mediate steroid hormone actions and are involved in transcriptional initiation, cofactor recruitment, elongation, RNA splicing and translation [4]. In different tissues, SRC-1 and SRC-2 are inversely regulated and these two coactivator proteins compete for binding to the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and transcription factors [4, 7]. Muscle specific ablation of SRC-2 leads to SRC-1-dependent enhanced skeletal muscle uncoupling via regulation of the uncoupling protein 3 (UCP3), resulting in increased whole body energy expenditure, which protects mice from type 2 diabetes and high fat diet (HFD)-induced obesity. Moreover, SRC-2 muscle knockout (KO) mice show enhanced oxidative capacity in comparison to age-matched control littermates due to increased transcription levels of PGC-1α and its target genes involved in fatty acid and β-oxidation. Thus, skeletal muscle SRC-2 is important to maintain low levels of SRC-1 in order for optimal mitochondrial function and skeletal muscle as well as whole body homeostasis [8]. Intriguingly, SRC-1/SRC-2 double KO animals exhibit no difference in UCP3 expression, body temperature, energy expenditure or mitochondrial function, indicating that the induction of SRC-1 is at least in part responsible for the phenotype of muscle-specific SRC-2 KO mice [4]. In myogenesis, SRC-1 and SRC-2 show likewise opposing roles in the regulation of myogenic differentiation (MyoD)-mediated transcription: domain-specific binding of SRC-1 results in coactivation and of SRC-2 in corepression of MyoD, respectively [9]. Furthermore, SRC-2 coactivates the myocyte enhancer factor-2C (MEF-2C) and myogenin, and thereby potentiates the differentiation of cultured C2C12 myoblasts into myotubes [10].

SRC-3 has been implicated in the regulation of long and very long chain fatty acid metabolism in skeletal muscle. SRC-$3^{-/-}$ mice show significantly reduced expression levels of the carnitine/acyl-carnitine translocase (CACT) in skeletal muscle, which leads to the accumulation of long chain fatty acids. The loss of SRC-3 resembles the genetic deficiency of CACT in humans and is accompanied by hypoketonemia, hypoglycemia, cardiac abnormality, hyperammonemia, abnormal electrical discharge in the brain and severe muscle weakness [11]. The modulation of muscle endurance and hypoglycemia in the SRC-3 KO can be alleviated by a short-chain fatty acid diet. In summary, similar to other tissues, SRC-1 and SRC-2 promote a program of energy expenditure and energy storage, respectively, while SRC-3 controls energy substrate usage and thereby affects endurance.

**2.2 Peroxisome proliferator-activated receptor γ coactivators-1 (PGC-1)**

The first member of the peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1 (PGC-1) family, PGC-1α, has been discovered as a coregulator protein interacting with PPARγ in brown adipose tissue (BAT) almost twenty years ago. Since then, two other family members have been identified termed PGC-1β and PGC-related coactivator (PRC). The PGC-1s are highly regulated, potent coactivators and are able to interact with a large variety of different TFs to induced distinct biological processes in a tissue-specific manner [12, 13]. Expression of PGC-1α in skeletal muscle is strongly controlled by contractile activity in humans and rodents. Accordingly, muscle-specific PGC-1α transgenic animals show increased oxidative metabolism, a higher proportion of slow-twitch muscle fibers and improved endurance capacity [12, 14, 15]. In contrast, muscle-specific PGC-1α KO mice display impaired exercise performance, myopathy, decreased oxidative metabolism and abnormal glucose tolerance [16, 17]. Curiously, the high-endurance phenotype is predominantly evoked by the specific PGC-1α isoforms PGC-1α1, PGC-1α2 and PGC-1α3 [18]. Recently, the so-called PGC-1α4

isoform has been described to be implicated in the regulation of muscle hypertrophy by inducing IGF-1 and repressing myostatin gene expression [19].
In contrast to the well-established role of PGC-1α in exercise-adaptation, the regulation and function of PGC-1β is less clear. Muscle-specific overexpression of PGC-1β drives the formation of oxidative type IIx fibers [20] and different PGC-1β global KO models show impaired muscle mitochondrial function [21]. Moreover, muscle-specific ablation of PGC-1β reduces exercise performance, oxidative capacity and increases oxidative stress [21, 22]. Thus, PGC-1α and PGC-1β are crucial for oxidative metabolism and mitochondrial function and loss of both family members in skeletal muscle leads to a dramatic reduction in exercise performance due to mitochondrial structural and functional abnormalities [23]. These results indicate that the two PGC-1 coactivators have overlapping, but also distinct functions in skeletal muscle.

### 2.3 Nuclear corepressor 1 (NCoR1) and silencing mediator for retinoid and thyroid hormone receptor (SMRT)

NCoR1 and SMRT (also known as NCoR2) have been found to interact with thyroid hormone receptor (TR), retinoic acid receptor (RAR) and other TFs to suppress target gene transcription. The two corepressors show a high degree of amino acid sequence homology and display similar functional domains [24]. Like the SRCs and the PGC-1s, NCoR1 and SMRT are scaffold coregulators and thus recruit heterogeneous corepressor complexes in a context-specific manner.
Loss of NCoR1 in skeletal muscle enhances exercise performance due to an increase in muscle mass, mitochondrial number and activity [25, 26]. Interestingly, NCoR1 muscle KO mice show a similar phenotype as PGC-1α muscle transgenic mice and in fact, NCoR1 and PGC-1α inversely control the transcription of a common subset of genes by competitive binding to the estrogen-related receptor α (ERRα) [26] and/or PPARβ/δ [25].
The corepressor SMRT may be involved in aging-associated metabolic processes, since mRNA and protein levels are induced in older mice in BAT and muscle. Furthermore, in mice with a disrupted SMRT receptor interacting domain 1 (RID1), muscles show reduced insulin-stimulated protein kinase B (PKB/Akt) phosphorylation, glucose transporter 4 (GLUT4) protein levels and a blunted insulin-induced glucose uptake [27]. These changes in glucose handling lead to premature aging and other metabolic diseases by shifting the SMRT repression to RID2- associated NRs such as the PPARs. Thus, these results suggest that SMRT might be involved in the development of insulin resistance induced by dietary conditions or aging. Importantly, both NCoR1 and SMRT modulate mitochondrial biogenesis and function in different tissues, thereby reducing oxidative metabolism and energy expenditure [24]. Thus, both corepressors are major factors in the regulation of energy homeostasis. Intriguingly, the repressive action of NCoR1 on clock gene expression could imply that this corepressor, and potentially SMRT, links metabolism to the circadian rhythm [24].

### 2.4 Thyroid hormone receptor-associated protein complex component/Mediator Complex Subunit 1 (TRAP220/MED1)

The Mediator complex forms a bridge from transcription factors to the RNA polymerase II transcriptional machinery. In fat cells, PGC-1α is a crucial interaction partner of the Mediator complex for the dynamic changes from chromatin remodeling to transcriptional initiation. Direct recruitment of PGC-1α to activated transcription factors results in the co-binding of CBP/p300 and other histone acetyltransferases to modify nucleosomes and thereby open the chromatin conformation. Subsequently, interaction between PGC-1α and the Mediator subunit Med1 engages the basal transcription machinery for transcriptional initiation [28]. Med1 binds to the C-terminus of PGC-1α,

displaces this coactivator from the transcription factor, and thereby promotes the formation of an enhanced complex for transcriptional activity [29]. Somewhat unexpectedly, chow-fed muscle-specific MED1 KO mice display increased glucose tolerance and insulin sensitivity suggesting a role of muscle MED1 in whole body glucose homeostasis. Furthermore, these MED1 KO mice are protected against HFD-induced obesity. Gene expression analyses of white muscles revealed elevated levels of the mitochondrial genes, but also the brown adipose tissue-typical uncoupling protein-1 (UCP-1) and Cidea, in MED1 KO mice. As a result, MED1 ablation in white muscles results in higher mitochondrial numbers and causes a switch toward slow oxidative fibers [30]. Interestingly, the increase in mitochondrial density and oxidative metabolism does not require an elevation in either PGC-1α or PGC-1β transcription suggesting that basal PGC-1 levels are sufficient to induce the respective metabolic and myofibrillar genes in the absence of MED1. It is thus conceivable that MED1 actively suppresses PGC-1 target genes, which can only get activated when PGC-1 expression itself is induced and overcomes the suppressive effect of MED1. This mechanism of action would ensure the fine-tuning of specific gene sets upon different external stimuli.

**2.5 Receptor interacting protein 140 (RIP140)**

RIP140 was first discovered in breast cancer cells as an estrogen receptor modulator and has now been identified as a corepressor for a large number of ligand-bound NRs involved in metabolism [31]. RIP140 transcript levels are most elevated in white adipose tissue (WAT) followed by skeletal muscle, where its mRNA levels are higher in glycolytic compared to oxidative muscle fibers [32, 33]. Ablation of RIP140 in skeletal muscle results in induced oxidative metabolism through enhanced fatty acid oxidation in addition to increased oxygen consumption of chow and HFD-fed mice while lowering the respiratory exchange ratio (RER). Furthermore, RIP140 regulates glucose trafficking in oxidative muscles. Deletion of muscle RIP140 increases the expression of UCP-1, leading to energy dissipation through mitochondrial uncoupling. Concomitantly, AMP-activated protein kinase (AMPK) gets activated, which in turn stimulates the translocation of GLUT4 vesicles to the plasma membrane enabling the entrance of glucose from the blood [34]. Thus, RIP140 functions as a transcriptional corepressor that reduces oxidative metabolism and inhibits glucose uptake into oxidative muscles. It is conceivable that these effects of RIP140 are achieved by competing with PGC-1α for binding to ERRs and PPARs in muscle [35].

**2.6 Protein arginine methyltransferases (PRMT)**

PRMT are coactivators that possess intrinsic enzymatic activity, which catalyze the formation of monomethylarginine as well as symmetrical and asymmetrical dimethylarginine. These posttranslational modifications affect the function of target proteins and regulate their ability to interact with DNA, RNA or other proteins [36].

PRMT4 (also known as CARM1) is the most abundantly expressed PRMT in skeletal muscle and controls glycogen metabolism. PRMT4 siRNA suppresses the expression levels of glycogen synthase 1 (GYS1), muscle phosphoglycerate mutase 2 (PGAM2) and muscle glycogen phosphorylase (PYGM) and decreases mRNA levels of myosin heavy chains (MyHC) type IIb and IIx. Moreover, expression of a mutant PRMT4 with attenuated methyltransferase and coactivator activities decreases glycogen levels in skeletal muscle cells [36]. These data indicate that expression of PRMT4 and the associated enzymatic activity are important for muscle glycogen metabolism and might play a role in human glycogen storage diseases. In myogenesis and differentiation, PRMT4 interacts with SRC-2 to recruit and activate MEF2 to the creatine kinase promoter. Ablation of PRMT4 gene expression reduces the expression of MEF2 and myogenin and thereby leads to impaired myogenesis [37].

### 2.7 Histone deacetylases (HDACs) and histone acetyltransferases (HATs)

HDACs are categorized into class I, IIa, IIb and IV HDACs, which require zinc as a cofactor for enzymatic activity and class III HDACs, better known as sirtuins, which require $NAD^+$ as a cofactor [38]. Some of these proteins deacetylate histones as well as other proteins. For example, in skeletal muscle, HDAC3, a class I HDAC, is often found in a complex with NCoR1/SMRT, and directly contributes to target gene promoter recruitment and the transcriptional repression activity via histone deacetylation. In addition, HDAC3 also deacetylates MEF2 and could thereby affect myogenesis and the expression of oxidative fiber genes [3, 38].

HDAC5, a member of the class IIa HDACs, also represses MEF2, which then inhibits transcription of MEF2 target genes such as PGC-1α [39]. The positive autoregulatory loop that controls PGC-1α expression in skeletal muscle thus hinges on the competition of HDACs and PGC-1α to bind to and repress and activate MEF2s, respectively, on the PGC-1α promoter [40]. Since class IIa HDACs exhibit only limited deacetylase activity, recruitment of HDAC3 most likely is responsible for the enzymatic effect [3]. HDAC5 activity is inhibited by phosphorylation through AMPK, which enables the MEF2-dependent induction of GLUT4 in myotubes in the right metabolic context [41]. HDAC4 and HDAC5 are furthermore involved in the induction of E3 ubiquitin ligases in neurogenic fiber atrophy [42]. In both of these scenarios, PGC-1α mediates opposing effects, e.g. by being activated by AMPK [43] or by reducing the denervation-induced expression of pro-atrophic E3 ubiquitin ligases [44]. Thus, collectively, several members of the class I and class II HDACs have been implicated in the metabolic reprogramming of skeletal muscle tissue [38].

Sirtuin 1 (SIRT1), a class III HDAC, exerts the most studied effects in skeletal muscle by deacetylation and thereby activation of PGC-1α [45]. An interdependent AMPK-SIRT1-PGC-1 axis ensures a tightly controlled sensing of the metabolic state of the cell based on AMP/ATP and NAD+/NADH ratios [46]. There are several open questions in regard to SIRT1 action in skeletal muscle. For example, SRT1720, a proposed, though disputed synthetic activator of SIRT1, improves muscle endurance and promotes an oxidative phenotype [47], even though the engagement of muscle PGC-1α seems non-obligatory for the systemic effects of SRT1720 and resveratrol to occur [48]. Directly opposed to SIRT1, GCN5 not only acetylates histones but also other targets, including PGC-1α [49]. The debate about the relative contributions of SIRT1 and the counteracting protein acetyltransferase GCN5 (also called KAT2A) to control oxidative metabolism in skeletal muscle remains currently unresolved [50].

In addition to GCN5, other HATs have also been implicated in the regulation of myogenesis and muscle function. For example, CBP/p300 and pCAF (also known as KAT2B) interact to control MyoD activity in myogenic differentiation [51]. However, even though a strong association of CBP/p300 and PGC-1α has been demonstrated [7], the relevance of this interaction in endurance exercise-induced muscle plasticity has not been studied so far.

### 2.8 cAMP-regulated transcriptional coactivators (CRTC)

CRTCs (also called transducers of regulated CREB-binding proteins, TORCs), have been identified as coactivators of the cAMP-responsive element binding protein (CREB) [3]. In most tissues, the CRTCs are strongly regulated by the hormonal and metabolic environment. CRTC1 emerged as the most potent activator of PGC-1α gene expression in a screen of 10’000 human full-length cDNAs in muscle cells [52]. In addition to CRTC1, the other two CRTC family members CRTC2 and CRCT3 likewise strongly induce PGC-1α transcription and downstream targets, including genes encoding mitochondrial oxidative phosphorylation enzymes, thereby linking external cues that activate calcium- and cAMP-

dependent signaling pathways to an oxidative muscle cell phenotype in a PGC-1α- and CREB-dependent manner [52], most likely via the cAMP-response element in the PGC-1α promoter [40, 52].

**2.9 Retinoblastoma proteins (pRbs)**

pRb was initially identified as a tumor suppressor gene in the regulation of the cell cycle [3]. E2F1, the target of the repressive action of pRb in this context, however also exerts potent functions in cellular metabolism. Transcriptional derepression of E2F1 by deletion of pRb thus results in the promotion of an oxidative phenotype in skeletal muscle, thereby potentially linking cell proliferation, differentiation and metabolism in this tissue [53]. Similarly, p107, another member of the pRb protein family, inhibits PGC-1α gene expression and hence an oxidative muscle phenotype by repressing the activity of E2F4 on the PGC-1α promoter [54].

## 3. Conclusion

In this review, we tried to summarize the still very rudimentary insights into the role of coregulator proteins in muscle plasticity (Figure 1 and Table 1). Even though the complex transcriptional networks that are controlled by these proteins are still very poorly understood [13], small steps have recently been made to understand the recruitment and activity of some of these proteins in muscle cells [55, 56]. The synergistic and antagonizing effects of coregulators, and the potential to modulate the activity of many different TFs not only increases the complexity of transcriptional regulation, but could also help to identify potential therapeutic targets in the treatment of metabolic and muscle diseases. For example, transgenic elevation of PGC-1α in skeletal muscle confers therapeutic effects on many different muscle pathologies, even though diet-induced insulin resistance is not ameliorated without additional exercise interventions [57]. Furthermore, chronic administration of a synthetic class IIa HDAC inhibitor enhanced muscle endurance, and ameliorated systemic lipid and glucose handling [58]. Thus, to design safe and specific drugs, future studies will hopefully unravel how coregulators orchestrate complex metabolic networks and how their transcriptional fine-tuning abilities are regulated in muscle tissue.

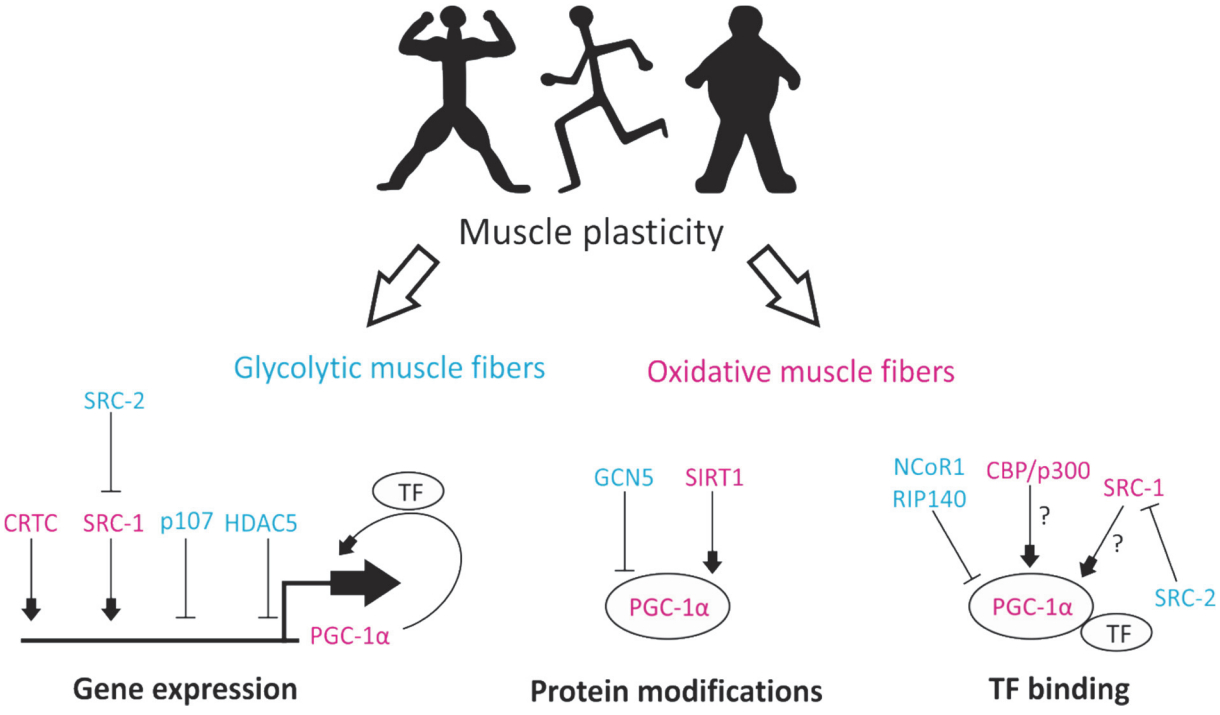


**Figure 1. The complex regulatory network of the coactivator PGC-1α.**

Gene expression: PGC-1α is induced by itself via the interaction with different transcription factors (e.g. MEF2, possibly PPARδ), CRTC family members and SRC-1, which in turn is repressed by SRC-2. Furthermore, PGC-1α is repressed by HDAC5 and p107; Protein modifications: PGC-1α activity is controlled by GCN5 and SIRT1, which acetylate or deacetylate it, respectively; TF binding: NCoR1 and RIP140 compete with PGC-1α in the binding to TFs while CBP/p300 and SRC-1 enhance its binding to the transcriptional machinery, even though this has only been shown in fat and not in muscle tissue, which is why the interaction is shown with a question mark.

Also, the direct correlation between the glycolytic and oxidative metabolism and the corresponding color-coded coregulators (blue: glycolytic; pink: oxidative) is often missing, however, KO studies strongly suggest this association.

Table 1. Coregulator proteins involved in skeletal muscle plasticity

| Family | Short name | Members | In skeletal muscle involved in … |
|---|---|---|---|
| Steroid receptor coactivators | SRC | SRC-1, SRC-2, SRC-3 | Steroid hormone metabolism, uncoupling, myogenesis, fatty acid metabolism |
| Peroxisome proliferator-activated receptor γ coactivators-1 | PGC-1; PRC | PGC-1α, PGC-1β, PRC | Oxidative metabolism, mitochondrial homeostasis, exercise performance |
| Nuclear corepressors | NCoR | NCor1, SMRT | Energy homeostasis, hypertrophy, aging, glucose homeostasis |
| Thyroid hormone receptor-associated protein complex component/Mediator Complex Subunit 1 | Mediator complex | TRAP220, MED1 | Initiation of transcription, glucose homeostasis, mitochondrial homeostasis |
| Receptor interacting protein 140 | RIP140 | RIP140 | Oxidative metabolism, uncoupling, glucose homeostasis |
| Protein arginine methyltransferases | PRMT | PRMT4 | Glycogen metabolism, myogenesis |
| Histone deacetylases | HDAC | HDAC3, HDAC4, HDAC5, sirtuins | Myogenesis, oxidative metabolism, atrophy, energy homeostasis |
| Histone acetyltransferases | HAT | GCN5, CBP/p300, pCAF | Oxidative metabolism, myogenesis |
| cAMP-regulated transcriptional coactivators | CRTC | CRCT1, CRCT2, CRCT3 | Oxidative metabolism |
| Retinoblastoma proteins | pRB | pRB, p107 | Oxidative metabolism |

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