HIGHLIGHTED TOPIC | Signals Mediating Skeletal Muscle Remodeling by Activity

Regulation of exercise-induced fiber type transformation, mitochondrial biogenesis, and angiogenesis in skeletal muscle

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processes are analogous to the control of the mechanical, power generation, and fuel supply components of a mechanical engine. A precise control of each individual component in a highly coordinated manner is a prerequisite to an efficient, controllable engine. Skeletal muscle is such a “biological engine.” Several excellent reviews have previously covered this topic (for reviews, see 12, 65, 117, 136, 145, 181). Here, we review the most recent findings in genetically engineered animal models focusing on the molecular signaling network responsible of exercise-induced adaptations.

FIBER TYPE TRANSFORMATION

The experiments of inducible phenotypic changes in skeletal muscle in a cross-innervation study by Buller et al. 50 years ago (14) triggered intense interests in elucidating the underlying mechanisms. The most investigated area is exercise-induced fiber type transformation as this phenotypic property correlates with physical performance (72) and the incidence of chronic diseases (62). Numerous studies have clearly demonstrated that endurance exercise readily promotes transformation from a glycolytic to an oxidative phenotype within the fast-twitch fiber types (type IIb/IId/x to IIa) (5, 49). It is important to note that although MHC I and IIa isoforms coexist in human skeletal muscle fibers following endurance training (81, 150), and professional athletes with extremely intense training for years have increased type I fibers (30, 150), exercise-induced transformation to type I fibers remains to be experimentally confirmed.

The advancement in molecular genetics has empowered recent research in exercise-induced fiber type transformation. An elegant study by Chin et al. (23) marked the beginning of intense research in intracellular signaling-transcription coupling that decodes exercise-induced skeletal muscle adaptation. They showed that rhythmic muscle contractions activated the Ca\(^{2+}\)/calmodulin-dependent serine/threonine protein phosphatase, calcineurin (also called protein phosphatase 3). The overall hypothesis is that activation of calcineurin promotes the expression of slow-twitch muscle genes through dephosphorylation and activation of the nuclear factor of activated T-cells (NFAT) (23). In the initial and subsequent studies, inhibition of the calcineurin-NFAT pathway by cyclosporine A (CsA), FK506, calcineurin inhibitory protein (CAIN/CABIN-1), or peptide VIVIT resulted in reduced percentage of slow-twitch fibers and/or blocked slow-twitch muscle promoter activity and gene expression in rodents (103, 108, 154, 170). Later, imaging experiments of inducible phenotypic changes in skeletal muscle focusing on the molecular signaling network responsible for exercise-induced adaptations.

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In soleus muscle (114). Importantly, deletion of the calcineurin-calcineurin-NFAT pathway in maintaining slow-twitch muscle (103, 156). Consistent with an essential function of the cal-cineurin-dependent and -independent mechanisms. Low-frequency electrical stimulation in skeletal muscle (95) and inhibited the MHC IIb (Myh4) promoter activity (103). Furthermore, gene disruption of calcineurin inhibitory protein calsarcin in a glycolytic muscle resulted in a shift toward slow-twitch, oxidative phenotype along with enhanced NFAT activity and increased expression of RCAN 1–4 (38). Thus enhanced calcineurin-NFAT signaling is sufficient to promote fiber type transformation toward an oxidative phenotype. It should be noted that none of these studies have determined whether exercise-induced IIb/IId/x-to-IIa fiber type transformation is dependent on the calcineurin-NFAT signaling pathway.

Ca\(^{2+}\)/calmodulin-dependent protein kinases (CaMK) may also play a role in exercise-induced genetic reprogramming in adult skeletal muscle. Several studies showed synergy between calcineurin and CaMKIV in stimulating the activities of transcriptional factors, myoeyen enhancer factor 2 (MEF2) and NFAT (189–191); however, other studies showed that CaMKIV is not expressed in skeletal muscle and therefore not required for exercise-induced IIb/IId/x-to-IIa fiber type transformation (4). CaMKII is known to decode frequency-dependent signal (31, 140) and be activated by endurance exercise (162). However, due to the complexity and redundancy of the CaMKII proteins, loss-of-function approach has not been employed to ascertain their function in exercise-induced fiber type transformation.

The mechanism by which CaMK activates MEF2 proteins was elucidated by several elegant studies. Class II histone deacetylases, such as HDAC4, HDAC5, and HDAC9, interact and inhibit MEF2, resulting in repression of the target genes. CaMK prevents the formation of MEF2-HDAC complexes, and induces nuclear export of HDAC4 and HDAC5 through phosphorylation (105) and 14-3-3-mediated nuclear export (106). In fact, low-frequency electrical stimulation-induced nuclear export of HDAC4 is dependent on CaMKII activity (157). More definitive evidence came from a study in which class II HDAC proteins failed to accumulate in oxidative soleus muscle (124), and compound deletion of the Hdac3 and Hdac9 genes led to increased type I and IIa fibers in soleus and plantaris muscles, whereas muscle-specific inducible expression of a nonphosphorylatable HDAC prevented voluntary running-induced fiber type transformation (124). Furthermore, deletion of the Mef2ca and Mef2d genes resulted in reduced percentage of type I fibers in soleus muscle, and skeletal muscle-specific overexpression of a constitutively active

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MEF2C chimera protein led to increased type I fibers and oxidative phenotype (124). These findings support the view that CaMK activates MEF2 through derepression of HDACs in fiber type transformation.

A broad kinase inhibitor, staurosporine, led to increased nuclear accumulation of HDAC4 in the presence of the CaMKII inhibitor KN62 in cultured muscle fibers (157), suggesting that a kinase other than CaMKII is involved in HDAC shuffling. Protein kinase D1 (PKD1), originally called PKC, is a member of a family of diacylglycerol (DAG)-stimulated serine/threonine protein kinases (77) that lacks the C2 domain responsible for Ca^{2+} sensitivity (77, 173) and is activated by PKC-mediated phosphorylation in response to phorbol ester and diacylglycerol (174, 197). Kim et al. (80) showed that PKD1 is predominantly expressed in type I myofibers, and muscle-specific overexpression of a constitutively active form led to increased percentage of type I fibers, enhanced myoglobin, Ild/x, and Ila MHC protein expression, and improved fatigue resistance (80). Interestingly, these phenotypic changes are not accompanied by enhanced mitochondrial biogenesis, whereas genetic deletion of PKD1 increases susceptibility to fatigue with no significant impact on fiber type composition (80). The functional role of PKD1 in exercise-induced fiber type transformation remains to be determined.

Metabolic cues may play important functional roles in skeletal muscle adaptation. AMP-activated protein kinase (AMPK), sensitive to metabolic stress and energy deprivation (59), is activated by contractile activity in skeletal muscle and has been linked to metabolic adaptations (39, 54, 183, 184). Although there is ample evidence that AMPK activation promotes mitochondrial biogenesis in skeletal muscle (42, 196), muscle-specific expression of a dominant-negative form of AMPKα2 blocked voluntary running-induced Iib-to-Ild/x/Ila fiber type transformation without affecting the induction of PGC-1α expression and mitochondrial enzyme activity (137). Conversely, muscle-specific expression of an active mutant of AMPKγ1 leads to a marked increase in type Ila/x fibers in triceps muscle (137). Therefore, AMPK appears to be functionally important for exercise-induced fiber type transformation and is sufficient, but not necessary, for mitochondrial biogenesis.

PGC-1α plays a pivotal role in endurance exercise-induced muscle adaptation. Skeletal muscle-specific PGC-1α overexpression led to increased percentage of slow-twitch myofibers (91) and improved volitional exercise capacity in mice (17). Global or muscle-specific deletion of the Pgc-1α (Ppard) gene led to a reduced oxidative phenotype in skeletal muscle (55, 89, 92) with only a moderate decrease of type I myofibers. Conversely, muscle-specific deletion of the Pgc-1c gene or the p38γmitogen-activated protein kinase (MAPK) (Mapk12) gene, an upstream stress-activated kinase for PGC-1α, led to normal fiber type transformation (type Iib/IId/x to Ila), but attenuated mitochondrial biogenesis and angiogenesis (43, 123). Finally, recent evidence based on the characterization of mice with combined PGC-1α/β deficient skeletal muscle indicates that the PGC-1 coactivators are dispensable for fiber type determination (194). These studies provide evidence for segregated signaling pathways in control of exercise-induced contractile and metabolic adaptations. PGC-1α may influence the maintenance of slow-twitch, type I fibers but is not required for exercise-induced fiber type transformation.

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent nuclear receptors. Muscle-specific overexpression of an active form of the PPARβ/δ gene (Ppard) led to an increased percentage of type I myofibers with improved volitional exercise capacity in mice (177), while deletion of the PPARβ/δ gene resulted in reduced slow-twitch muscle gene expression (153). Consistent with a function of PPARβ/δ in slow muscle maintenance, mice with gene deletion and overexpression of the RIP40 corepressor, which interacts with and inhibits multiple nuclear receptors, have increased and decreased type I myofibers, respectively (155). It remains to be demonstrated that exercise-induced fiber type transformation is dependent on PPARβ/δ function.

It is extremely important to consider two technical issues in studying exercise-induced fiber type transformation. First, many studies employed myofibrillar actomyosin ATPase histochemistry for determination of fiber type composition (23, 80, 91, 113, 124, 177, 189, 191). This analysis appears to be significantly different from antibody-based analyses. For example, immunoblot and immunofluorescence analyses have shown clear evidence of increased type Ila MHC protein and type I fibers in mouse plantaris muscle following voluntary running with no evidence of increased type I MHC protein and type I fibers (4, 43, 123, 137), whereas metachromatic ATPase staining repeatedly showed significant increases of type I fibers in the same muscle following voluntary running (124) and other interventions with increased contractile activities (23, 80, 91, 113, 114, 177, 189, 191). Since myofibrillar actomyosin ATPase histochemistry is vulnerable to subtle changes in pH and requires staining of serial sections, caution should be taken when interpreting the data, particularly with regard to changes in type I fibers. Second, although the molecular and pharmacological approaches to augment or reduce the expression of a gene of interest are powerful for studying fiber type regulation, these interventions may lead to changes in fiber type composition due to their impact on skeletal muscle development and/or fiber type maintenance instead of exercise-induced adaptation. An altered fiber type composition does not warrant a conclusion of gene function in exercise-induced fiber type transformation. A physiological exercise model needs to be employed as was done in some of the aforementioned studies (4, 43, 123, 124, 137).

MITOCHONDRIAL BIOGENESIS

Mitochondria are critical for aerobic ATP synthesis and proper cell function. Mitochondrial DNA (mtDNA) encodes 13 subunits of the electron transport system, 22 tRNAs, and 2 ribosomal RNAs. The vast majority of proteins in oxidative metabolism in mitochondria are nuclear encoded and subsequently transported to the mitochondria (25, 26, 149, 175). Mitochondrial quantity and quality in skeletal muscle are not only important for performance but also relevant to health. Mitochondrial dysfunction in muscle, likely resulting from inactivity (169), is associated with muscle atrophy (138); diabetes (99, 152), and aging (32, 35). Conversely, upregulation of mitochondrial mass and function, also referred to as mitochondrial biogenesis, is instrumental in exercise training-induced improvement of muscle function and whole body metabolic homeostasis (85, 93).
Holloszy (63) in 1967 first showed that endurance exercise training led to mitochondrial biogenesis in skeletal muscle. This original study and several subsequent studies set the stage for investigating molecular mechanisms involved in exercise-induced adaptation (61, 64, 146). Recent studies showed that resistance and interval training regimens could also lead to skeletal muscle mitochondrial biogenesis in humans (10, 15, 44). Great progress has been made since the identification of PGC-1α in brown fat (129). It is now known that PGC-1α interacts with nuclear transcription factors, such as PPARs (112), estrogen-related receptor α (ERRα) (70, 71, 129), thyroid receptor (TR) (129), nuclear respiratory factor 1 (NRF1) (192), NRF2 (109), and MEF2 (57, 107) in stimulating the expression of nuclear-encoded mitochondrial genes. PGC-1α coactivation of NRF1 and NRF2 also induces mitochondrial transcription factor A (TFAM) expression (192), which regulates mtDNA transcription. Therefore, PGC-1α coordinates the expression of both nuclear- and mitochondrial-encoded genes in mitochondrial biogenesis (128, 148, 179).

*Pgc-1α* mRNA and protein are readily upregulated by endurance exercise (9, 48, 74, 122, 142, 166). However, it has only been determined recently whether PGC-1α is required for exercise-induced mitochondrial biogenesis. Leick et al. (88) observed that mice with global disruption of the *Pgc-1α* gene (*PGC-1α KO*) are incapable of upregulating cytochrome c (*Cyc*) mRNA in soleus muscle after an acute bout of treadmill running. Conversely, these animals present normal upregulation of *Cyc*, cytochrome oxidase 1 (*Cox1*), aminolevulinate synthase 1 (*Alas1*) mRNA and protein in response to endurance exercise training. Adhiketty et al. (1) reported that *PGC-1α KO* mice have normal voluntary running activity despite reduced basal mitochondrial respiratory function and that this limitation could be reversed by endurance exercise training. More recently, Leick et al. reported that exercise training-induced attenuation of age-associated decline in citrate synthase (CS) activity in skeletal muscle is absent in *PGC-α* knockout mice (87), suggesting a critical role for PGC-1α in skeletal muscle in aging. These contrasting findings may be related to compensatory adaptations in different tissues due to the global disruption of the *Pgc-1α* gene. In fact, PGC-1α knockout mice have lesions in the central nervous system causing hyperactivity and circadian rhythm abnormalities (56, 92, 94). To avoid these complications, muscle-specific *Pgc-1α* knockout mice (*PGC-1α MKO*) were employed. These mice have reduced locomotor activity and exercise tolerance, impaired muscle function, and reduced oxidative capacity in skeletal muscles (55, 56); however, voluntary running-induced CYC and COXIV protein expression in plantaris muscle was significantly attenuated in PGC-1α MKO (43). These findings provide strong evidence for a critical role for PGC-1α in exercise-induced mitochondrial biogenesis in skeletal muscle but also suggest some redundancy.

Considering the central role of PGC-1α in exercise-induced mitochondrial biogenesis, it is important to know how PGC-1α is regulated. Current evidence supports a fundamental role of p38γ MAPK. First, different exercises cause activation of p38 MAPK in skeletal muscle in animals and humans (47, 180, 187), phosphorylating and activating PGC-1α (127), MEF2 (195), and activating transcription factor 2 (ATF2) (21). In a series of studies, Akimoto et al. demonstrated that p38 MAPK acts through MEF2 and ATF2 in stimulating the *Pgc-1α* promoter, and muscle specific overexpression of an upstream MAPK kinase (MKK6) promotes the expression of PGC-1α and mitochondrial proteins without a significant change in fiber type composition (3). *Pgc-1α* transcriptional activation requires functional interaction of ATF2 with the *Pgc-1α* promoter (2), and forced expression of a kinase dead form of PKD1 or a nonphosphorylatable HDAC5 prevents upregulation of the *Pgc-1α* gene induced by contractile activity (2). In addition, Wright et al. (188) reported that p38 MAPK and ATF2 phosphorylation occur in parallel with PGC-1α nuclear translocation after an exhaustive bout of swimming exercise and that these events coincide with increases in Cs and Cyc mRNAs before the upregulation in PGC-1α protein. More recently, Pogozelski et al. demonstrated that mice with muscle-specific deletion of the p38γ gene (*Mapk12*) have attenuated upregulation of PGC-1α and markers of mitochondrial biogenesis (i.e., CYC and COXIV) in response to voluntary running with similar phenotype to the PGC-1α MKO mice (43), but not in p38α or p38β MKO mice (123). These findings underscore that the p38γ MAPK-PGC-1α regulatory axis is required for exercise-induced mitochondrial biogenesis in skeletal muscle. Therefore, PGC-1α activation occurs before the induction of PGC-1α protein expression, which may be mediated by p38 MAPK-dependent phosphorylation. PKD1- and p38γ-mediated activation of ATF2 and MEF2 and their functional interaction with the *Pgc-1α* promoter are required for the exercise-induced PGC-1α expression in skeletal muscle.

Exercise elicits other intracellular signals contributing to PGC-1α regulation and mitochondrial biogenesis. Transgenic overexpression of a constitutively active calcineurin in skeletal muscle increases myoglobin, GLUT4, pyruvate dehydrogenase kinase 4 (PDK4), mitochondrial enzymes, and PGC-1α expression (113, 143) with enhanced lipid oxidation in glycolytic muscles (98, 143) and improved volitional exercise capacity (76) similar to muscle-specific PGC-1α transgenic mice (17, 91, 179). In contrast, animals treated with the calcineurin inhibitor, CsA, have normal upregulation of PGC-1α and mitochondrial enzymes in response to endurance exercise (41). A direct role of the calcineurin-NFAT pathway remains to be ascertained in the upregulation of PGC-1α and metabolic adaptations in skeletal muscle in the context of exercise.

CaMKs have been shown to act synergistically with calcineurin in activating slow muscle gene expression in myocytes (190), and forced expression of a constitutively active form of CaMKIV in skeletal muscle in transgenic mice increases expression of the *Pgc-1α* gene and enhances mitochondrial biogenesis along with reduced fatigability of EDL muscle (189). However, genetic disruption of the *Camk4* gene did not prevent exercise-induced upregulation of PGC-1α (4), and CaMKIV is not detectable in skeletal muscle (141). CaMKII is the main CaMK isoform in skeletal muscle (140, 141) and is activated by endurance exercise (130, 140, 141, 162), and pharmacological inhibition of CaMKII blocks exercise- and intracellular calcium-induced Glut4 gene transcription (110, 162). Due to the presence of multiple isoforms, verification of functional importance of this protein kinase has not been obtained in exercise-induced mitochondrial biogenesis models.

AMPK is activated by contractile activity (39, 54, 58, 183, 184, 186), and multiple mechanisms have been postulated for AMPK-mediated PGC-1α regulation. Exercise-induced AMPK activation is associated with HDAC5 phosphorylation and nuclear export...
in human skeletal muscle (104). PGC-1α phosphorylation at threonine-177 and serine-338 (75) and subsequent deacetylation by histone deacetylase SIRT1 (19) are required for AMPK action, including upregulation of PGC-1α and mitochondrial genes (19, 74). Endurance exercise in humans can also stimulate SIRT1 (28, 40), and a single bout of exercise induces PGC-1α deacetylation in glycolytic muscles along with up-regulation of PGC-1α target genes, such as Pdk4, Glut4, and carnitine palmitoyl transferase 1B (Cpt1b) (18), where SIRT1 activity, rather than expression, appears to play a prominent role (50). On the contrary, muscle-specific expression of a dominant-negative form of AMPKα2 fails to block the induction of PGC-1α expression and mitochondrial enzyme activity (136), and genetic deletion of functional AMPK isoforms fails to block exercise-induced PGC-1α gene expression in skeletal muscle (78). More recently, gain-of-function mutation of regulatory γ3 subunit of AMPK in mouse glycolytic fibers presents an increased expression of PGC-1α and mitochondrial biogenesis (42), and exercise-induced PGC-1α activation (deacetylation) is blunted in AMPKγ3 knockout mice (20). Therefore, the issue regarding the role of AMPK in exercise-induced mitochondrial biogenesis in skeletal muscle remains controversial.

Skeletal muscle contraction increases the production of reactive oxygen species (ROS) (27, 79, 102, 120, 132, 159). Production of hydrogen peroxide (H2O2) in contracting skeletal muscle has been shown to be required for PGC-1α upregulation (186), and increased H2O2 production has been proposed as a mechanism by which lactate, a by-product of glycolysis, upregulates PGC-1α (60). ROS may be functionally important for endurance exercise-induced PGC-1α expression and metabolic adaptation in skeletal muscle (45, 79, 133). Pharmacological inhibition of xanthine oxidase (XO) with allopurinol suppresses the exercise-induced upregulation in PGC-1α in parallel to reduced activation (i.e., phosphorylation) of p38 MAPK. These findings suggest that ROS, most likely H2O2 as a by-product of XO, acts upstream of p38 MAPK in the induction of PGC-1α in response to contraction in vivo (79). Interestingly, a recent study showed that antioxidant supplementation in humans does not alter endurance training adaptation (193), clearly indicating the complexity in the role of redox signaling in muscle adaptation.

Finally, micro RNA-dependent regulation of PGC-1α in response to exercise has also been postulated. An acute bout of endurance exercise downregulates the expression of miR-23, a putative regulator (inhibitor) of PGC-1α translation, which is negatively correlated with PGC-1α mRNA after exercise (144). This is clearly a fertile area of research, which will provide new insights into exercise-induced mitochondrial biogenesis in the near future.

The precise coordination of all the aforementioned regulatory pathways relevant to exercise training and their importance to PGC-1α expression and mitochondrial biogenesis remains to be fully elucidated. There is no doubt that the mechanisms responsible for mitochondrial biogenesis in response to exercise are extremely elegant and complex and will likely provide a venue for investigation for years to come.
ANGIOGENESIS

Exercise requires an increase in blood flow to the skeletal muscle to provide additional supply of oxygen and nutrients, which cannot solely be achieved by an increase in the cardiac output (7). The major vascular adaptations in skeletal muscle in response to endurance exercise include an increase in flow capacity due to an increase in the radius of large-caliber vessels and an increase of muscle capillarity through angiogenesis (for review, see 126). Here we focus on the adaptive process of angiogenesis, an expansion of the capillary network from preexisting capillaries that improves gas and nutrient exchange in peripheral tissues, which has been speculated to contribute significantly to improved physical performance (147). The expansion of the capillary network occurs primarily as intussusception, which involves the longitudinal division of the capillary within the lumen, and sprouting, which refers to the branching out of endothelial cells from an existing capillary (126). Endurance exercise-induced angiogenesis is thought to be mediated by a combination of growth factors, hypoxia and shear and mechanical stresses (126).

Early studies showed that exercise training induces an increase in capillarity in skeletal muscle (22, 29, 100), which could be recapitulated by chronic motor nerve stimulation (69, 111, 131). The fact that capillary-to-fiber ratio differs among different types of muscle fibers (73, 178) and exercise training results in fiber type-dependent angiogenic responses (52, 53, 178) strongly suggests that the signals for angiogenesis originate from within the contracting muscle fibers. In fact, a single bout of endurance exercise is sufficient to induce mRNA expression of multiple angiogenic growth factors and related receptors in skeletal muscle, including vascular endothelial growth factor (Vegfa) mRNA (13, 51), in a fiber type-specific manner (96). Existing evidence strongly supports that muscle fiber expression and secretion of VEGF promote angiogenesis through its paracrine effects. Of particular interest are the findings that treadmill running in rats induces significant increases in Vegfa mRNA in type IIB myofibers (11), and voluntary running in mice induces angiogenesis in type IIB/IId/x fibers before switching to type IIA fibers (178). The findings raise the question as to whether induced expression of VEGF plays an essential role in exercise-induced angiogenesis in skeletal muscle and whether exercise-induced angiogenesis dictates fiber type transformation.

In addressing the functional importance of VEGF, Lloyd et al. (97) showed that treadmill running-induced angiogenesis in skeletal muscle is partially blocked by the employment of a VEGF receptor inhibitor, ZD4190, in rat in vivo. It is not clear if the incomplete inhibition of exercise-induced angiogenesis is due to the partial dependency of this process on VEGF function or the partial potency of the inhibitor in vivo. More recently, it was reported that skeletal muscle-specific deletion of the Vegfa gene led to significantly reduced capillarity in skeletal muscle with compensatory increases in oxidative enzymes, but reduced volitional exercise capacity on the treadmill (115). More importantly, muscle deficiency in VEGF attenuates exercise training-induced angiogenesis and improvement of physical performance (116). These findings strongly support the notion that exercise-induced VEGF expression from contracting muscle fibers plays a pivotal role in directing angiogenesis around them through paracrine-like actions.

A remaining question is what signaling cascade within the muscle fibers decodes muscle contractile activity signals in regulating VEGF expression. PGC-1α has recently emerged as one of the key regulators of angiogenesis in skeletal muscle under the condition of hypoxia in a hypoxia-inducible factor (HIF)-independent manner (8). In this process, PGC-1α activates the orphan nuclear receptor estrogen-related receptor-α (ERRα) (8). Whole body knockout of the Pgc-1α gene led to reduced VEGF protein expression and blunted response to acute and chronic exercise training (86). More convincing data of the functional importance of PGC-1α in exercise-induced angiogenesis in skeletal muscle were obtained in mice with muscle-specific deletion of the Pgc-1α gene, showing significant attenuation of contractile activity-induced VEGF expression and exercise-induced angiogenesis (24, 43). Mechanistically, the functional role of PGC-1α in exercise-induced VEGF expression and angiogenesis is dependent on the upstream p38 MAPK (123) and the downstream ERRα (24). Interestingly, transgenic mice with muscle-specific expression of an inactive form of AMPK have lower capillarity compared with the wild-type littermates, but have normal induced angiogenesis in response to voluntary running exercise (198).

SUMMARY

In summary, a sophisticated signaling-transcription network within individual muscle fibers mediates exercise-induced skeletal muscle adaptation (Fig. 1). Current experimental evidence from various genetically engineered animal models supports the view that multiple regulatory factors sense Ca\(^{2+}\) (calcineurin and CaMK) and metabolic stress (AMPK and PKD1) converging on transcriptional factors (NFAT and PKD1) and repressors (HDACs) in mediating endurance exercise-induced slow-twitch muscle gene expression and type IIB/IId/x to IIA fiber type transformation. On the other hand, oxidative and metabolic stresses induced by contractile activity stimulate PGC-1α activity and expression, which in turn promote mitochondrial biogenesis through interactions with transcription factors (NRF1, NRF2, and Tfam) on nuclear-encoded and mitochondria-encoded genes. PGC-1α also promotes angiogenesis through an interaction with ERRα in activating the gene that encodes VEGF. Continued research efforts using more precisely controllable animal models, such as tissue-specific inducible transgenic and knockout mice, will elucidate the highly coordinated remodeling processes in skeletal muscle and will unveil the mysteries of this beautiful “biological engine” in the body.

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