

Transcriptional Control of Mitochondrial Biogenesis and Function

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Abstract

Mitochondria play central roles in energy homeostasis, metabolism, signaling, and apoptosis. Accordingly, the abundance, morphology, and functional properties of mitochondria are finely tuned to meet cell-specific energetic, metabolic, and signaling demands. This tuning is largely achieved at the level of transcriptional regulation. A highly interconnected network of transcription factors regulates a broad set of nuclear genes encoding mitochondrial proteins, including those that control replication and transcription of the mitochondrial genome. The same transcriptional network senses cues relaying cellular energy status, nutrient availability, and the physiological state of the organism and enables short- and long-term adaptive responses, resulting in adjustments to mitochondrial function and mitochondrial biogenesis. Mitochondrial dysfunction is associated with many human diseases. Characterization of the transcriptional mechanisms that regulate mitochondrial biogenesis and function can offer insights into possible therapeutic interventions aimed at modulating mitochondrial function.

Oxidative phosphorylation (OxPhos):

the process of ATP generation by five inner mitochondrial membrane complexes that oxidize NADH and FADH₂—transferring electrons to molecular oxygen and pumping protons across the membrane—and use the ensuing electrochemical gradient to phosphorylate ADP

Mitochondrial transcription factor A (TFAM) and transcription factor B1/B2,

mitochondrial (TFB1M/TFB2M): mitochondrial DNA-binding proteins that are encoded by the nuclear genome and that control transcription and replication of the mitochondrial genome

Nuclear respiratory factor-1 (NRF-1) and GA-binding protein (GABP or NRF-2):

nuclear DNA-binding factors that regulate transcription of OxPhos and mitochondrial transcription/import genes

Peroxisome proliferator-activated receptors (PPAR α , PPAR δ , and PPAR γ):

nuclear receptors that regulate genes involved in lipid transport and metabolism in response to fatty acid-derived ligands

INTRODUCTION

Mitochondria are essential eukaryotic organelles that process glycolysis and lipolysis products to generate, via oxidative phosphorylation (OxPhos), the cellular energy carrier ATP. In addition, mitochondria contain enzymes critical for multiple biosynthetic processes—including lipid, cholesterol, nucleotide, heme, and steroid synthesis—and play important roles in amino acid metabolism and ion homeostasis. Mitochondria also signal, via reactive oxygen species (ROS) and Ca²⁺, and are critical regulators of cell death pathways. Given their central bioenergetic, metabolic, and signaling roles, tight regulation of mitochondrial mass and mitochondrial function is vital. Notably, mitochondrial mass, function, and morphology differ significantly in different cell types and are dynamically regulated in response to a wide range of physiological cues (e.g., physical activity, nutrient availability, temperature, circadian cues, exposure to infectious agents).

Mitochondrial biogenesis is a complex process that requires the synthesis, import, and incorporation of proteins and lipids to the existing mitochondrial reticulum, as well as replication of the mitochondrial DNA (mtDNA). The mitochondrial proteome comprises ~1100 to 1500 proteins (1). The vast majority of them are encoded by nuclear genes, and we refer to them in this review as simply mitochondrial genes. The mitochondrial genome encodes only 13 proteins, a small but essential group because all 13 are OxPhos components. Comparison of mitochondria across different tissues shows significant concordance between protein levels and mRNA levels (2), suggesting that mitochondrial mass in a cell is controlled largely, although not solely, at the level of transcription. Thus, mitochondrial biogenesis requires the coordinated transcription of the large number of mitochondrial genes in the nucleus, as well as of the fewer but essential genes in mitochondria. The coordination of the two genomes is achieved by nucleus-encoded mitochondrial proteins, such as TFAM, TFB1M, and TFB2M,

that control the transcription and replication of mtDNA and are induced in response to signals promoting mitochondrial biogenesis (3–5).

Mitochondrial biogenesis is a long-term adaptive response and is not always required to meet transiently increased energetic needs. Transient changes in energy demands can be met by increases in the expression of a subset of mitochondrial genes or of critical regulators and by the enhancement of mitochondrial function. Similarly, expression of subsets of mitochondrial genes is important for the specialized functions of mitochondria in different tissues (e.g., steroid synthesis in adrenal gland or cholesterol in liver) and different physiological states [e.g., expression of uncoupling proteins (UCPs) upon exposure to cold or after a meal, leading to increased thermogenesis]. Strikingly, ~50% of the mitochondrial genes are expressed in a tissue-specific manner (2), suggesting that a large part of the mitochondrial proteome is dedicated to specialized functions.

The regulation of mitochondrial biogenesis and function presents a transcriptional challenge. Regulatory mechanisms must provide for the induction of the broad mitochondrial gene set and at the same time enable tissue- and signal-specific inductions of gene subsets. Pioneering studies by Scarpulla and colleagues started addressing this challenge by identifying transcription factors that recognize conserved motifs at the promoters of mitochondrial OxPhos genes, leading to the identification of nuclear respiratory factor (NRF)-1 and GA-binding protein (GABP) (also known as NRF-2) (5). In parallel, efforts in the nuclear receptor field to elucidate the function of orphan receptors led to the realization that the peroxisome proliferator-activated receptors (PPARs) control mitochondrial gene subsets with roles in fatty acid oxidation (FAO) and uncoupling (5, 6). A major breakthrough in our understanding of how the different gene subsets are coordinately regulated was the identification of PPAR γ coactivator-1 α (PGC-1 α) as a transcriptional coactivator of NRF-1, GABP, and PPARs and the appreciation of the ability of PGC-1 α to integrate physiological

signals and to enhance mitochondrial biogenesis and oxidative function (7, 8). PGC-1 α also led to the identification of related coactivators [PGC-1 β and the PGC-1-related coactivator (PRC)] and other transcription factors [the nuclear receptors ERRs (estrogen-related receptors)] that function in the same or similar pathways (9, 10). This review discusses the transcriptional regulators that control mitochondrial biogenesis and function and the mechanisms by which these regulators sense energetic and metabolic demands associated with different physiological states.

TRANSCRIPTIONAL REGULATORS OF MITOCHONDRIAL BIOGENESIS AND FUNCTION

Overview

Expression of the large number of genes required for mitochondrial biogenesis and function is under the control of a network of nuclear DNA-binding transcription factors and coregulators (**Figure 1**). This network allows for broad and robust activation of the mitochondrial biogenesis program in response to varied physiological cues, as well as specialized tissue- or signal-specific modifications of mitochondrial gene expression and function. In this section, we first discuss the DNA-binding factors, which target overlapping but distinct sets of mitochondrial genes. Notably, each of these factors targets not only mitochondrial genes but also genes with nonmitochondrial functions, which poses the interesting question of how the factors sort out mitochondrial and non-mitochondrial roles. For each factor, we review mechanisms and signals that regulate their activity and expression so as to provide the context in which they contribute to mitochondrial gene expression. Next, we discuss the transcriptional coregulators that enhance or repress the activity of the DNA-binding factors. The ability of the coregulators to interact with multiple DNA-binding factors enables the integration of signals into the broad mitochondrial

gene expression program, as best illustrated for PGC-1 α .

DNA-Binding Transcription Factors

Nuclear respiratory factor-1, regulator of OxPhos and mtDNA replication/transcription factors. NRF-1 was identified as a transcription factor binding to a conserved regulatory site of the *cytochrome c* promoter (11). NRF-1 binding sites are evolutionarily conserved in the proximal promoters of many mitochondrial genes (5). Accordingly, NRF-1 activates the expression of OxPhos components, mitochondrial transporters, and mitochondrial ribosomal proteins. In addition, NRF-1 regulates expression of *Tfam*, *Tfb1m*, and *Tfb2m* and thereby coordinates the increased expression of nuclear mitochondrial genes with increases in mtDNA replication and expression (5). NRF-1 may also affect expression of mitochondrial and metabolic genes via indirect mechanisms, e.g., by inducing expression of the transcription factor MEF2A, which activates *Cox* genes, *Glut4*, and *PGC-1 α* (12).

Silencing of NRF-1 leads to a significant suppression of mitochondrial target genes, suggesting that endogenous NRF-1 is constitutively active and important for the basal expression of mitochondrial targets (13–15). Nevertheless, NRF-1 activity can also be regulated by phosphorylation and/or interactions with PGC-1 α , PGC-1 β , PRC, and cyclin D1. Phosphorylation of NRF-1 occurs upon exposure of quiescent fibroblasts to serum (which correlates with induction of *Cycs*) and exposure of hepatoma cells to oxidants (which leads to an NRF-1-dependent induction of *Tfam*). Depending on the context, phosphorylation affects NRF-1 translocation to the nucleus, DNA binding, and/or transcriptional activity (5). Physical interactions of the PGC-1 family members with NRF-1 enhance NRF-1-dependent gene expression (8, 16, 17). Finally, cyclin D1, which suppresses mitochondrial biogenesis, associates with NRF-1 and represses NRF-1 activity (14, 18).

Fatty acid oxidation (FAO) or β -oxidation:

the mitochondrial degradation of fatty acids by a cycle of oxidation, hydration, oxidation, and thiolysis reactions, generating acetyl CoA and reducing equivalents (NADH and FADH₂)

PPAR γ coactivators [PGC-1 α , PGC-1 β , and PGC-1-related coactivator (PRC)]:

coactivators of ERRs, PPARs, NRF-1, GABP, and other transcription factors

Estrogen-related receptors (ERR α , ERR β , and ERR γ):

orphan nuclear receptors that regulate a broad set of mitochondrial genes

signals regulate NRF-1 activity directly, and not simply NRF-1 expression, is not yet known.

In support of a role for NRF-1 as a critical transcription factor for expression of mitochondrial genes, NRF-1 null animals show early embryonic lethality, and NRF-1^{-/-} blastocysts have reduced mtDNA content and mitochondrial membrane potential (27). Although NRF-1 seems necessary for mitochondrial biogenesis, its expression alone is not sufficient to drive this program. Transgenic overexpression of NRF-1 in muscle increases expression of select NRF-1 targets but does not enhance respiratory capacity, suggesting that activation of parallel transcription pathways must complement NRF-1 during exercise-induced muscle mitochondrial biogenesis (28).

Although identified as a transcriptional regulator of mitochondrial genes, NRF-1 also regulates many genes with nonmitochondrial functions and in particular genes with roles in cell-cycle control and proliferation (13). The breadth of NRF-1 function is the likely explanation for why NRF-1 null mice die at an earlier stage [embryonic day (E)3.5–6.5] than do mice lacking the mtDNA replication factor TFAM (E8.5–10.5). In addition, NRF-1 may have developmental functions, as shown for the *Drosophila* and zebra fish NRF-1 orthologs, which play roles in nervous system and muscle development (5).

GA-binding protein. Scarpulla and colleagues (29) identified GABP (also referred to as NRF-2) as an activator of the *CoxIV* promoter. It is a heterotetramer of two distinct and unrelated subunits: GABP α , which contains an ETS domain and serves as the DNA-binding subunit, and GABP β (β 1 or β 2, encoded by two homologous genes), which contains a transcriptional activation domain. Functional GABP binding sites have been identified in the proximal promoters of many mitochondrial genes, including ones for OxPhos components, mitochondrial import, and *Tfam*, *Tfb1m*, and *Tfb2m* (which encode the mtDNA transcription factors) (5). Moreover, motifs with the consensus site for GABP, although

common to many promoters, are enriched in a set of coregulated OxPhos genes that show reduced expression in diabetes (30). Consistent with a role of GABP for OxPhos and other mitochondrial gene expression, knockdown of GABP α expression in cells leads to the reduced expression of all 10 nuclear-encoded *Cox* genes (as well as *Tfam*, *Tfb1m*, and the import machinery component *Tomm20*) and a 20% decrease in cellular COX activity (31).

The GABP protein integrates signaling information relevant to mitochondrial biogenesis and function. GABP α and GABP β become phosphorylated in muscle cells treated with neuregulin, a factor that promotes expression of OxPhos genes (32, 33). In addition, phosphorylated GABP together with host-cell factor 1 (HCF1) recruit the transcriptional coactivators PGC-1 α and PRC, which further enhance GABP-dependent transcription (33, 34). The third member of the PGC-1 family, PGC-1 β , also interacts with HCF1 (17), suggesting that it may also coactivate GABP.

GABP expression is broad (35) and regulated by developmental and physiological signals that impact mitochondria. GABP α levels increase at times of mitochondrial biogenesis during brown adipose tissue (BAT) development in mice and during brown adipocyte differentiation in vitro (36). Likewise, GABP α is induced in myotubes by Ca²⁺ (19) and in skeletal muscle by exercise (22, 25). In liver, GABP α is induced by treatment with thyroid hormone, which enhances respiratory rate (37). Conversely, GABP α expression is reduced under pathological conditions in which mitochondrial gene expression is dysregulated, such as a rat model of congestive heart failure (38). The GABP α promoter contains regulatory binding sites for the nuclear receptor ERR α and for GABP itself, which enable transactivation of the promoter by PGC-1 α (30). Thus, signals that activate PGC-1 α , ERR α , or GABP are also likely to enhance GABP α expression.

Although often discussed as a transcription factor for mitochondrial genes, GABP has much wider functions, regulating cell-cycle, ribosomal, myeloid, and neuromuscular

junction genes (39). Consistent with a wide range of targets, *Gabpa* disruption in mice results in preimplantation lethality (35), whereas immune-specific loss of GABP α reveals a critical role in B cell development and function (40). Mice lacking GABP α specifically in muscle show no overt muscle defects, with normal distribution and appearance of mitochondria, suggesting that GABP is not essential for muscle mitochondrial biogenesis (41, 42).

Peroxisome proliferator-activated receptors (PPAR α , PPAR γ , and PPAR δ): regulators of lipid metabolism. PPARs are nuclear receptors that sense lipids and control lipid homeostasis. PPAR α and PPAR δ are primarily regulators of lipid oxidation, whereas PPAR γ promotes lipid synthesis and storage. The three receptors have distinct tissue distributions and physiological functions. PPAR α levels are highest in the liver, although also expressed strongly in the heart and BAT. PPAR α promotes FAO and liver ketogenesis and is important for the response to fasting (6). PPAR δ is expressed widely and is particularly abundant in skeletal muscle and heart. PPAR δ , which has a broader function in oxidative metabolism than does PPAR α , promotes glucose as well as lipid oxidation, enhances metabolic rate, and promotes the formation of oxidative fiber types in skeletal muscle (43, 44). PPAR γ is most abundant in adipose tissue, where it promotes adipocyte differentiation and lipogenesis, and is present at lower levels in macrophages, muscle, and liver (6). In addition to endogenous ligands, PPARs are activated by synthetic ligands and drugs: PPAR α ligands include the hypolipidemic fibrates, whereas PPAR γ is the target of thiazolidinedione (TZD) class of insulin sensitizers (6).

PPARs act as heterodimers with retinoid X receptors (RXRs) to regulate a broad set of genes involved in lipid uptake, storage, and metabolism, including genes encoding mitochondrial FAO enzymes (6). Lipid uptake and metabolism provide substrates for mitochondrial oxidation and are thereby intimately related to mitochondrial function. PPARs also

regulate the expression of genes encoding UCPs, i.e., transporters that reside in the inner mitochondrial membrane and play roles in thermogenesis, ROS production, and oxidative capacity. Thus, via their ability to regulate genes of lipid metabolism and mitochondrial UCPs, PPARs are poised to confer cell-type specialization to mitochondria and in particular to enable the use of lipids as high-energy sources for ATP production. Because PPAR ligands are endogenously produced (likely by lipolysis) at specific physiological states and in response to environmental signals (e.g., fasting, exposure to cold, exercise), PPARs also enable mitochondrial adaptation to changing energetic and metabolic needs. Importantly, these regulatory actions of PPARs are integrated with those of other regulators of mitochondrial biogenesis and function, such as NRF-1 and GABP, via PGC-1 α and PGC-1 β , which interact physically with PPARs and enhance their ability to induce target genes (7, 45, 46). Interestingly, the coactivation function of PGC-1 α with PPAR γ is gene-specific, suggesting that PGC-1 α enhances a selective subset of PPAR targets and may thereby drive PPAR function to specific pathways (7).

In addition to their effects on lipid transport and metabolism, PPAR γ and PPAR δ promote mitochondrial biogenesis in a cell-type-specific manner. When one thinks of mitochondrial biogenesis, the focus is often on tissues rich in mitochondria, even though mitochondria are critical organelles for all cell types. White adipose tissue (WAT) is not particularly rich in mitochondria. Nevertheless, WAT mitochondrial biogenesis and activity respond dynamically to physiological signals. They become suppressed in animal models of diabetes and diet-induced obesity and are enhanced by treatment with the insulin-sensitizing PPAR γ ligands (47–49). Treatment with the PPAR γ ligand pioglitazone also increases mitochondrial biogenesis in subcutaneous adipose tissue in humans (50). The ability of PPAR γ agonists to enhance mitochondrial biogenesis in adipocytes in vitro suggests that the effects are due to a cell-autonomous function of PPAR γ

in WAT and are not just a response to systemic changes brought about by PPAR γ ligands in other tissues (49, 51). Notably, in all these studies PPAR γ agonists induced the expression of endogenous PGC-1 α , suggesting that PPAR γ affects mitochondrial biogenesis indirectly by enhancing the transcription of PGC-1 α . In support of this mechanism, Hondares et al. (52) have identified a functional PPAR response element (PPRE) in the PGC-1 α promoter that determines PPAR γ -dependent transcription in adipocytes (**Figure 2**). Because PGC-1 α coactivates PPAR γ , this element also enables PGC-1 α to enhance its own expression in an autoregulatory fashion. Notably, these studies suggest that changes in mitochondrial biogenesis in WAT may underlie both diabetes-related pathogenesis and TZD-induced improvements in glycemic control. The PPAR γ /PGC-1 α -stimulated WAT mitochondrial activity may ameliorate symptoms of metabolic disease by increasing energy expenditure, mitochondrial capacity for lipogenesis, and/or the synthesis and secretion of adipokines. Finally, TZDs and PPAR γ may increase not only PGC-1 α but also PGC-1 β expression (49).

Activation of PPAR δ affects mitochondrial biogenesis and function in skeletal muscle. Treatment of mice with an agonist PPAR δ ligand enhances muscle lipid uptake, FAO, and mitochondrial biogenesis; it also increases expression of UCPs, GLUT4, and PGC-1 α (53). Similarly, transgenic mice expressing PPAR δ or a constitutively active PPAR δ -VP16 chimera specifically in muscle show enhanced expression of oxidative metabolism and uncoupling genes and a shift to more oxidative muscle fiber types (46, 54). Conversely, mice lacking PPAR δ specifically in muscle show a decrease in mitochondrial gene expression and in oxidative capacity (55). Studies with PPAR δ ligands in vitro indicate that these effects are largely due to PPAR δ -regulated gene expression in muscle (56, 57). Although PPAR δ acts directly on genes of lipid metabolism and UCPs, via characterized PPREs, there is no evidence so far for a direct PPAR δ effect on mitochondrial biogenesis and OxPhos genes. Thus, it is possible that,

analogous to PPAR γ in adipocytes, PPAR δ impacts mitochondrial biogenesis via its ability to induce PGC-1 α expression in muscle. In support of this, PPAR δ ligands induce PGC-1 α in muscle in vitro and in vivo, and mice lacking PPAR δ show reduced levels of muscle PGC-1 α expression (52, 53, 58). The same PPRE that mediates PPAR γ -dependent induction of PGC-1 α in adipocytes mediates PPAR δ -dependent induction in myotubes (52, 55, 59).

Similar pathways of PPAR-dependent enhancement of PGC-1 α and/or PGC-1 β may take place in other tissues. PPAR γ and PPAR δ promote oxidative metabolism and mitochondrial biogenesis during alternative activation in macrophages (60, 61). PGC-1 β , which is important for macrophage alternative activation (62), is expressed at reduced levels in PPAR δ null macrophages (63). Finally, although no effect of PPAR α or PPAR α ligands on PGC-1 expression has yet been reported, given the central and common pathways of regulation and function of PPAR α and PGC-1 α in liver, we speculate that PPAR α contributes to the fasting-induced expression of PGC-1 α in this tissue. Importantly, these observations suggest that PPARs, primarily appreciated for their effects on lipid metabolism, may have a wider impact on mitochondrial biogenesis and function by acting as transcriptional regulators of PGC-1 coactivators.

Estrogen-related receptors (ERR α , ERR β , and ERR γ): regulators of a broad mitochondrial program. ERR α , ERR β , and ERR γ are members of the nuclear receptor superfamily and the most recent discoveries in the mitochondrial gene expression regulatory network. As their name implies, ERRs show sequence similarities to the estrogen receptor, particularly in the DNA-binding and ligand-binding domains (64). Despite this similarity, ERRs are not activated by estrogens or estrogen-like molecules and can attain constitutively active ligand-binding domain conformations in the absence of a ligand (65, 66). The transcriptional activity of ERRs is instead regulated via

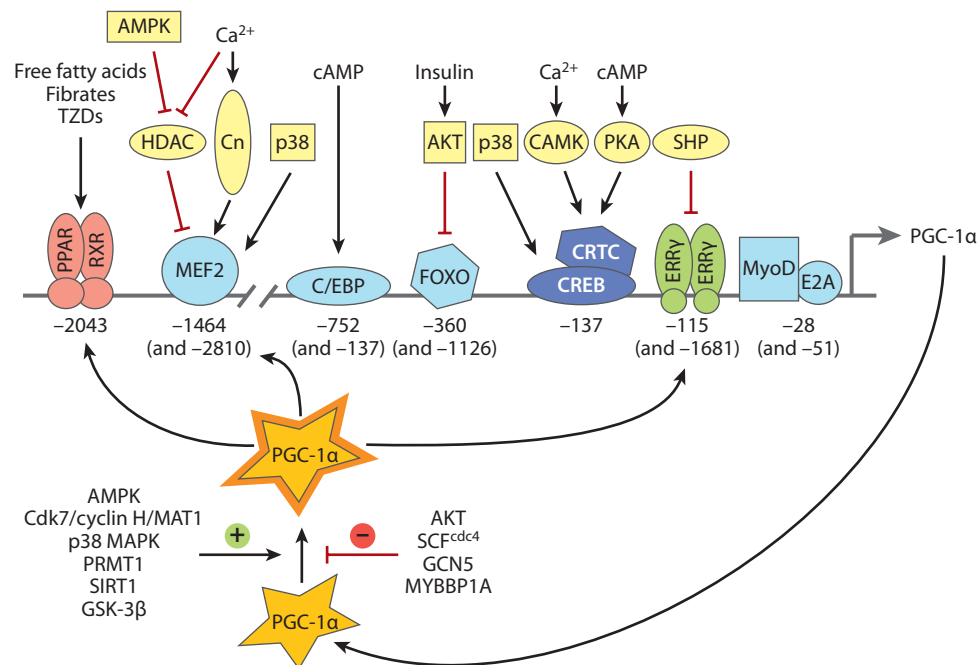


Figure 2

Positive and negative signals that regulate mitochondrial biogenesis and converge at the PGC-1 α promoter and/or the PGC-1 α protein. The upper part of the figure shows regulatory sites of the PGC-1 α promoter, the corresponding DNA-binding transcription factors, and signals activating (black arrows) or repressing (red bars) these factors. The promoter is not drawn to scale; where multiple *cis*-regulatory elements have been identified, only one is shown; and numbering is based on Reference 145. PGC-1 α can coactivate several transcription factors that bind the PGC-1 α promoter (PPARs, MEF2, and ERR γ , indicated by arrows below the promoter). As a result, signals that enhance or repress PGC-1 α protein activity (shown at bottom and indicated by the black arrow/green plus sign and red bar/red minus sign, respectively) can similarly affect PGC-1 α transcription. Many of the factors and signals shown here are expressed or active in a tissue-specific manner, so this diagram does not represent PGC-1 α regulation in all tissues. An alternative promoter, upstream to the one studied so far and shown here, was described recently (178). The alternative promoter drives the expression of a cDNA with an alternatively spliced first exon and is reported to be the one induced by exercise and cold in skeletal muscle and BAT, respectively (178).

physical interaction with coregulators, such as coactivators of the SRC and PGC-1 family or corepressors like receptor-interacting protein 140 (RIP140) (10, 64). ERR α , in particular, enhances gene expression only when partnered with the PGC-1 coactivators, which convert ERR α from a latent to a potent transcriptional activator (67–69). Conversely, ERRs in complex with RIP140 are thought to repress gene expression (70). ERRs are also subject to regulation by phosphorylation and sumoylation, which affect DNA binding, dimerization, and coactivator interaction (64). Although the func-

tional consequences of these modifications for the regulation of mitochondrial gene expression are yet to be determined, one activator of ERR α is neuregulin, which also promotes mitochondrial function (32).

ERRs bind as monomers, homodimers, or heterodimers of different ERRs to ERR response elements (ERREs) (64). The identification of one of the first ERREs as a regulatory site in the promoter of the FAO gene *Acadm* suggested that ERRs could be regulators of FAO. Recent studies have indeed established a role for ERR α , the best characterized of the

Receptor-interacting protein 140 (RIP140 or NRIP1):

a corepressor of many nuclear receptors

three ERRs, in the regulation of lipid oxidation genes, as well as a wider set of mitochondrial genes, including components of OxPhos, tricarboxylic acid (TCA) cycle, mitochondrial import, mitochondrial dynamics, and oxidative stress defenses (10, 64). The actions of ERR α are mediated via ERREs present at the regulatory regions of many mitochondrial genes (71–74). ERREs are significantly enriched in OxPhos and PGC-1 α -regulated gene sets and are often found in association with NRF-1 or GABP sites (30, 72). ERR α also acts on mitochondrial gene expression through indirect mechanisms by regulating the expression of GABP α and PPAR α (30, 75). siRNA and pharmacological approaches have shown that endogenous ERR α is required for the ability of exogenously expressed PGC-1 α to induce mitochondrial biogenesis and respiration (30, 71). Conversely, overexpression of ERR α in cardiac myocytes acts similarly to PGC-1 α , increasing lipid oxidation rates (75). Expression of an ERR α -VP16 chimera, which no longer requires PGC-1 α or PGC-1 β to be transcriptionally active, can by itself induce mitochondrial biogenesis, suggesting that activation of ERR target genes is central to the regulation of mitochondrial function (71).

Consistent with a role in mitochondrial biogenesis and function, ERRs are expressed at high levels in tissues with high energetic demands (64). Moreover, ERR α , which is induced by PGC-1 α via a positive autoregulatory loop (30, 69, 76), responds to signals central to the regulation of mitochondrial biogenesis or function, such as upon exposure to cold (in BAT and muscle), fasting (in liver), and exercise (in skeletal muscle) (25, 69, 77). Studies of ERR α null mice have provided further support and clarification on the physiological role of ERR α for mitochondrial function. The BAT of ERR α null mice shows a 40% decrease in mitochondrial content and oxidative capacity. Although mild, the energetic deficiency renders these mice unable to defend their body temperature when challenged with even mildly cold temperatures (13°C), despite normal expression of the thermogenic *Ucp1* (74). An en-

ergetic deficiency, without alteration in mitochondrial content, is also seen in the heart. The defect manifests as signs of heart failure when animals are challenged with increased workload (78). Finally, ERR α is necessary for increased rates of respiration and ROS production in macrophages stimulated with interferon β (IFN β). Consequently, ERR α null macrophages have a decreased ability to clear pathogens, and ERR α null mice have impaired survival rates when infected with *Listeria* (73).

Changes in mitochondrial gene expression or oxidative capacity are also seen in other tissues of ERR α null mice, such as WAT, intestine, and skeletal muscle (75, 79, 80), supporting a wide role of ERR α in mitochondrial function. Nevertheless, ERR α null mice are viable and fertile, suggesting that the mitochondrial defects are mild. The mild phenotype can be interpreted in at least two not mutually exclusive ways. First, ERR α may simply be part of the mechanism conferring adaptation to tissue- and physiology-specific cues and may not be important for basal levels of mitochondrial gene expression. This would be consistent with the defects in ERR α null mice being most apparent in tissues with highest mitochondrial content and in states of increased energy demand. Second, loss of ERR α function may be compensated by increased activity of other ERRs or other factors with similar roles. Consistent with this idea, ERR α null mice show increased expression of ERR γ and PGC-1 α in heart; ERR γ in skeletal muscle; and ERR γ , PPAR α , and PGC-1 β in adipose tissue (75; J.A. Villena & A. Kralli, unpublished data). Furthermore, recent studies show that ERR α and ERR γ target highly overlapping sets of mitochondrial genes in heart (72) and that ERR γ null mice, which die perinatally, have signs of mitochondrial dysfunction and decreased oxidative capacity in the heart (81). The extent to which ERR β may compensate for the absence of ERR α is not yet clear.

Given the evidence that ERR α activates the expression of many mitochondrial genes, a striking phenotype of ERR α null mice is decreased adiposity and a resistance to high-fat diet-induced obesity (79). The underlying

Tricarboxylic acid (TCA) cycle: the mitochondrial matrix pathway that oxidizes acetyl CoA (as well as other products of amino acid metabolism) to produce ATP and reducing equivalents (NADH and FADH₂) for OxPhos

mechanism(s) for this phenotype is not yet clear but may include a decrease in lipid absorption in the intestine (80); a developmental role for ERR α in adipocyte differentiation and function (82); defective lipogenesis, possibly due to an energetic and/or TCA cycle deficiency (79); and increased energy expenditure due to the increased expression of compensating regulators, such as PGC-1 α , PGC-1 β , and ERR γ .

As seen with other transcription factors that regulate mitochondrial gene expression, ERRs also have roles as regulators of nonmitochondrial programs. ERR-regulated targets include genes with roles in Ca²⁺ homeostasis, contractile function, glucose metabolism, angiogenesis, lung maturation, ion channel and transporter expression, and other cellular processes (64). ERR β in particular plays important roles in extraembryonic cells during development (83), in embryonic stem cell biology (84), and in the development of the endolymph-producing cells of the inner ear (85).

Other nuclear transcription factors: CREB, c-Myc, and YY1. Additional transcriptional regulators with broad biological functions contribute to the control of mitochondrial gene expression. The cAMP response element-binding (CREB) protein regulates *Cycs* expression; binding sites for CREB protein are present not only at the *Cycs* but also at the *Cox5a*, *Cox8a*, *Irb3g*, *Nnt*, and *Ucp1* genes (5). Increased cAMP signaling is associated with states of changing energetic demands (e.g., adrenergic stimulation in BAT upon exposure to cold, and the fasting response in liver), and CREB contributes to mitochondrial function both directly, by acting at specific mitochondrial genes, as well as indirectly, by inducing PGC-1 α expression (86, 87).

An increasing number of studies support the role of c-Myc as a regulator of mitochondrial genes (5). Recent genome-wide association studies show c-Myc binding to 107 mitochondrial genes, including the mitochondrial DNA polymerase γ (88). Moreover, c-Myc may affect mitochondrial biogenesis via its ability to activate the expression of PGC-1 β (89). Con-

sistent with the binding and gene expression studies, c-Myc null cells have diminished mitochondrial mass (90). The context in which c-Myc regulates mitochondrial genes is not yet clear. An interesting possibility is that c-Myc links mitochondrial biogenesis to cell growth and proliferation.

Finally, the transcription factor YY1 has been implicated in both positive and negative regulation of COX genes (5). Recent studies show that YY1 in muscle is in a complex with PGC-1 α , enhancing mitochondrial gene expression and cellular respiration (91). The interaction of YY1 with PGC-1 α requires the activity of mammalian target of rapamycin (mTOR), suggesting that YY1 integrates information from two nutrient-sensing pathways: PGC-1 α , which relays signals of low cellular energy state (92, 93), and mTOR, which promotes cell growth in the presence of nutrients. The physiological state during which this mechanism becomes important for mitochondrial biogenesis is not clear.

Transcriptional Coregulators

PPAR γ coactivator-1 family (PGC-1 α , PGC-1 β , and PRC): promoters of mitochondrial biogenesis programs. PGC-1 coactivators play important roles in the control of mitochondrial biogenesis and function by integrating physiological signals and coordinately enhancing the function of diverse transcription factors acting at mitochondrial genes. PGC-1 α was first identified by Spiegelman and colleagues (7) as a protein interacting with PPAR γ , selectively expressed in BAT, and induced by exposure to cold. PGC-1 β and PRC were identified on the basis of their similarity to PGC-1 α (16, 17, 94). The three coactivators regulate expression of a broad mitochondrial gene set and promote mitochondrial biogenesis (9). They also carry important functions outside the mitochondrial gene expression program (9), which are not discussed here.

The PGC-1 proteins share three molecular features that are important for the regulation of mitochondrial genes. First, they

contain protein surfaces that enable interactions with NRF-1, GABP, PPARs, ERRs, and YY1 and are thereby recruited to target regulatory sites. These protein surfaces include leucine-rich motifs that mediate interactions with nuclear receptors (16, 45, 94, 95); a conserved DHDY motif that binds HCF and presumably enables interactions with GABP (17, 33, 34); and less well-characterized interfaces for NRF-1, YY1, and other transcription factors (8, 91, 96). Second, the three PGC-1 proteins share similar transcriptional activation domains that enable the enhancement of gene expression (16, 45, 94, 97, 98). The molecular mechanisms are best characterized for PGC-1 α and include the ability to recruit the histone acetyltransferases CBP/p300 and Mediator (9). Finally, PGC-1 proteins contain sites of posttranslational modifications or interaction with regulatory proteins. Some of these sites are conserved in the three members, suggesting common mechanisms of regulation (99). In summary, the mode of PGC-1 action at mitochondrial genes seems deceptively simple: PGC-1 docks on transcription factors bound at their respective response elements and enables the recruitment of histone acetyltransferases and the Mediator complex, thereby enhancing transcription initiation and/or elongation. PGC-1 proteins also have domains proposed to regulate posttranscriptional steps, such as RNA splicing (100, 101); the importance of this mechanism for mitochondrial function has not been addressed.

Overexpression of PGC-1 α and PGC-1 β in many cell types induces mitochondrial biogenesis and enhances respiration, suggesting that the two coactivators are limiting for the mitochondrial gene expression program (9). The functional properties of mitochondria in PGC-1 α - and PGC-1 β -expressing cells differ in terms of coupling and oxidative stress defenses, suggesting that PGC-1 α and PGC-1 β induce similar but not identical programs (102). Differential effects of PGC-1 α and PGC-1 β may be due to selective preferences in associations with DNA-binding transcription factors and/or differences in the communication with the gen-

eral transcription machinery. Overexpression of PRC induces OxPhos genes, and knockdown of PRC decreases cytochrome oxidase activity; however, it is not clear if increased PRC expression is sufficient to induce mitochondrial biogenesis (34).

The central roles of PGC-1 α and PGC-1 β in mitochondrial gene expression and biogenesis have been demonstrated in mice with gain- and loss-of-function studies. Transgenic expression of PGC-1 α or PGC-1 β in skeletal muscle leads to an increase in mitochondrial content, increased expression of mitochondrial genes, and enhanced exercise performance (103–105). PGC-1 α and PGC-1 β activate expression of distinct muscle contractile proteins (PGC-1 α promotes type IIa and type I, and PGC-1 β promotes type IIx fibers), consistent with the notion that the two proteins carry some distinct physiological roles (103, 104). Conversely, loss of PGC-1 α by genetic inactivation results in viable mice with modest but significant decreases in expression of mitochondrial genes; decreased mitochondrial enzymatic activities; and phenotypes of mild to moderate mitochondrial dysfunction, such as a failure to defend body temperature when exposed to cold, reduced capacity to sustain running, and energetic impairments in heart in response to β -adrenergic stimulation or cardiac pressure overload (106–109). Similarly, PGC-1 β null or hypomorph mice show decreased mitochondrial gene expression and defects in thermogenesis and cardiac performance (73, 110, 111). Overall, mitochondrial biogenesis defects are subtle, with decreases in mitochondrial volume seen only in some tissues [e.g., skeletal muscle of PGC-1 α (108) and PGC-1 β hypomorph (111) mice].

The mild mitochondrial biogenesis defects seen in mice lacking just PGC-1 α or PGC-1 β suggest that PGC-1 α and PGC-1 β compensate for each other's loss in vivo. In support of this notion, the induction of mitochondrial biogenesis during in vitro brown adipocyte differentiation is not affected by the lack of a single PGC-1 but is abolished when both PGC-1 α and PGC-1 β are knocked down (112). Further

Sirtuin 1 (SIRT1): NAD⁺-dependent protein deacetylase homologous to the yeast silent information regulator (Sir2) and implicated in caloric restriction and aging pathways

Histone deacetylase (HDAC): a family of enzymes that deacetylate histones and other proteins

confirmation is provided by the recent generation of double PGC-1 α /PGC-1 β null mice, which show severe reductions in BAT mitochondrial density, late fetal arrest in cardiac mitochondrial biogenesis, small hearts, reduced cardiac output and other signs of heart defects and die shortly after birth (113). These findings suggest that PGC-1 α and PGC-1 β are essential for the developmental program that drives high levels of mitochondrial biogenesis in tissues with high energy demands, such as BAT and heart, but not for basal levels of mitochondrial biogenesis (by comparison, *Tfam* null mice die at E10.5).

One of the most interesting aspects of PGC-1 biology is the potential of these coregulators to sense signals of energetic or metabolic needs and to relay such signals to changes in gene expression. PGC-1 α has served as the prototype PGC-1 family member in understanding this role (9). Signaling information is to a large extent integrated at two levels: transcriptional regulation and posttranslational regulation (**Figure 2**). At the transcriptional level, both PGC-1 α and PGC-1 β are expressed in a tissue-selective manner, with high levels in tissues with high energy demands, suggesting that their transcription depends on tissue-specific developmental cues (9). Moreover, PGC-1 α , but not PGC-1 β , is highly inducible in response to signals of increased energy needs (e.g., in BAT and muscle upon exposure to cold, in liver upon fasting, in skeletal muscle in response to exercise), suggesting that PGC-1 α plays a role in long-term adaptation to such needs (7–9). At the posttranslational level, PGC-1 α activity is regulated via phosphorylation by mitogen-activated protein kinase (MAPK) p38, AKT, AMPK, and glycogen synthase kinase-3 (GSK-3) (93, 95, 99, 114, 115), (de)acetylation by GCN5 and Sirtuin 1 (SIRT1) (92, 116), arginine methylation by PRMT1 (117), ubiquitination by SCF^{Edc4} (99), and interaction with the repressor MYBBP1A (118). Several of these modifications are likely to affect PGC-1 β activity as well because the PGC-1 α target modification sites are conserved. The signaling pathways that regulate PGC-1 α expression and

activity, and the physiological context in which these pathways act, are discussed in the next section.

Receptor-interacting protein 140: a brake on mitochondrial biogenesis. The nuclear receptor corepressor RIP140 functions as the antithesis of PGC-1 coactivators and acts as a transcriptional brake on mitochondrial biogenesis. Like PGC-1 α / β , RIP140 interacts with a broad set of nuclear receptors (including ERRs and PPARs) via a series of LXXLL motifs (70, 119). However, RIP140 docking to nuclear receptors recruits additional corepressors, such as CtBP and histone deacetylases (HDACs), and leads to suppression of gene transcription. In vitro and in vivo studies support the role of RIP140 in mitochondrial function. Silencing of RIP140 in 3T3L1 cells leads to increased expression of many mitochondrial genes, including ones with roles in the TCA cycle, OxPhos, FAO, and organelle biogenesis (120). The ability of RIP140 to repress at least some of these genes depends on endogenous ERR α (120), indicating that the same transcription factor (i.e., ERR α) can mediate positive and negative effects on mitochondrial gene expression, depending on the cellular context and type of coregulator present. RIP140 null animals have increased oxygen consumption and expression of mitochondrial genes (121). Muscle-specific deletion of RIP140 results in increased mitochondrial volume and number of oxidative fibers, i.e., effects similar to ones seen in mice overexpressing PGC-1 α (103, 122).

Even though RIP140 is expressed widely, there is some correlation of high RIP140 levels and low mitochondrial content. For example, RIP140 levels are higher in WAT than in BAT and higher in glycolytic than in oxidative muscle fibers (70). RIP140 expression is also induced by many nuclear receptors, including ERR α (123). The ERR α -mediated induction of RIP140 may serve as a mechanism that limits mitochondrial gene induction in amplitude and/or temporally. Like PGC-1 α , RIP140 is regulated by protein modifications. Sumoylation (124) and acetylation (125) have both been proposed to

enhance the repressive ability of RIP140. Interestingly, the same arginine methyltransferase, PRMT1, modifies RIP140 and PGC-1 α (117, 126). PRMT1-mediated methylation enhances the activity of PGC-1 α and suppresses that of RIP140, suggesting that PRMT1 can act as a switch in the cellular balance of PGC-1 α versus RIP140. It will be interesting to define physiological signals that regulate PRMT1.

PHYSIOLOGICAL STATES THAT PROMOTE MITOCHONDRIAL BIOGENESIS

Overview

Energetic demands vary not only among cell types but also in different physiological states. Thus, gene expression programs of mitochondrial biogenesis and function are regulated in response to physiological signals that accompany increased demands for energy or energetic efficiency. One of the best-understood paradigms is endurance exercise training—in which increased mitochondrial biogenesis contributes to muscle performance (3, 127). Similarly, long-term cold exposure induces mitochondrial biogenesis in BAT of small animals, which enables a higher capacity for adaptive thermogenesis (128). Finally, and of particular interest to today's calorie-ridden society, caloric restriction induces mitochondrial biogenesis (4, 129). In this section, we first present an overview of the signals associated with exercise, exposure to cold, and caloric restriction and then review how each of these signals communicates to the transcription factors that control mitochondrial gene expression.

Endurance exercise activates signals that are associated with physical activity, such as muscle contraction-induced increases in cytoplasmic Ca²⁺, as well as signals that relay energy deficits, such as AMPK (127) (**Figure 3**). Exercise also activates the sympathetic nervous system, leading to adrenergic stimulation and increased cAMP signaling. Ca²⁺-derived signals, AMPK, cAMP, and other signals (e.g., nitric oxide) then activate the transcription fac-

tors controlling mitochondrial gene expression (5, 9, 130). Single bouts of exercise lead to transient increases in the levels of PGC-1 α , PRC, NRF-1, GABP, ERR α , PPAR δ , and downstream mitochondrial targets (22, 24, 25, 127, 131). The increase in expression of these transcription factors is likely mediated by post-translational modifications that enhance their activity, as proposed for PGC-1 α (132, 133). Repeated bouts of exercise are necessary for long-term adaptive responses, including a stable increase in PGC-1 α protein and increased mitochondrial biogenesis (3, 127).

Exposure to cold leads to the activation of the sympathetic nervous system, adrenergic stimulation of BAT, and increased cAMP and cAMP-dependent pathways [i.e., activation of protein kinase A (PKA), p38 MAPK, and transcription factors CREB/ATF2], which induce PGC-1 α (87) (**Figure 3**). PGC-1 α and CREB/ATF2 induce the thermogenic *Ucp1*, which uses the mitochondrial proton gradient to generate heat (7, 87). PGC-1 α also induces *deiodinase 2*, which generates local thyroid hormone and further enhances mitochondrial function (112). As with exercise, acute short-term exposure to cold induces a small set of mitochondrial genes, whereas long-term exposure results in mitochondrial biogenesis.

Caloric restriction without malnutrition enhances mitochondrial biogenesis in rodents and humans (4, 134–136). The molecular signals implicated in caloric restriction, which likely imposes a demand for increased energetic efficiency, include increased SIRT1 activity, increased AMPK activity (possibly due to an increase in circulating adiponectin levels), and the induction of endothelial nitric oxide synthase (eNOS) (**Figure 3**). All three signals converge on PGC-1 α by regulating PGC-1 α activity and expression levels (92, 93, 137).

Induction of mitochondrial biogenesis is also seen in “stressed” cells, in which stress may be due to (a) an energetic deficiency, as seen in treatment of cells with uncoupling agents, (b) DNA damage, as seen in cells exposed to ionizing radiation or the drug etoposide, or (c) microtubule disruption (20, 133, 138–140).

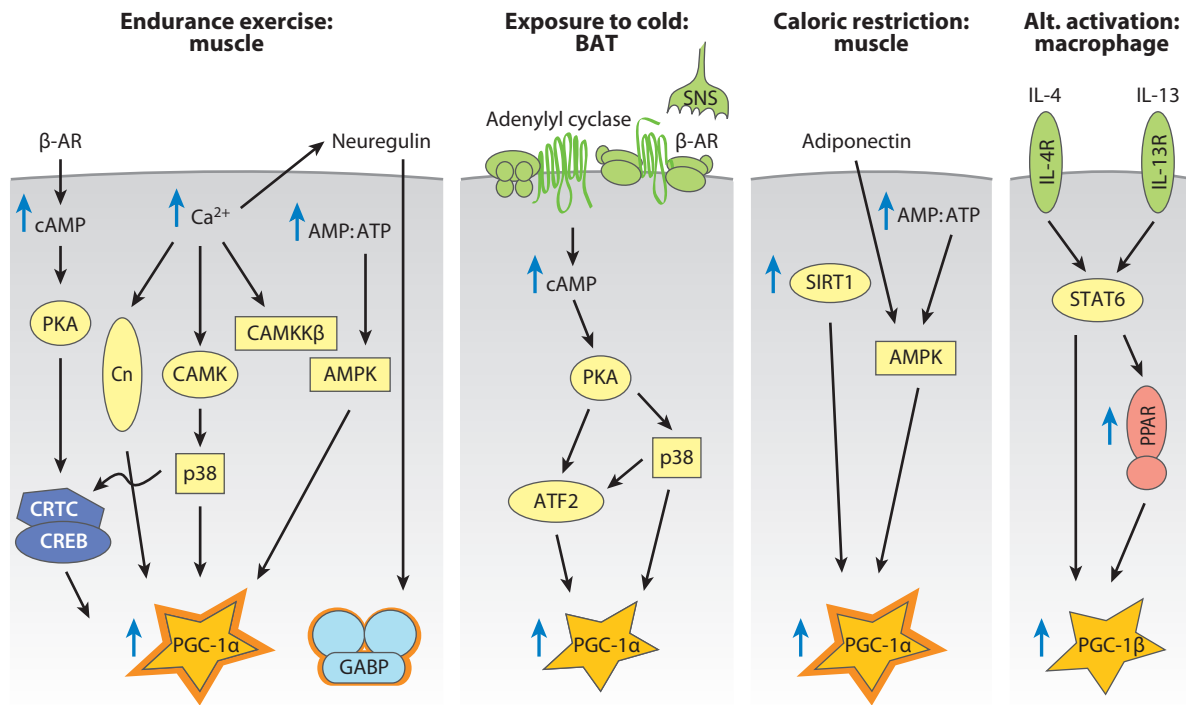


Figure 3

Diverse physiological signals regulate mitochondrial biogenesis in a tissue-specific manner. Shown are signaling pathways that induce mitochondrial biogenesis in skeletal muscle in response to endurance exercise or caloric restriction, in BAT in response to cold exposure, and in macrophages in response to signals promoting alternative activation. The signals enhance activity (orange outlines) and/or expression (upward blue vertical arrows) of transcriptional regulators PGC-1 α , GABP, or PGC-1 β .

An emerging theme from these studies is the repeated use of similar signals as in physiological states of mitochondrial biogenesis: AMPK, activated by uncoupling agents and the DNA damage-responsive kinase ATM (as in exercise and caloric restriction) (20, 139), and bursts of Ca^{2+} , which mediate the uncoupling-induced response and retrograde signaling from mitochondria to nucleus (as in exercise) (139, 141).

Ca^{2+} -Induced Pathways

Muscle contraction leads to Ca^{2+} bursts that signal to mitochondrial gene expression programs via the Ca^{2+} -dependent phosphatase calcineurin, Ca^{2+} /calmodulin-dependent kinases (including CAMKII, CAMKIV, and CAMKK β), and p38 MAPK (127) (**Figure 3**).

Several lines of evidence support the roles of these molecules in mitochondrial biogenesis and function. First, caffeine treatment of cultured myotubes, which leads to Ca^{2+} release, activates p38 in a CAMK-dependent manner and mimics the effects of exercise, inducing PGC-1 α , NRF-1, GABP, and TFAM (19). Inhibitors of CAMK or p38 block these effects (19, 142). Second, transgenic mice expressing constitutively active calcineurin or CAMKIV in muscle show increased mtDNA content, mitochondrial volume, and PGC-1 α levels (143, 144). Third, the calcineurin, CAMK, and p38 signals converge at regulatory sites of the PGC-1 α promoter, where they act on transcription factors of the MEF2 family (activated via calcineurin and p38) and the CREB/ATF2 family (activated by CAMKIV and p38) to

induce PGC-1 α expression (**Figure 2**) (145–148). A CAMK-dependent phosphorylation of HDAC5 may also export HDAC5 from the nucleus and relieve the inhibitory effect of HDAC5 on MEF2, thereby further enhancing PGC-1 α expression (149).

In addition to inducing PGC-1 α expression via the activation of MEF2 and CREB/ATF2, the MAPK p38 phosphorylates and enhances the activity of PGC-1 α , thereby promoting PGC-1 α to coactivate MEF2 and induce its own expression (**Figure 2**) (95, 114). Thus, in vivo, activation of the PGC-1 α protein may precede the induced expression of PGC-1 α (132). p38 also regulates stability of the PGC-1 α protein. In cells with low SCF^{cd4} E3 ubiquitin ligase activity (e.g., 293 cells), phosphorylation of PGC-1 α by p38 leads to increased protein stability (114). Conversely, in cells that have SCF^{cd4} and active GSK-3 β , p38- and GSK-3 β -mediated phosphorylation of PGC-1 α promotes ubiquitination and ubiquitin-mediated degradation, thereby decreasing protein stability (99). The effects of GSK-3 β and SCF^{cd4} on PGC-1 α in muscle have not been examined. However, activation of p38 in myotubes exposed to palmitate leads to decreased PGC-1 α expression, suggesting that p38 can act both positively and negatively, depending on cellular context (150).

AMPK: Cellular Energy Status Sensor

AMPK senses cellular energetic deficiencies as an increase in the AMP:ATP ratio and becomes activated in endurance exercise, caloric restriction, and other stressor-induced states. Several studies have established a role for AMPK in mitochondrial biogenesis and oxidative metabolism (127). Briefly, rodents treated with chemical activators of AMPK [e.g., 5'-aminoimidazole-4-carboxamide-1- β -ribofuranoside (AICAR)] or expressing constitutively active AMPK have enhanced muscle mitochondrial biogenesis, FAO, and expression of PGC-1 α , NRF-1, and PPAR α (26, 127, 151, 152). The ability of AMPK to induce PGC-1 α in muscle is lost in PGC-1 α null

mice, consistent with AMPK enhancing the activity of PGC-1 α protein, which then promotes PGC-1 α transcription (**Figure 2**). Indeed, AMPK phosphorylates PGC-1 α and enhances PGC-1 α activity (93). AMPK also phosphorylates and inactivates the MEF2-associated repressor HDAC5, thereby further enhancing PGC-1 α transcription (**Figure 2**) (148, 153). PGC-1 α is important for the AMPK-dependent induction of some mitochondrial genes, like *Cycx*, but not others, like *Ucp3* and *Pdk4*, suggesting that AMPK activates other transcription factors besides PGC-1 α (93). Interestingly, AICAR-mediated activation of AMPK in mice enhances not just muscle mitochondrial biogenesis but also the capacity for exercise, suggesting a central and wide role of AMPK in the program induced by endurance exercise (154).

Finally, AMPK is activated by other hormones and signals that enhance mitochondrial biogenesis and function, such as adiponectin, leptin, thyroid hormone, and the DNA double-strand break-sensing kinase ATM, suggesting that AMPK plays a central role in multiple pathways that enhance mitochondrial biogenesis (20, 129, 155–157).

SIRT1: A Nutrient Deprivation Sensor

SIRT1 is a NAD⁺-dependent deacetylase and the mammalian homolog of the yeast Sir2, which mediates effects of caloric restriction on yeast life span. Similar to the yeast Sir2, the mammalian SIRT1 is activated in states of nutrient deprivation, such as fasting and caloric restriction (158). SIRT1 deacetylates and activates PGC-1 α , thereby reversing the effects of the acetyltransferase GCN5, which acetylates and represses PGC-1 α (158). In muscle, SIRT1 promotes the deacetylation of PGC-1 α and the increased expression of PGC-1 α , ERR α and many mitochondrial genes, including *Tfam*, TCA cycle, OxPhos, and FAO genes (92). Increasing SIRT1 activity, by feeding mice the SIRT1 activator resveratrol, induces muscle mitochondrial biogenesis and enhances exercise performance, suggesting

an important role of SIRT1 for mitochondrial function in vivo (159). Besides SIRT1, resveratrol may also activate AMPK (160). Thus, studies with specific SIRT1 activators will be necessary to define the in vivo role of SIRT1 (161). Finally, the effects of SIRT1 on PGC-1 α may depend on cellular context because SIRT1 represses PGC-1 α activity in PC12 cells (162). There are 13 acetylated lysines in PGC-1 α (158); some of them may enhance, whereas others may repress, PGC-1 α activity.

Other Signals: cAMP, Neuregulins, and Nitric Oxide

Several other signals have been implicated in the regulation of mitochondrial biogenesis. Induction of PGC-1 α in muscle by exercise is blunted in mice lacking β -adrenergic receptors, indicating that adrenergic stimulation and cAMP signaling contribute to the adaptive responses (130) (**Figure 3**). Moreover, exercise and Ca²⁺ induce the expression of neuregulins, which activate ErbB tyrosine kinases (163). Neuregulins enhance expression of PPAR δ , PGC-1 α , and mitochondrial genes and increase oxidative capacity in muscle cells (164). Interestingly, neuregulins may act at multiple steps because the ErbB pathway also activates GABP and ERR α (33, 165). Another signal that impacts mitochondrial biogenesis is the gas nitric oxide (NO), which induces PGC-1 α expression via a cGMP-dependent mechanism (166). Mice lacking eNOS, an NO-producing enzyme that is induced by caloric restriction, show mitochondrial defects in multiple tissues (135).

Molecular studies of PGC-1 α have also identified regulators whose role in the physiological pathways of mitochondrial biogenesis is not yet clear. Some of these regulators affect mitochondrial function in vitro and in vivo. For example, the kinase cyclinH/Cdk7/MAT1 regulates the expression of PGC-1 α and OxPhos genes in HIB1B cells, and mice lacking MAT1 in heart show decreased PGC-1 α and PGC-1 β activity and mitochondrial and energetic deficiencies (167, 168). The underlying mechanism

for this regulation is not known. Similarly, future studies need to elucidate the physiological contributions of other regulators, such as SCF^{Fcd4} (which is regulated in neurons by oxidative stress), MYBBP1A, and PRMT1 (99, 117, 118).

(Patho)physiological States Associated with Decreased Mitochondrial Biogenesis

Decreased mitochondrial biogenesis and function are seen in aging, physical inactivity, obesity, and insulin resistance. They often parallel decreases in the expression of transcriptional regulators, like PGC-1 α , PGC-1 β , and NRF-1 (9, 169). One likely cause for the decreased mitochondrial biogenesis is simply reduced input in the positive signals discussed above. For example, aging is associated with a blunted AMPK stimulation by exercise, insulin resistance with decreased plasma adiponectin levels, obesity with increased cytokines that suppress eNOS expression, and so on (129, 169, 170). Signals that specifically repress the transcriptional program of mitochondrial biogenesis may include lipids. Lipid infusion or a high-fat diet in humans leads to decreased expression of PGC-1 α , PGC-1 β , and their mitochondrial targets (171, 172). Similarly, exposure to palmitate downregulates PGC-1 α and mitochondrial gene expression, as well as oxygen consumption in C2C12 myotubes (150). However, increasing plasma free fatty acids and high-fat diets in rats induce PGC-1 α and PPAR β/δ expression and mitochondrial content (173, 174). The conflicting results may be due to differences in fatty acid and diet composition, suggesting that it is the types rather than simply the levels of lipids that signal to mitochondrial gene expression programs. Finally, insulin can negatively regulate PGC-1 α by two distinct mechanisms: first, by repressing FOXO-dependent PGC-1 α expression (175, 176) and second, via AKT-dependent phosphorylation and repression of PGC-1 α activity (115) (**Figure 2**). The significance of the AKT effect for mitochondrial biogenesis in muscle is not clear.

FEATURES OF THE TRANSCRIPTIONAL NETWORK AND THE REGULATING SIGNALS

One of the remarkable features of the network of transcription factors regulating mitochondrial biogenesis and function is the extensive use of feed-forward and feedback loops (**Figures 1 and 2**). Increases in one network component often enhance the expression of others. For example, PGC-1 α not only coactivates ERR α , GABP, and NRF-1 but also increases their expression levels. ERR α enhances the expression of PPAR α , GABP, and the negative regulator RIP140. PPAR γ , PPAR δ , ERR γ , and CREB induce the expression of PGC-1 α . ERR α and PGC-1 α induce their own expression. These regulatory loops are likely to be important in enhancing the amplitude of the mitochondrial gene response, as well as in limiting it temporally. Moreover, modeling of biological feedback loops suggests that such coupled positive

and negative feedback systems are better able to respond faithfully to signals in the presence of noise (177).

A second interesting feature is the parallel activation of multiple signaling pathways in physiological states that enhance mitochondrial biogenesis and function (e.g., Ca²⁺ and AMPK in exercise, AMPK and SIRT1 in caloric restriction) (**Figure 3**). The importance of parallel pathways is nicely demonstrated in a recent study showing that, although pharmacological activation of PPAR δ by itself does not enhance exercise performance, the combination of the PPAR δ agonist with exercise training results in the synergistic enhancement of exercise performance (154). It seems reasonable to assume that a robust and specific induction of an expensive process, such as mitochondrial biogenesis, requires concurrent activation of more than one pathway, as well as multiple transcription factors.

SUMMARY POINTS

1. Mitochondrial biogenesis and function are dynamically regulated in a tissue- and signal-specific manner to enable cellular adaptation to energetic and metabolic demands.
2. Mitochondrial biogenesis in response to physiological signals is a long-term adaptive response and requires changes in the transcription of nuclear genome-encoded mitochondrial genes.
3. Short-term adaptation can be achieved by the increased expression of a subset of mitochondrial genes that enhance mitochondrial function without inducing mtDNA replication and organelle expansion.
4. Mitochondrial biogenesis and function are regulated by a transcriptional network comprising (a) DNA-binding factors that target distinct but overlapping sets of mitochondrial genes and (b) coregulators that integrate signals and coordinate the action of multiple DNA-binding factors. The network allows the concerted regulation of a broad mitochondrial gene set while also permitting tissue- and signal-specific expression patterns of subsets of mitochondrial genes.
5. A series of regulatory feed-forward and feedback loops among the transcription factors of the mitochondrial gene expression network allows robust and specific transcriptional responses to physiological signals.
6. Distinct physiological stimuli that induce mitochondrial biogenesis use common signals, including activity-dependent bursts of Ca²⁺ and the cellular energy status sensor AMPK. Cellular stress can induce the same signals.

7. The coactivator PGC-1 α plays a central role in adaptive responses by integrating diverse signals that impact mitochondrial biogenesis and coordinating multiple DNA-binding factors to induce broad sets of mitochondrial genes.

FUTURE ISSUES

1. The central role of PGC-1 α in integrating most if not all signals known to regulate mitochondrial biogenesis may largely reflect the attention allotted to this coactivator. Future studies on the mechanisms that regulate activity of PGC-1 β , PRC, RIP140, and the downstream DNA-binding factors will likely elucidate contexts in which these other regulators integrate signals, and thus may decipher possible “codes” that determine activity of the transcriptional network.
2. The field has made major advances in characterizing the signals and mechanisms that induce mitochondrial biogenesis. Signals or states resulting in mitochondrial dysfunction are less well understood. Studies on the molecular mechanisms that may underlie decreased mitochondrial biogenesis and function in (patho)physiological states will provide insights into basic science questions regarding such decreases (e.g., do they have causal roles, or are they secondary to disease?), as well as suggest novel modes of intervention.
3. There are a large number of transcriptional regulators of mitochondrial biogenesis and function. Some of them seem, at first glance, to have similar roles. It will be important to understand the specific roles and contributions of individual regulators in different tissues and at different physiological states. This knowledge will help identify targets for intervention in cases of cell-type-specific mitochondrial dysfunction. It may also help in the design of drugs that spare tissues where increased mitochondrial function may not be safe.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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