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The PGC-1 Cascade as a Therapeutic Target for Heart Failure

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Abstract

The PPAR γ coactivator-1 (PGC-1) family of transcriptional coactivators, together with estrogen related receptors (ERRs), play a key role in regulating genes involved in myocardial fuel metabolism and cardiac function. Increasing evidence implicates dysregulation of this transcriptional regulatory circuit in the metabolic and functional disturbances that presage heart failure due to common diseases such as hypertension and diabetes. Accordingly, the PGC-1/ERR axis is a plausible candidate therapeutic target for novel therapeutics aimed at reversing the energy metabolic disturbances that contribute to heart failure. This review describes the biologic actions of the PGC-1 and ERR cascade and summarizes the evidence that dysregulation of this transcriptional regulatory circuit contributes to heart failure. Potential strategies to modulate this target pathway are reviewed.

The constant generation of ATP is vital for the heart to perform its contractile function. Cardiac myocytes must also be able to dynamically re-program fuel and energy metabolic capacity in response to environmental and physiological cues to ensure that energy supply meets demands. One important mechanism by which this is achieved is at the level of metabolic gene expression. The transcriptional coactivators, PPAR γ coactivator-1 (PGC-1) α and β , and their target nuclear receptors (NRs), estrogen-related receptors α and γ (ERR α and γ), comprise a key gene regulatory network controlling the expression of cardiac genes involved in multiple mitochondrial energy transduction and ATP-generating pathways. The purpose of this article is to review the function of the PGC-1/ERR axis in the normal heart and the evidence that dysregulation of this circuit contributes to the metabolic and functional disturbances that lead to heart failure. The PGC-1/ERR gene regulatory pathway as a novel therapeutic candidate for metabolic modulation in cardiovascular disease will also be discussed.

PGC-1/ERR gene regulatory axis

PGC-1 Coactivators

PGC-1 α was originally described as a coactivator of peroxisome proliferator-activated receptor γ (PPAR γ), a brown adipose enriched NR, where it was shown to regulate adaptive thermogenesis and mitochondrial function [1]. Subsequently, a structurally-related protein,

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PGC-1 β , was found to be capable of regulating many of the target pathways known to be controlled by PGC-1 α [2]. It is now well-established that PGC-1 α and β are inducible, transcriptional coregulators that play a vital role in the control cellular ATP-producing capacity and mitochondrial function under basal conditions and in response to physiological stressors. The PGC-1 coactivators exert their biologic effects by directly binding to, and enhancing, the transcriptional activity of NR and non-NR transcription factors [3]. Known targets of PGC-1 coactivators expressed in heart include NR (ERR α , ERR γ , PPAR α , PPAR β/δ) and non-NR (NRF-1 and MEF2) transcription factors [4]. Together, the PGC-1 network serves to coordinately regulate the expression of numerous genes involved in mitochondrial pathways such as fatty acid oxidation (FAO), oxidative phosphorylation, and ATP synthesis along with the regulatory machinery involved in mitochondrial biogenesis (Figure 1) [5].

PGC-1 α and β are enriched in tissues with high oxidative capacity such as heart, brown adipose, kidney, and slow-twitch skeletal muscle [1,2,6]. The expression of PGC-1 α coactivators is highly inducible at the transcriptional level via the action of a variety of upstream signaling pathways (Figure 1). For example, PGC-1 α gene expression is induced by cold exposure, fasting, and exercise, all of which demand increased mitochondrial oxidative flux for ATP production or thermogenesis [1,7,8]. Transcription of the PGC-1 α gene can be influenced by CaM kinase, calcineurin, β -adrenergic receptor (β -AR)/cAMP, nitric oxide (NO) and AMP-activated protein kinase (AMPK) [9–13]. Transcription factors that transduce upstream signals to the control of PGC-1 α gene expression include cAMP response element-binding protein (CREB) and MEF2 [9,14]. The PGC-1 α promoter can also be suppressed by the action of class II histone deacetylases (HDACs) via inhibition of MEF2 activity [14]. In contrast to PGC-1 α , less is known about the transcriptional regulation of PGC-1 β ; however, recent investigations have shown that both interleukin-4 (IL-4) and interferon (IFN)- γ activate the PGC-1 β promoter via STAT6 or STAT1, respectively [15,16]. Relevant to these findings, cytokine-mediated induction of PGC-1 β is important for the oxidative burst and microbicidal function of activated macrophages [15].

PGC-1 α activity is also modulated at the post-translational level via acetylation and phosphorylation [17,18]. Acetylation of PGC-1 α can occur at multiple sites and serves to decrease its transcriptional activity. Recent evidence indicates that PGC-1 α acetylation status is regulated in large part by the balance between the deacetylase silent information regulator (SIRT)1 and acetyltransferase GCN5 [17]. When cellular energy stores are reduced, the level of NAD⁺ increases and this activates SIRT1. Subsequently, SIRT1 deacetylates PGC-1 α thereby boosting the generation of ATP and reducing equivalents via mitochondrial substrate oxidation [17]. In addition, AMPK and p38 MAPK activate PGC-1 α via direct phosphorylation [18,19]. AMPK can also facilitate activation of SIRT1, further increasing PGC-1 α transcriptional activity [20]. Similar to PGC-1 α , PGC-1 β was recently shown to be negatively regulated by acetylation [21].

PGC-1 α is also produced in variant forms via alternative splicing. One of the better characterized alternatively spliced forms of PGC-1 α contains only the amino terminal portion of the protein (termed NT-PGC-1 α), but is still capable of coactivating many of the known downstream targets [22]. Interestingly, in contrast to full-length PGC-1 α which resides in the nucleus, NT-PGC-1 α cycles between the nucleus and cytoplasm and in many conditions is predominantly cytoplasmic. Protein kinase A (PKA), and possibly other kinases can phosphorylate NT-PGC1 α , trapping it in the nucleus leading to enhanced transcription of PGC-1 α target genes [23].

ERR α / γ

ERR α and related family members, ERR β and ERR γ , were originally discovered through a screen to identify steroid hormone receptors related to the estrogen receptor (ER) [24]. However, in contrast to ER, the ERRs do not have known ligands (thus termed “orphan” nuclear receptors). ERR α was also identified in a screen for novel PGC-1 α binding partners [25]. It is now well-accepted that ERR α and γ serve key roles in the gene regulatory control of cardiac mitochondrial energetic pathways. Interestingly, current evidence indicates that ERR family members must interact with PGC-1 coactivators to be transcriptionally active, leading to the notion that PGC-1 α and β should be considered “protein ligands” for these NRs [26]. Conversely, ERR α is required for many PGC-1-dependent effects on metabolism and mitochondrial function, suggesting that this co-activator/NR pairing is intimately intertwined in a feed-forward cycle [27].

The PGC-1/ERR axis in cardiac metabolism and physiology

Significant insight into the role of PGC-1 α and β in the control of cardiac metabolism has been gained from studies of genetically-modified mouse models (Table 1). During the early postnatal period, the heart undergoes a dramatic shift in fuel utilization from glucose and lactate oxidation during the fetal period, to a high reliance on mitochondrial FAO after birth. This metabolic shift is accompanied by a surge in the expression of PGC-1 α and β mRNA and a burst of mitochondrial biogenesis [7,28]. The importance of PGC-1 coactivators in controlling perinatal mitochondrial biogenesis is supported by the observation that PGC-1 α overexpression in cardiac myocytes in vitro and in vivo in transgenic mice is sufficient to trigger mitochondrial proliferation [7]. Conversely, in mice with combined PGC-1 α / β gene disruption, perinatal mitochondrial biogenesis is arrested and the mice die within days after birth from heart failure [28]. Together, these results indicate that the PGC-1 coactivators are necessary and sufficient for postnatal metabolic maturation and cardiac function.

PGC-1 α and β also serve important functions in the adult heart. PGC-1 α -deficient mice are developmentally normal, but have reduced FAO capacity, lower exercise tolerance, and reduced cardiac reserve with dobutamine challenge or aging [28-32]. In addition, cardiac mitochondrial and FAO gene expression is modestly decreased in the absence of PGC-1 α . Of note, PGC-1 β expression is increased in PGC-1 α -deficient mice and this appears to partially compensate for the loss of PGC-1 α [28]. Similar to PGC-1 α -deficient mice, animals lacking PGC-1 β have a modest downregulation in FAO and mitochondrial gene expression and display reduced contractile reserve with dobutamine treatment [28,33-35]. The effects of PGC-1 α overexpression in the adult heart have also been investigated. Forced cardiac expression via a tetracycline-inducible, myocyte-specific transgenic system, demonstrated that PGC-1 α drives a modest mitochondrial biogenic response [36]. However, chronic overexpression of PGC-1 α in heart leads to significant mitochondrial structural abnormalities and a severe, but reversible cardiomyopathy [36]. Thus, PGC-1 α and β are potent regulators of mitochondrial proliferation/function and fuel metabolism in the adult heart.

In addition to the regulation of mitochondrial function and energy metabolism, PGC-1 α and β can also regulate the expression of genes encoding reactive oxygen species (ROS) scavengers. The production of ROS has been implicated in the pathogenesis of many diseases including heart failure, atherosclerosis, diabetes, and neurodegeneration. In cell culture, oxidant stress induced by hydrogen peroxide results in the upregulation of PGC-1 α and β and the ROS scavengers superoxide dismutase (SOD)1, SOD2, catalase, and glutathione peroxidase 1 (GPX1) [37]. Interestingly, the upregulation of ROS defense molecules is dependent on the PGC-1 coactivators [37]. The in vivo relevance of this

response is supported by the observation that PGC-1 α KO mice have reduced expression of antioxidant molecules and may be more susceptible to neurodegeneration [37].

ERR α and ERR γ mediate a number of the biologic functions of the PGC-1 coactivators. Genetically-modified mice have helped provide insight into the function of the ERRs in heart (Table 1). Several lines of evidence support the importance of ERR α and γ in the cardiac PGC-1 gene regulatory circuit. First, ERR α and γ expression in heart increases dramatically after birth in parallel with the expression pattern of PGC-1 coactivators and their target genes [25,38]. Second, ERR γ KO mice fail to make the postnatal transition to oxidative FA metabolism in the heart, similar to PGC-1 α/β double deficient mice [28,38]. Third, overexpression of ERR α leads to induction of the expression of mitochondrial and FAO genes in a profile that mimics PGC-1 overexpression [39]. Finally, PGC-1 α overexpression fails to induce the expression of genes involved in mitochondrial respiration and oxidative stress protection in cells lacking ERR α [27]. Thus, the PGC-1 coactivators and ERR family members are central partners in the regulation of cardiac metabolism and mitochondrial oxidative flux.

The PGC-1/ERR axis in cardiac pathophysiology

Fuel and energy metabolic disturbances are a well-described signature of cardiac hypertrophy and heart failure [40]. The development of pathologic cardiac hypertrophy due to pressure overload is associated with a relative increase in glucose utilization and reduction in FAO, a shift towards a fetal metabolic profile [41,42]. This metabolic shift is related to the downregulation of expression and activity of PGC-1 α , ERR α and downstream target genes (Figure 2) [43]. Although this fuel shift may initially serve an adaptive function to divert flux away from mitochondrial pathways [44], over the long-term this response is likely maladaptive leading to energy starvation and heart failure. Indeed, studies in animal models and humans have shown high energy phosphate reserves are reduced in the hypertrophied heart [45–47]. In line with the observed energetic deficiency, PGC-1 α and ERR α null mice subjected to the stress of aortic constriction develop more severe heart failure compared to WT animals [43,48]. These results suggest that chronic progressive deactivation of the PGC-1/ERR axis and consequent reduction in capacity for ATP production may play a causative role in the transition from compensated hypertrophy to heart failure.

Similar to what has been observed in cardiac hypertrophy, cardiomyopathic hearts also exhibit a reduction in oxidative fuel metabolism [49]. The extent to which this metabolic shift occurs appears to be dependent on the severity and etiology of the LV dysfunction. Positron emission tomography (PET) has shown reduced rates of FAO in patients with idiopathic dilated cardiomyopathy [49]. Animal models and human tissue have provided additional evidence that the expression and activity of PGC-1 α and ERR α is diminished in heart failure [50–52]. Although it remains unclear as to the extent that changes in PGC-1 expression are causal for heart failure, the phenotype of PGC-1 loss-of-function mice demonstrates that reduced PGC-1/ERR activity can lead to cardiac dysfunction [28,43,48]. Similarly, inhibiting PGC-1 expression via cardiac-specific overexpression of HDAC5 also produces a cardiomyopathy that is associated with mitochondrial abnormalities and myocardial lipid accumulation [14]. The upstream signals that deactivate the PGC-1/ERR circuit in heart failure are unknown, but is an area of active investigation.

In contrast to cardiac hypertrophy and heart failure, obesity-related insulin resistance and diabetes leads to increased activation of PGC-1/ERR dependent pathways, at least in the early stages (Figure 2). Obesity and insulin resistance are also associated with myocardial triglyceride (TAG) accumulation which has led to the term cardiac “lipotoxicity”. Both

animal and human studies have shown that myocardial FAO capacity is increased in response to this fat load [53–55]. Moreover, insulin resistant hearts undergo a mitochondrial biogenic response that is mediated by PGC-1 α [56]. The upregulation of PGC-1-related pathways appears to be an early compensatory mechanism to handle the excess lipid delivered to the heart in obese and diabetic states. However, in later stages of diabetes the expression of PGC-1 α and PPAR α is diminished [55–57]. Once this occurs, it is speculated that the excess fatty acids can no longer be effectively oxidized in the mitochondrion, perhaps leading to the generation of toxic lipids, accumulation of reactive oxygen species, and increased risk of heart failure [58].

Manipulating the PGC-1/ERR axis as a candidate therapeutic target

As summarized above, the PGC-1/ERR transcriptional regulatory circuit is deactivated during the development of heart failure. This observation, coupled with the known potential for PGC-1 α/β and ERR α/γ to stimulate energy production and reduce oxidative stress suggests that this transcriptional regulatory circuit could be an attractive target for prevention and treatment of heart failure and metabolic diseases. Two major proof-of-concept questions must be addressed prior to pursuing this strategy with vigor. First, how can the PGC-1/ERR cascade be activated in a way that harnesses the powerful regulatory effects without producing toxicity? In this regard, the delivery strategy is an important concern given that chronic, persistent PGC-1 overexpression in the hearts of mice produces a cardiomyopathy [7,36]. However, acute induction of PGC-1 α in skeletal muscle has been shown to increase mitochondrial respiratory capacity and augment skeletal muscle refueling after exercise without evidence of significant toxicity [59]. Thus, it may be possible to therapeutically augment PGC-1 activity using intermittent dosing regimens. Secondly, does reactivation of the PGC-1/ERR circuit prevent or ameliorate heart failure in pre-clinical models?

Assuming that proof-of-concept studies suggest that the PGC-1/ERR axis is a viable therapeutic target, it will be important to define optimal strategies to modulate this pathway. Conceptually, this could be achieved through approaches that increase either the expression or activity of one or several of these molecules. Given that PGC-1 α/β are master regulators of ERR α/γ expression and mitochondrial function, targeting the coactivators is an obvious approach. Several mechanisms to augment PGC-1 expression could be considered based on the known regulators of the PGC-1 promoter. For example, molecules that increase the activity of PKA or calcium signaling, or inhibit HDAC activity, could increase PGC-1 gene expression via CREB and/or MEF2. However, augmenting PKA activation via β -AR/cAMP signaling is counter-intuitive for the treatment of heart failure given the poor outcomes of heart failure patients treated chronically with β -adrenergic agonists [60]. Moreover, interfering with calcium signaling in heart failure would have the potential for significant off-target effects and arrhythmias. Targeting AMPK-mediated activation of PGC-1 α could also prove effective [19,61]. Interestingly, AMPK is activated by metformin, an FDA-approved drug for the treatment of diabetes. Recent evidence based on human and animal studies suggests that metformin may improve cardiac function and outcomes in patients with diabetes and heart failure [62,63]. Intriguingly, a recent report demonstrated that metformin-mediated activation of AMPK improved survival and cardiac function after myocardial infarction in animals, and that this was associated with increased levels of PGC-1 α mRNA in the heart [64]. Whether the benefit of metformin and AMPK activation is dependent on PGC-1 α is not known. Moreover, given the potential risk of lactic acidosis with the use of metformin, larger clinical studies will be necessary to determine the value and safety of metformin for the treatment of heart failure in diabetic and non-diabetic patients.

PGC-1 α and β protein activity is negatively regulated by acetylation. Thus, strategies to reduce PGC-1 acetylation represent another approach to modulate these coactivators. Published data suggests that the sirtuin SIRT1 is the predominant deacetylase for PGC-1 α/β [17,21]. The compound resveratrol activates SIRT1 enzyme activity [65], which subsequently deacetylates the PGC-1 coactivators and amplifies PGC-1 activity. Interestingly, resveratrol has been shown to be cardioprotective in a variety of heart failure models [66–68]. Whether these effects are mediated through modulating PGC-1 activity is not known. As an alternative approach, inhibiting the acetyltransferase GCN5 could reduce PGC-1 acetylation. However, both SIRT1 and GCN5 have other targets besides the PGC-1 coactivators and, thus, the potential for off-target effects is significant. Further investigation into manipulating PGC-1 acetylation status for therapeutic gain is warranted.

One potential negative aspect of activating PGC-1 activity is that it coactivates many targets, setting the stage for effects beyond the mitochondrial targets. Accordingly, targeting ERR or the PGC-1/ERR interface would activate the pathways known to be deactivated in the hypertrophied and failing heart. Agonists of ERR α have not been described. However, a recent study described a compound that activates ERR γ and its downstream mitochondrial targets in cells [69]. Moreover, it has been shown that additional coactivators, such as Bcl3, can physically interact with and modulate the transcriptional activity of PGC-1 α /ERR α [70]. This raises the possibility that targeting the PGC-1/ERR interface, rather than ERR, could have therapeutic application. The use of chemical biology screens to identify new small molecules that alter the ERR/PGC-1 transcriptional complex would be one approach to explore this concept.

Summary

The PGC-1/ERR axis is a central regulator of energy metabolism and mitochondrial function in heart. Together, these molecules orchestrate coordinated shifts in cardiac fuel and energy metabolism during cardiac development and in response to physiological stressors. Given that the activity of PGC-1 coactivators and ERRs are suppressed in heart failure caused by hypertension or late stages of diabetes, the PGC-1/ERR axis represents a novel potential therapeutic target for cardiovascular diseases. Further proof-of-concept studies investigating the consequences of PGC-1/ERR activation in animal models of heart failure are needed to address the potential benefit of this approach. If such studies prove promising, many strategies aimed at modulating this transcriptional regulatory axis can be considered.

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Figure 1. PGC-1 α and β : Inducible transcriptional coregulators of cardiac myocyte fuel and energy metabolism

The PGC-1 coactivators and their ERR nuclear receptor targets are shown schematically. A variety of upstream signaling pathways can upregulate (black arrows) or downregulate (red lines) the expression and/or activity of the PGC-1 coactivators (described in text). Together via ERR α or γ , PGC-1 α and β influence the expression of a number of genes involved in mitochondrial biogenesis, respiratory function, and mitochondrial fatty acid oxidation.

Figure 2. Dysregulation of the PGC-1/ERR axis in hypertensive and diabetic forms of cardiomyopathy

Hypertension (HTN) and diabetes (DM) lead to distinct early myocardial energy metabolic derangements that likely contribute to the pathogenesis of heart failure. HTN elicits LV hypertrophy and downregulation of PGC-1 α and ERR α related pathways. Subsequently, a decline in mitochondrial function leads to reduced capacity to generate ATP (“energy starvation”), and may contribute to the development of heart failure. In DM, myocyte lipid overload leads to an early activation of PGC-1/ERR as an adaptive response to increase capacity to burn fats in the mitochondrion. However, as the disease progresses, PGC-1 becomes “deactivated” via unknown mechanisms setting the stage for the development of lipotoxicity, energy starvation, and subsequent cardiomyopathy.

Table 1

Cardiac phenotypes of genetically modified PGC-1/ERR animal models.

Genetic Model	Comments	Cardiac Phenotype	References
PGC-1 α KO	1) Disruption of PGC-1 by insertion of additional exon 3 between exons 5-6.	1) Mild bradycardia, blunted heart rate response to dobutamine, reduced myocardial FAO capacity, slightly reduced expression of mitochondrial and FAO genes, reduced ATP generation, increased expression of PGC-1 β .	31,32
	2) Disruption of PGC-1 α gene by deletion of exons 3-5.	2) Blunted contractile response to dobutamine infusion in Langendorff ex vivo heart, reduced cardiac function with aging or pressure overload, reduced ATP generation slightly reduced expression of mitochondrial and FAO genes.	29,30,48
PGC-1 β KO	4 independent KO/KD mouse models generated	Mild bradycardia, blunted heart response to dobutamine, reduced ATP generation, slightly reduced expression of mitochondrial genes in heart and skeletal muscle, increased expression of PGC-1 α .	28,33–35
PGC-1 α/β DKO	PGC-1 α global KO mice crossed with a cardiac-specific KO of PGC-1 β	Arrest in cardiac perinatal mitochondrial biogenesis, marked reduction in cardiac mitochondria, death from heart failure in first day of life.	28
ERR α KO	Global knockout	Increased expression of PGC-1 α and ERR γ , heart failure after aortic banding; reduction of cardiac ATP/energy reserves.	39,43
ERR γ KO	Global knockout	Increased expression of PGC-1 α and ERR α , absent mitochondrial biogenesis after birth, QT prolongation on ECG, early mortality	38
PGC-1 α OE	PGC-1 α expression driven by MHC promoter	Uncontrolled mitochondrial proliferation, severe cardiomyopathy and death from heart failure	8
PGC-1 α COE	Tetracycline inducible double transgenic mouse using MHC-rtTA and TRE- PGC-1 α	Increased expression of mitochondrial genes, modest mitochondrial biogenesis, dilated cardiomyopathy within 2 weeks of PGC-1 α induction (reversible)	36

KO (knockout), KD (knockdown), DKO (double knockout), OE (overexpression), COE (conditional overexpression), TAC (transaortic constriction), rtTA (tetracycline transactivator), TRE (tetracycline response element)