Transcriptional Control of Mitochondrial Biogenesis and Maturation

Rick B. Vega, Teresa C. Leone, and Daniel P. Kelly

Abstract The mitochondrion is the main site for ATP production in the adult heart and comprises up to 40 % of the cardiac myocyte volume. It is now recognized that a complex network of nuclear transcription factors is essential for the coordinated regulation of mitochondrial biogenesis, maturation and function. These transcription factors guide developmental changes in mitochondrial number, structure, and dynamics as well as respond to various physiologic and pathophysiologic cues to meet the energetic needs of the adult heart. The peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) orchestrates the actions of many of these transcription factors to maintain a high level of mitochondrial ATP production. There is increasing evidence that during the development of cardiac hypertrophy and in the failing heart, the activity of this network, including PGC-1, is altered. This review summarizes our current understanding of the perturbations in the gene regulatory pathways that occur during the development of heart failure. An appreciation of the role this regulatory circuitry serves in the regulation of cardiac energy metabolism may guide the development of novel therapeutic targets aimed at the metabolic disturbances that presage heart failure.

Keywords Mitochondria • PGC-1 • Transcription factors • Fatty acid oxidation • Heart failure

R.B. Vega • T.C. Leone • D.P. Kelly, M.D. (✉)
Diabetes and Obesity Research Center, Cardiovascular Pathobiology Program,
Sanford-Burnham Medical Research Institute, 6400 Sanger Road, Orlando, FL 32827, USA
e-mail: dkelly@sanfordburnham.org

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1 Introduction: Nuclear Transcription Factors Controlling Cardiac Mitochondrial Biogenesis and Function

1.1 Transcriptional Control of the Mitochondrial Genome

The mitochondrial genome encodes 13 essential protein subunits of the electron transport chain (ETC) along with several rRNAs and tRNAs necessary for the translation of the mitochondrial-encoded transcripts. The human cardiac myocyte is estimated to contain approximately 7,000 mtDNA copies per diploid genome [1], reflective of the high mitochondrial density in the cell. Several nuclear-encoded factors act within the mitochondria to activate transcription of mitochondrial-encoded products. Factors such as the mitochondrial transcription factor A (Tfam), the mitochondrial transcription factor B2 (TFB2M) and others are critical for mtDNA transcription, organization, and maintenance (Reviewed in [2]).

1.2 Nuclear Respiratory Factors (NRFs)

The nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2) are nuclear transcription factors that control many fundamental aspects of mitochondrial number and function. The importance of NRF-1 as a nuclear factor involved in mitochondrial biogenesis was first demonstrated by its regulation of cytochrome c gene expression [3]. Subsequently, it was shown that NRF-1 regulates expression of several proteins that act directly on regulators of the mitochondrial genome including Tfam and TFB2M [4, 5]; providing the first evidence for a direct connection between the transcriptional control of the nuclear and mitochondrial genomes. Gene deletion of NRF-1 results in embryonic lethality at E6.5 with diminished mtDNA levels and respiratory chain activity [6]. NRF-2, the human homolog of the murine GABP, is a polypeptide transcription factor containing an ETS-domain DNA subunit. NRF-1, together with NRF-2, regulates all ten nuclear-encoded cytochrome oxidase subunits [7, 8]. More recently, chromatin immunoprecipitation followed by deep sequencing (ChIP-seq) has confirmed NRF-1 binding sites in promoters of genes encoding components present in all electron transport chain complexes (Table 1) [9].

1.3 Nuclear Receptor Transcription Factors

A subset of the nuclear receptor superfamily exerts transcriptional control on cardiac mitochondrial fuel metabolism and respiratory function. Some of these nuclear receptors are ligand-activated and, as such, can respond directly to cellular signals and metabolite levels (substrate availability). One relevant family, the peroxisome proliferator-activated receptors (PPARs), was originally identified as regulators of

Table 1 Transcription factors important for cardiac mitochondrial energy production

Transcription Factor	Class	Gene targets	Phenotype
NRF-1	Nrf1 DNA-binding	• ETC components, all Cytochrome C subunits • mtDNA (*Tfam*, *Tfb2m*) • Transcription (*Mef2a*)	Embryonic lethality of KO at E6.5 with reduced mtDNA and ETC activity
NRF-2/GABP	ETS-domain	Similar to NRF-1	Embryonic lethality prior to implantation
PPARα	Nuclear receptor	• FA uptake (*Cd36*, *Slc27a1*, *Acsl1*) • FAO (*Cpt1b*, *Acadm*, *Hadha*, *Hadhb*)	• KO has reduced FAO rates • Cardiac transgene leads to increased FA uptake, storage and oxidation; recapitulates diabetic cardiomyopathy phenotype
PPARδ	Nuclear receptor	• FAO (*Cpt1b*, *Acadm*, *Hadha*, *Hadhb*) • Glucose (*Slc2a4*, *Ldhb*)	• KO has reduced FAO and glucose oxidation • Cardiac transgene has increased FAO and glucose oxidation, protected against lipotoxicity
ERRα	Nuclear receptor	• FAO (*Cpt1b*, *Acadm*, *Hadha*, *Hadhb*) • Glucose (*Slc2a1*, *Slc2a4*, *Pdk4*) • ETC (*Atp5b*, *Cycs*, *Cox6c*, *Ndufa4*) • Transcription (*Ppargc1a*, *Ppara*)	Cardiomyopathy in KO following pressure overload with phosphocreatine depletion and reduced ATP synthesis rate
ERRγ	Nuclear receptor	Similar to ERRα	Postnatal lethality in KO with inability to shift to oxidative metabolism in heart
YY1	GLI-Kruppel zinc finger	• Transcription (*Ppargc1a*) • ETC (*Cycs*)	KO displays defects in mitochondrial structure and energy production
c-Myc	Basic helix-loop-helix/leucine zipper	• Glycolysis (*Eno1*, *Ldha*) • Mito DNA (*Tfam*, *Polg*, *Polg2*)	Cardiac transgene results in mitochondrial biogenic and ETC defects leading to cardiomyopathy

peroxisomal fatty acid oxidation (FAO) enzymes [10]. The PPARs bind to cognate DNA elements as an obligate heterodimer with the retinoid X receptor (RXR). A variety of FA derivatives have been shown to serve as ligands for the PPARs, yet the endogenous ligands have not been fully delineated. All three isoforms, PPARα,

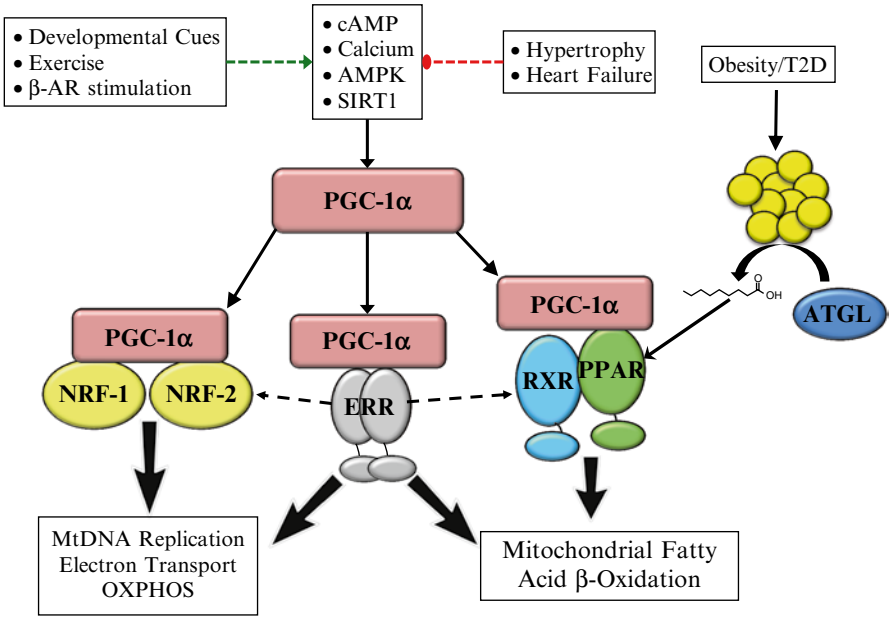

Fig. 1 The PGC-1 gene regulatory circuit controls cardiac mitochondrial function and fuel utilization capacity. PGC-1α integrates signals from diverse physiologic stimuli including developmental cues, exercise and β-adrenergic signaling. Coactivation of multiple downstream transcription factors drives the expression of proteins involved in virtually all aspects of mitochondrial energy production, regulating capacity for ATP production. Activity of PGC-1α and this circuit is inhibited during cardiac hypertrophy and heart failure. PGC-1α, PPARγ coactivator-1 alpha; PPARα, peroxisome proliferator-activated receptor alpha; RXR, retinoid X receptor; ERR, estrogen-related receptor; NRF, nuclear respiratory factor; OXPHOS, oxidative phosphorylation; ATGL, adipose triglyceride lipase; AMPK, AMP-activated protein kinase

δ(β), and γ are expressed in the cardiac myocyte with overlapping but distinct functions, with PPARα and PPARδ exhibiting the highest level of expression. PPARα target genes comprise many proteins and enzymes involved in FA uptake and mitochondrial FAO (Table 1). Insight into the function of PPARα in heart has been gained by loss- and gain-of-function mouse models. Mice lacking PPARα have reduced cardiac FAO rates [11–13] while overexpression of PPARα in the heart leads to increased uptake, storage and oxidation of fatty acids [14]. As discussed further below, the metabolic phenotype of mice overexpressing PPARα in heart recapitulates many aspects of the insulin resistant diabetic heart. Interestingly, recent evidence suggests that PPARα-activating ligands are released from intracellular triglyceride stores (Fig. 1). Specifically, adipose triglyceride lipase (ATGL) was shown to be necessary for the generation of PPARα ligands in the cardiac myocyte; ATGL knockout mice display profoundly reduced expression of PPARα target genes involved in FAO [15]. These new results also suggest that lipolysis of intracellular triglyceride stores is an important source of long-chain fatty acids for mitochondrial FAO [16]. These collective results suggest a metabolic control

mechanism whereby PPARα senses substrate availability to regulate capacity for mitochondrial FAO in heart.

PPARδ also drives high rates of mitochondrial FAO in the cardiac myocyte as its deletion reduces FAO capacity and leads to cardiac dysfunction [17]. However, unlike PPARα, cardiac overexpression of PPARδ does not lead to lipid accumulation and associated lipotoxicity. In fact, PPARδ appears to protect against myocyte lipid accumulation on a high-fat diet and cardiac dysfunction caused by pressure overload [18, 19]. In addition, PPARδ activates glucose uptake and oxidation at least in part due to its regulation of the insulin-responsive glucose transporter, Glut4 [17, 18]. Thus, PPARδ appears to drive a more balanced energy substrate utilization pattern. Cardiac-specific deletion of PPARδ also leads to a reduction of mitochondrial FAO and glucose oxidation rates resulting from a decrease in expression of enzymes in both pathways [17]. Therefore, PPARα and PPARδ share many similar targets, however these 2 nuclear receptors drive distinct metabolic pathways in the cardiac myocyte.

The estrogen-related receptors (ERRs) form a second group of nuclear receptors critical for maintaining mitochondrial function in the cardiac myocyte. All three ERR isoforms (ERRα, ERRβ, and ERRγ) are expressed in the heart and are known as "orphan" nuclear receptors due to the lack of a known ligand. ERR target genes overlap with that of the PPARs but also regulate genes involved in virtually all aspects of mitochondrial energy production including the TCA cycle, respiratory chain and oxidative phosphorylation (Table 1) [20]. Loss-of-function studies in mice have revealed roles for the ERRs in the heart. ERRα knockout mice display cardiac dysfunction when subjected to pressure-overload related to reduced capacity for maintaining phosphocreatine stores and mitochondrial ATP synthesis rates in response to energetic stress [21]. Likewise, gene deletion of ERRγ results in cardiomyopathy and death immediately following birth [22] related to the loss of the normal postnatal shift to oxidative metabolism and fatty acid utilization. As such, ERRs are required for the establishment and maintenance of cardiac energy production.

1.4 Other Nuclear Transcription Factors

Additional transcription factors have also been shown to regulate mitochondrial pathways and function in heart. A computational approach identified Yin Yang 1 (YY1) binding sites in the promoter regions of many mitochondrial genes regulated by the nutrient sensor mammalian target of rapamycin, mTOR (Table 1) [23]. YY1 deletion in skeletal muscle results in profound defects in mitochondrial structure and energy production [24]. The oncoprotein c-Myc has also been shown to activate expression of genes involved in mitochondrial biogenesis [25, 26]. Although expressed at very low levels in the normal heart, c-Myc is induced by a variety of pathologic stimuli including pressure overload [27]. The major effects of c-Myc expression in the heart are the activation of glucose utilization and downregulation of FAO (Table 1) [28]. Forced expression of c-Myc in the heart also leads to abnormal mitochondrial

biogenesis with respiratory change defects leading to cardiac dysfunction [29]. These data are consistent with a role of c-Myc in cardiac myocyte cell-cycle re-entry and activation of the fetal gene program during pathologic hypertrophy.

2 The PPARγ Coactivator 1 (PGC-1) Transcriptional Coregulators: Transducers of Physiological Cues to the Control of Cardiac Mitochondrial Biogenesis and Function

A huge breakthrough in our understanding of how mitochondrial biogenesis and function is regulated in accordance with energy demands came with the discovery of the PGC-1 coregulators. PGC-1α was first discovered in brown adipocytes as an activator of PPARγ [30]. The closely related PGC-1β [31, 32] and more distant relative, PGC-1 related coactivator (PRC) [33] comprise the other members of the family. The PGC-1 coactivators are characterized by an LXXLL motif that mediates interaction with nuclear receptors, an RNA recognition motif (RRM), and a host cell factor-1 (HCF) binding domain. PGC-1α and PGC-1β are expressed in tissues with a high oxidative capacity including the heart. Remarkably, PGC-1α is a highly inducible factor that responds to stimuli such as cold exposure and exercise [34–36]. PGC-1α expression in the heart increases during cardiac development and coincident with the large mitochondrial biogenic response that occurs just before birth [37]. Overexpression of PGC-1α in the cardiac myocyte leads to a robust mitochondrial biogenic response and increased expression of nuclear-encoded mitochondrial genes involved in multiple energy production pathways [37]. This function is orchestrated by PGC-1's interaction with and activation of PPARα [38], PPARβ/δ [39], ERRα and ERRγ [40–42]. In this manner, PGC-1α integrates multiple physiologic and developmental cues to regulate most aspects of mitochondrial function and energy production (illustrated in Fig. 1).

The importance of PGC-1 coactivators in the control of mitochondrial number and function is reinforced by loss-of-function studies in mice. Mice with loss of either PGC-1α [43, 44] or PGC-1β [45, 46] are viable and fertile with no obvious defect in cardiac energy metabolism or mitochondrial density. In the heart, pressure-overload induced hypertrophy results in accelerated heart failure in PGC-1α knockout mice [47]. A similar phenotype is also observed in PGC-1β knockouts subjected to pressure-overload hypertrophy [48]. In contrast to the single knockouts, deletion of both PGC-1α and PGC-1β results in perinatal lethality within 24 h of birth due to an arrest in mitochondrial biogenesis leading to heart failure [49]. This work was key to defining the important role played by PGC-1α/β in the perinatal cardiac mitochondrial biogenic response. In addition to its role in mitochondrial biogenesis during cardiac development, recent studies indicate that PGC-1α and PGC-1β are necessary for mitochondrial maturation including regulation of the mitochondrial fusion genes mitofusion 1 (Mfn1) and mitofusin 2 (Mfn2) among others during postnatal cardiac development [50, 51]. The regulation of Mfn1 and Mfn2 are at least in part, driven

by PGC-1 coactivation of ERRα [50, 52]. Interestingly, inhibition of mitochondrial fusion blocks cardiac myocyte differentiation [53], providing a potential link between PGC-1, mitochondrial dynamics, and cardiac development.

3 Control of Mitochondrial Function by Cellular and Metabolic Signaling

3.1 PGC-1 Responds to Cellular Signals

The PGC-1 coactivators are dynamically regulated at both transcriptional and post-transcriptional levels to integrate a variety of physiologic and pathophysiologic cues to match energy production with cardiac energy demands. Consistent with this role, multiple cellular signaling pathways converge on the PGC-1α gene including calcineurin, calmodulin-dependent kinase (CaMK), cAMP signaling, and AMP-activated protein kinase (AMPK) [54–57]. The activation of PGC-1α expression by cAMP downstream of adrenergic stimulation is mediated through direct regulation by the cAMP response element binding protein (CREB) [56].

PGC-1 activity is also modulated by post-translational modifications including phosphorylation and acetylation. AMPK has been shown to directly phosphorylate and activate PGC-1 [58]. AMPK is an energy sensing kinase that is activated by energy depletion, i.e. higher AMP/ATP ratios. Accordingly, phosphorylation of PGC-1 by AMPK provides a mechanism to boost mitochondrial energy production upon increased physiologic demands such as exercise. In addition to AMPK, the nicotinamide adenine nucleotide (NAD^+)-dependent deacetylase, Sirtuin 1 (SIRT1), is another metabolic sensor that regulates PGC-1 activity. AMPK and SIRT1 act cooperatively to activate PGC-1α activity providing a compelling link between mitochondrial biogenesis and metabolic signaling pathways sensing changes in cellular energy status [59, 60]. The effect of PGC-1 acetylation is supported by the observation that PGC-1 acetylation status is increased in muscle in mice fed a high-fat diet [61].

4 Dysregulation of Transcriptional Networks Controlling Mitochondrial Function Relevant to Heart Disease

4.1 Deactivation of Transcriptional Circuits in the Hypertrophied and Failing Heart

Similar to the expression of many structural and contractile proteins, there is a switch to the “fetal gene program” evident in metabolic enzyme gene expression during the development of cardiac hypertrophy and failure, including a decrease in

the expression of genes encoding mitochondrial FAO enzymes [62]. There is significant evidence that this fetal metabolic switch in the hypertrophied and failing heart involves alterations in the expression and activity of the transcription factors controlling mitochondrial function and biogenesis. PPARα expression is decreased in human and animal models of pressure overload-induced cardiac hypertrophy and in heart failure [62–65]. Evidence also exists that during cardiac hypertrophy PPARα, in addition to decreased expression, is regulated at the post-transcriptional level by phosphorylation via p38 to impair activity [66]. This is in agreement with the observed metabolic shift from FAO to glucose metabolism that occurs during the transition to cardiac hypertrophy and heart failure [67–69]. ERRα expression has also been shown to be decreased in animal models and human heart failure samples [70–72]. Coordinated repression of both PPARα and ERRα could represent major determinants in the regulation of mitochondrial energy production in the failing heart. As ERRα can directly regulate PPARα [73], it is tempting to speculate that repression of ERRα establishes this vicious cycle.

Given its role as a "master regulator" of mitochondrial biogenesis and function, a logical question is whether dysregulation of PGC-1 is involved in the pathogenesis of the "energy-starved" phenotype of the failing heart. Indeed, changes in fuel selection and mitochondrial function in the hypertrophied and failing heart are likely consequences of dysregulation of the PGC-1 circuit. Consistent with this notion, the expression of PGC-1α has been found to be downregulated in both animal models and human heart failure samples [62, 70, 74]. Similar findings have been reported for PGC-1β [48]. It should be noted however, that not all studies have shown a downregulation in PGC-1 in human heart failure samples [71, 72]. These differences likely reflect different etiologies, timepoints, or other variables that could influence PGC-1 expression secondarily. In addition, the role of altered PGC-1 signaling as an early (causal?) versus late event in the metabolic remodeling of heart failure remains to be determined.

4.2 Dysregulation of Transcriptional Circuits in the Diabetic Heart

The metabolic derangements that occur in the obese, insulin resistant, and diabetic patient appear to be quite distinct from that of hypertensive or ischemic heart disease. Insulin-resistant and diabetic hearts exhibit reduced capacity for glucose utilization, higher rates of mitochondrial FAO. Increased cardiac fatty acid uptake and β-oxidation have been observed in experimental models as well as obese and diabetic patients [75–78]. Interestingly, upregulation of cardiac mitochondrial FAO enzyme expression has been observed in a number of diabetic animal models consistent with an activation of FAO rates [79–81]. There is also increasing evidence that impaired glucose tolerance, even before the onset of diabetes, is associated with cardiac steatosis [82]. In the obese and diabetic patient population, myocardial lipid

accumulation has been shown by some to be associated with diastolic and, in some studies, systolic ventricular dysfunction [78, 83, 84]. Collectively, this metabolic inflexibility in the setting of neutral lipid accumulation and resulting cardiac dysfunction has been termed cardiac "lipotoxicity" [85].

The high rates of mitochondrial FAO observed in both experimental models and human patients indicate activation of transcriptional networks controlling these pathways. Indeed, mice that overexpress PPARα exclusively in the heart (MHC-PPARα) exhibit increased FAO associated with a decrease in glucose utilization resulting in an accumulation of triglyceride and a diabetic-like phenotype [14, 86, 87]. These animals exhibit left ventricular hypertrophy and cardiac dysfunction that can be inhibited by deletion of CD36 or the LDL receptor, thus depriving PPARα of activating ligands [88, 89]. Furthermore, the activity of the PGC-1/PPARα circuit is increased in the insulin resistant mouse heart [90]. However, during transition to diabetes in mouse models the activity of PGC-1α appears to fall leading to a proposed vicious cycle of mitochondrial dysfunction and myocyte lipotoxicity [91]. The relevance of this latter observation to humans remains to be determined.

5 Conclusions

The healthy heart has an amazing capacity to generate ATP and shift fuel utilization preferences in response to pathophysiologic stimuli to meet its energy needs. Much of this control occurs at the level of gene regulation through a complex circuit involving the PGC-1 coactivators and nuclear receptors. This circuit becomes constrained during the development of heart failure. The unmet needs in the heart failure arena suggest a prime opportunity to develop therapeutics that modulate mitochondrial function and fuel metabolism by targeting this circuitry. In the long-term, such therapies could, perhaps, be tailored to the etiology of heart failure and the accompanying metabolic derangements.

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