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PGC-1: The Energetic Regulator in Cardiac Metabolism

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Abstract
The peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1s (PGC-1s) can induce the expression of several downstream genes that play pivotal roles in the regulation of mitochondrial biogenesis and metabolism in the heart. Moreover, PGC-1 signaling pathways have also been reported to play a critical role in cardioprotection. Given the significance of PGC-1 coactivators, we summarize the current literature on the molecular mechanisms and roles of PGC-1s in cardiac metabolism. Thus, in this review, we first introduce the basic knowledge regarding PGC-1 signaling pathways. We then discuss their roles in heart metabolism. Moreover, we describe several significant treatments that target the PGC-1 signaling pathway. This review presents the significant roles of PGC-1s in cardiac metabolism and may contribute to the promotion of PGC-1 signaling pathway as a novel therapeutic target.

1. Introduction

The human heart consumes a huge amount of energy in form of adenosine triphosphate (ATP) every day. However, ATP reserves are merely sufficient for 10 s of cardiac function; thus, a constant supply of fuel is essential. Mitochondria serve as a power plant for cardiomyocytes and provide them with ATP to sustain contractile function. Free fatty acids (FAs) are the preferred energy substrate in healthy adult heart, supplying about 70% of total ATP, whereas other substrates such as glucose and lactate may provide additional fuel sources in diverse physiological and nutritional circumstances (Palomer et al., 2013). Short term energy supply is primarily modulated by the adenosine diphosphate (ADP)/ATP ratio and cytoplasmic free Ca^{2+} in the process of the oxidative phosphorylation (OXPHOS) and the tricarboxylic acid cycle (TAC), respectively. Long term transcriptional regulation is strongly linked to cardiac function: several upstream signals, such as Ca^{2+} as a mediator of excitation-contraction (E-C) coupling and 3'-5'-cyclic adenosine monophosphate (cAMP) as a messenger of β-adrenergic pathway, activate the expression of peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1s (PGC-1s) (Tuomainen et al., 2017). PGC-1s are a family of transcriptional coactivators that consist of PGC-1α, PGC-1β, and PGC-1-related coactivator (PRC). The PGC-1 family can be regulated at both the transcriptional and post-translational levels, and they coactivate their specific partners, including estrogen-related receptors (ERRs), PPARs, and nuclear respiratory factors (NRFs). PGC-1 coactivators together with their specific partners regulate a myriad of transcription factors responsible for both energy metabolism and cardiac function, controlling mitochondrial biogenesis and

function, mediating a shift in fuel usage, and modulating reactive oxygen species (ROS) homeostasis under physiological and pathological conditions. Moreover, cardiac PGC-1 coactivators appear to exert cardioprotective effects.

The focus of this review is to summarize the latest research progress on cardiac metabolism and protective effects of the PGC-1 coactivators against cardiac diseases. First, we introduce the biology and regulation of these coactivators as well as their coactivated targets. We then discuss some of their important functions in the cardiac system. Finally, we describe several significant cardiac disease treatments that target the PGC-1 signaling pathway, including medications, exercise training, and caloric restriction. Collectively, this review presents a comprehensive picture of the roles played by PGC-1 coactivators in cardiac metabolism, and it may contribute to the design of further experimental research and the promotion of PGC-1s as new therapeutic targets.

2. An overview of PGC-1 signaling pathway

2.1. Biology of PGC-1

PGC-1s are members of a family of transcriptional coactivators that consists of PGC-1α, PGC-1β, and PRC, all of which play key roles in the regulation of mitochondrial biogenesis and metabolism. PGC-1α, the most studied member of the family, was originally identified in a yeast 2-hybrid screen as a coactivator of PPARγ following cold exposure in brown adipose tissue, where it regulates adaptive thermogenesis and mitochondrial function (Puigserver et al., 1998). The other two PGC-1s were subsequently identified by their sequence homologies to PGC-1α. PGC-1β, which is also known as PGC-1-related estrogen receptor coactivator (PERC), is capable of regulating many downstream targets controlled by PGC-1α (Lin et al., 2002). PRC, the least known member of the family, largely due to the embryonic lethal phenotype of *PRC* knockout mice, performs several functions in the regulation of mitochondrial biogenesis and inflammatory responses (He et al., 2012; Gleyzer et al., 2013). PGC-1α and PGC-1β are mainly expressed in tissues that demand high energy consumption, such as the heart, brain, brown adipose tissue, skeletal muscle, liver, and kidney, whereas PRC is expressed in all tissues. The PGC-1 family members have relatively short half-lives as a consequence of their rapid ubiquitination and proteasomal degradation (Trausch-Azar et al., 2015).

The amino acid sequence homology among the three members of the PGC-1 family is particularly high within both the N- and C-terminal ends of the proteins, where a few conserved domains have been described. (Figure 1) The N-terminal regions of PGC-1s contain a highly conserved activation domain that interacts with proteins with histone acetyltransferase (HAT) activity, including cAMP

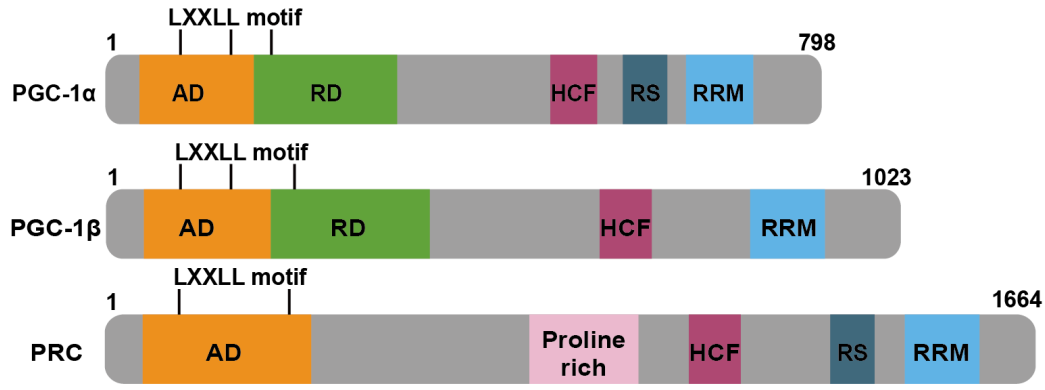

Figure 1. Domain structure of PGC-1 coactivators. The N-terminal region of PGC-1 contains a highly conserved activation domain, responsible for the interaction with coactivator complexes. Adjacent to the N-terminal region is a domain involved in the inhibition of PGC-1 activity. Moreover, the N-terminal domain contains several leucine-rich LXXLL motifs. The C-terminal region of PGC-1 contains several domains that play important roles in mRNA splicing, including RS and RRM. The C-terminal moiety also contains HCF binding site, which is implicated in cell cycle regulation and can regulate PGC-1 activity. In addition, proline-rich region is a domain involved in multiple protein associations.

response element-binding protein (CREB)-binding protein/p300 (CBP/p300) and steroid receptor coactivator-1 (SRC-1) (Puigserver et al., 1999). These HAT complexes promote the remodeling of histones within chromatin, which facilitate the access of transcriptional machinery to target genes. Although CBP/p300 and members of the p160/SRC family have intrinsic HAT activity that promotes chromatin remodeling and gene transcription, the PGC-1 family members lack such enzymatic activity (Scarpulla, 2011). Moreover, their N-terminal domains contain several leucine-rich LXXLL motifs, namely nuclear receptor (NR) boxes. NR boxes have the crucial function of mediating the interactions of PGC-1 proteins with the hydrophobic pockets of the ligand-binding domains of a wide variety of hormone NRs. Adjacent to the N-terminal region of PGC-1s is a domain of ~200 amino acids involved in the inhibition of their activity. A second activating complex that docks on the C-terminal domains of PGC-1s, namely the thyroid hormone receptor-associated protein/vitamin D receptor-interacting protein (TRAP/DRIP) complex, is responsible for activation of DNA transcription (Wallberg et al., 2003). Furthermore, the C-terminal regions of PGC-1s contain several domains that play important roles in mRNA splicing, including the serine/arginine-rich stretch (RS) domain and RNA recognition motif (RRM) (Monsalve et al., 2000). Their C-terminal moieties also contain two very well-conserved motifs of unknown functions. One of the two motifs consists of a DHDY tetrapeptide, and it has been identified as a binding site for host cell factor (HCF), the binding of which enhances PGC-1 transcriptional activity and further regulates gene expression during cell cycle progression. In addition, several interaction sites for other transcription factors have also been mapped to the C-terminal regions of PGC-1 proteins, such as myocyte enhancer factor 2C (MEF2C), PPARc, yin yang-1 (YY1) and forkhead box O1 (FoxO1), in addition to co-regulators, such as mediator complex subunit 1 (MED1) and BRG1-associated factor 60a (BAF60a) (Villena, 2015).

2.2. Regulation of PGC-1

PGC-1α expression is highly inducible at the transcriptional level in response to a variety of upstream signaling pathways. (Figure 2) For instance, PGC-1α gene expression in cardiac myocytes can be modulated by Ca^{2+}/calmodulin-dependent protein kinase (CAMK), calcineurin (Schaeffer et al., 2004), AMP-activated protein kinase (AMPK) (Zhu et al., 2010), β-adrenergic receptor (β-AR)/cAMP (Watson et al., 2007), nitric oxide (NO) (Koka et al., 2014), and autoregulatory positive feedback by PGC-1α itself (Handschin et al., 2003). The underlying mechanism involves the transduction of these upstream mediators in variable forms of cardiac stress, which results in the regulation of PGC-1α gene expression by transcription factors, such as CREB and MEF2. In addition, PGC-1α can be induced by some external stimuli that increase energy demand and ATP

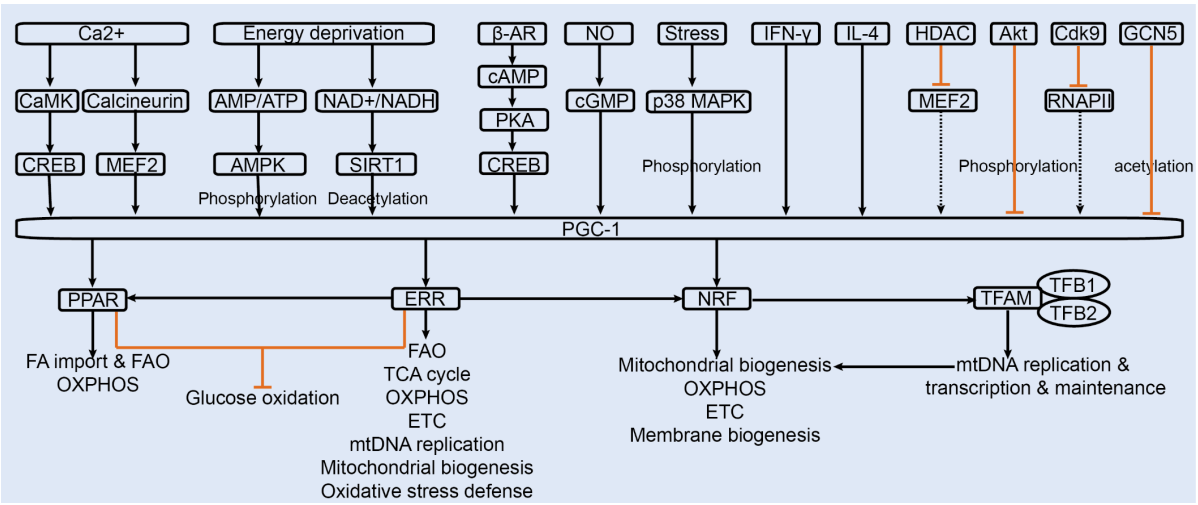

Figure 2. PGC-1 signaling pathways. The schematic indicates the potential upstream regulators of PGC-1, a variety of downstream target genes, and their related effects implicated in the cardiac system.

production, such as fasting, exercise, and cold exposure. On the other hand, a number of molecules suppress PGC-1α gene expression. For example, class II histone deacetylases (HDACs) inhibit the *PGC-1α* promoter by suppressing MEF2 activity, which plays a critical role in maintenance of cardiac mitochondrial function (Czubryt et al., 2003). Moreover, RNA polymerase II (RNAPII) can be phosphorylated by cyclin-dependent kinase 9 (Cdk9), which blocks the recruitment of RNAPII and the general transcription factor TATA-binding protein (TBP) to the endogenous *PGC-1* promoter and impedes assembly of the PGC-1 pre-initiation complex, leading to mitochondrial dysfunction in the heart (Sano et al., 2004). Thus, PGC-1α expression is regulated by multiple signals that integrate important cardiometabolic states.

PGC-1α is also widely regulated at the post-translational level via protein modifications, such as phosphorylation, acetylation, methylation, ubiquitination, and small ubiquitin-related modifier (SUMO)ylation. Importantly, protein modifications not only regulate the activities of PGC-1s but also adjust them according to specific gene programs by regulating their interactions with specific transcriptional regulators. For example, PGC-1α can be phosphorylated directly by AMPK and p38 mitogen-activated protein kinase (MAPK), which further stimulate its transactivation activity and inhibit its degradation (Gundewar et al., 2009; Scharf et al., 2013; Yu et al., 2017). AMPK also facilitates the activation of silent information regulator 1 (SIRT1), which further increases PGC-1α transcriptional activity (Canto et al., 2009; Jiang et al., 2017; Liang et al., 2017). Conversely, PGC-1α activity can be inhibited by Akt-mediated phosphorylation (Whittington et al., 2013). The underlying mechanisms may involve the direct phosphorylation of PGC-1α by Akt, which prevents the recruitment of PGC-1α to its cognate promoter regions (Li et al., 2007). In addition, multiple sites of PGC-1α can be acetylated, which has a negative effect on its transcriptional activity. Accumulating evidence suggests that PGC-1α acetylation is largely modulated by the balance between general control non-derepressible 5 (GCN5) and SIRT1 (Schilling et al., 2011). GCN5 is an acetyltransferase that are involved in the repression of PGC-1α by binding to 13 conserved arginines in PGC-1α (Lerin et al., 2006). However, SIRT1 is induced by an increase in the nicotinamide adenine dinucleotide (NAD^+) level in the presence of reduced cellular energy stores (Zhang et al., 2017). SIRT1 binds to PGC-1α in the central regulatory region between amino acids 200 and 400 and subsequently deacetylates PGC-1α, thereby promoting the production of ATP and reducing equivalents via mitochondrial substrate oxidation (Schilling et al., 2011). In addition to phosphorylation and acetylation, PGC-1α also undergoes methylation at several arginine residues in the C-terminal domain by protein arginine methyltransferase 1 (PRMT1) (Teyssier et al., 2005). Arginine methylation has been implicated in the regulation of many cellular processes that involve chromatin remodeling and transcriptional activation. In addition, PGC-1α can be SUMOylated, which attenuates its transcriptional activity (Rytinki et al., 2009). Therefore, PGC-1α expression can be regulated by various upstream signaling pathways at both the transcriptional and post-translational levels.

In contrast, the other two members of the PGC-1 family are generally less inducible. Changes in PGC-1β expression have been observed in differentiating osteoclasts, whereas the PRC level changes with cell cycle progression (Andersson et al., 2001; Vercauteren et al., 2009; Wei et al., 2010). Recent studies have demonstrated that interferon-γ (IFN-γ) and interleukin-4 (IL-4) activate the *PGC-1β* promoter via signal transducers and activators of transcription 1 (STAT1) and STAT6, respectively (Vats et al., 2006; Sonoda et al., 2007). Similar to PGC-1α, PGC-1β has recently been demonstrated to be negatively regulated by acetylation (Kelly et al., 2009). However, post-translational modifications of PGC-1β and PRC have been studied much less extensively. Above all, the expression of PGC-1 family members is influenced by numerous upstream mediators that are important for mitochondrial biogenesis and metabolism.

2.3. PGC-1-coactivated targets

Both PGC-1α and PGC-1β regulate the expression of a variety of coactivated genes, including nuclear receptors (NRs) (e.g., ERRs and PPARs), non-NRs (e.g., NRFs and MEF2), and other transcription factors. Generally, ligand-activated proteins encoded by PGC-1-coactivated genes regulate virtually all aspects of cardiac mitochondrial energy transformation, and they have been considered to be valuable therapeutic targets for metabolic and cardiac diseases. Because a detailed description of all of the coactivated targets is apparently beyond the limited length of this review, we will focus on several molecules that have been mechanistically implicated in the pathogenesis and progression of cardiac diseases and that may become potential

therapeutic targets in the future (Table 1 and Figure 2).

2.3.1. ERRs

ERRs are a group of transcription factors that include ERRα, ERRβ, and ERRγ, which activate the expression of a large number of mitochondrial genes that cover many aspects of mitochondrial oxidative metabolism, including glucose utilization, FA β-oxidation (FAO), the tricarboxylic acid (TCA) cycle, and OXPHOS (Laganiere et al., 2004). All these ERRs are abundantly expressed in the heart

Table 1. The target genes and downstream biological effects that are potentially regulated by PGC-1 coactivators in cardiac system.

Target genes	Experimental models	Downstream biological effects	Reference
ERRα	ERRα-null mouse	ERRα-null mouse exhibits mild defects but with normal mitochondrial function	(Dufour et al., 2007)
ERRα	ERRα-null mouse subjected to LV pressure overload	ERRα null results in growth defect with preserved contractile function, pathologic remodeling in response to pressure overload, and reduced high-energy phosphate reserve and ATP synthetic capacity	(Huss et al., 2007)
ERRγ	ERRγ-null mouse	ERRγ null results in inability to transition from glucose utilization to FAO, lactatemia, electrocardiographic abnormalities, cardiomyopathy, and death shortly after birth	(Alaynick et al., 2007)
PPARα	Cardiac-restricted overexpression of PPARα (MHC-PPAR) mouse	Increased myocardial FAO rates and decreased glucose uptake and oxidation	(Finck et al., 2002)
PPARα	MHC-PPARα mouse	Increased PPARα activity in the diabetic heart leads to defects in insulin signaling and STAT3 activity, cardiac insulin resistance, and reduced cardiac function	(Park et al., 2005)
PPARα	ERRα overexpression mouse	ERRα activates PPARα expression via direct binding of ERRα to the PPARα gene promoter, which further increases cellular FAO rates	(Huss et al., 2004)
PPARβ/δ	Transgenic mouse model that PPARβ/δ is constitutively activated in cardiomyocytes	Upregulation of mitochondrial biogenesis and defense, and oxidative metabolism at basal and pressure-overload conditions	(Liu et al., 2011)
PPARβ/δ	MHC-PPARβ/δ mouse	Increased myocardial glucose utilization, not accumulated myocardial lipid, and normal cardiac function	(Burkart et al., 2007)
PPARβ/δ	MHC-PPARβ/δ mouse subjected to I/R injury	Increased capacity for myocardial glucose utilization and reduced myocardial injury following I/R injury	(Burkart et al., 2007)
PPARδ	PPARδ-knockout mouse	Substantial transcriptional downregulation of lipid metabolic proteins, reduced rates of palmitate and glucose oxidation, amelioration of cardiac expression of endogenous antioxidants, increased oxidative damage to the heart, and cardiac hypertrophy	(Wang et al., 2010)
PPARδ	Cardiomyocyte-restricted deletion of PPARδ mouse	Decreased myocardial FAO, cardiac dysfunction, progressive myocardial lipid accumulation, cardiac hypertrophy, lipotoxic cardiomyopathy, congestive heart failure, and reduced survival	(Cheng et al., 2004)
PPARγ	Cardiomyocyte-specific PPARγ-knockout mouse	Suppressed Akt phosphorylation, inhibited cardiac growth and embryonic gene expression, suppressed NF-κB activity, cardiac hypertrophy, and preserved systolic cardiac function	(Duan et al., 2005)
NRF-1	NRF-1 disruption mouse	Impaired mitochondrial membrane potential and decreased mtDNA content	(Huo et al., 2001)
TFAM	TFAM disruption mouse	Mosaic cardiac-specific progressive respiratory chain deficiency, dilated cardiomyopathy, blocked atrioventricular heart conduction, and death at 2-4 weeks of age	(Wang et al., 1999)
TFAM	Transgenic mouse overexpressing human TFAM	Amelioration of the decrease in mtDNA copy number and mitochondrial complex enzyme activities, higher survival rate, improved LV function, and decreased myocardial hypertrophy, apoptosis, interstitial fibrosis and oxidative stress	(Ikeuchi et al., 2005)

Abbreviations: PGC-1, peroxisome proliferator activated receptor (PPAR)-γ coactivator-1; ERR, estrogen related receptor; LV, left ventricular; FAO, fatty acid (FA) β-oxidation; TAC, transverse aortic constriction; MHC-PPAR, myosin heavy chain-PPAR; STAT3, signal transducers and activators of transcription 3; I/R, ischemia/reperfusion; NF-κB: nuclear factor-κB; NRF-1, nuclear respiratory factor-1; mtDNA, mitochondrial DNA; TFAM, transcription factor A, mitochondrial.

and are regulated by PGC-1α. Notably, PGC-1α regulates not only the activity of ERRα but also its expression (Schreiber et al., 2003). The associated mechanism involves the binding of ERRα to conserved ERR response elements (ERREs) in its own promoter, thereby inducing its transcription in a positive autoregulatory loop once it is activated by PGC-1α (Laganiere et al., 2004). ERRs have been demonstrated to act as nonobligatory heterodimers and to target a common set of promoters involved in cardiac mitochondrial energetic pathways through the coactivation of PGC-1α (Dufour et al., 2007). Conversely, PGC-1-independent ERRα expression fails to induce target gene expression (Schreiber et al., 2004). Huss and colleagues have studied the role of the PGC-1α-ERRα signaling pathway in a mouse model subjected to left ventricular pressure overload and have revealed that ERRα is required for the adaptive response to hemodynamic stressors (Huss et al., 2007). ERRα suppression can lead to decompensated heart failure, the underlying mechanisms of which may involve myocardial phosphocreatine depletion and reduced maximal ATP synthesis. Furthermore, *ERRγ* knockout mice display downregulation of several ERR target genes in the heart, such as *Ghrpr*, *Eno1*, and *H6pd*, reflecting the inability to transition from glucose utilization to FA utilization, which eventually leads to cardiomyopathy and subsequently to death shortly after birth (Alaynick et al., 2007). It is noteworthy that ERRα and ERRγ exhibit a compensatory effect in the heart. Dufour and colleagues have found that PGC-1α and ERRγ are upregulated in the *ERRα* knockout heart, which exhibits only mild defects and normal mitochondrial function under physiological conditions (Dufour et al., 2007) and more severe phenotypes under pathological conditions such as pressure overload, with dilated hypertrophy or early heart failure, possibly caused by decreased energy reserves (Huss et al., 2007). Similar to the deletion of *ERRα*, that of ERRγ promotes the upregulation of PGC-1α and ERRα and hence alters the expression of OXPHOS genes, causing severe mitochondrial defects and eventually the death of most *ERRγ* knockout mice due to failure of the postnatal transition to oxidative FA metabolism in the heart (Alaynick et al., 2007). ERRβ is the least studied among the three ERRs, and its role in regulating mitochondrial function in the heart is unclear. Shortly, diverse PGC-1-activated ERRs have a compensatory effect and they are the master executors controlling the mitochondrial biogenic gene network in the heart. Activating PGC-1-ERR signaling pathway may present an emerging avenue for the treatment of cardiac diseases.

2.3.2. PPARs

PPARs, including PPARα, PPARβ/δ, and PPARγ, are members of the extended nuclear hormone receptor family (Issemann et al., 1990). All these PPARs are known to play essential roles in the regulation of FA uptake and oxidation in the heart. PGC-1α-activated PPARs form heterodimers with retinoic acid-activated receptors (RXRs) and bind to a specific DNA sequence or PPAR response element (PPRE) to regulate genes involved in FA metabolism (Huss et al., 2004; Rowe et al., 2010). Cardiac overexpression of *PPARα* induced by PGC-1 dysregulation causes increased FA uptake and oxidation and concomitantly decreased glucose oxidation, which can lead to spontaneous left ventricular dysfunction and lipotoxic cardiomyopathy (Finck et al., 2002; Park et al., 2005). In contrast to PPARα, cardiac overexpression of *PPARβ/δ* is relatively protective against lipotoxic cardiomyopathy and myocardial infarction (MI) (Wang et al., 2010; Liu et al., 2011). The differences in the effects of *PPARα* and *PPARβ/δ* overexpression may result from the failure of *PPARβ/δ* overexpression to induce FA import genes, such as cluster of differentiation 36 (CD36), thereby preventing the toxic accumulation of intracellular lipids (Burkart et al., 2007). On the other hand, inhibition of the PGC-1α-PPAR signaling pathway can result in decreased expression of FAO genes, which eventually leads to a series of cardiac disorders, such as cardiac dysfunction and lipotoxic cardiomyopathy (Cheng et al., 2004; Duncan et al., 2010; Wang et al., 2010). The underlying mechanism may involve a shift in substrate utilization from mainly FAO toward glucose oxidation, leading to less O_2 consumption per ATP produced. The role of cardiac PPARγ is less well understood. Although PPARγ is expressed in the heart at a level far below PPARα and PPARβ/δ, cardiac overexpression or deletion of *PPARγ* also has many detrimental effects on the heart, such as myocardial hypertrophy and heart failure (Duan et al., 2005). Therefore, these findings strongly indicate that the maintenance of balanced levels and activities of PPARs is critical for proper cardiac function in mouse PPARs genetic models. However, homozygous knockout and transgenic expression models are at the ends of the spectrum of experimental modulation. In the case of clinically relevant pharmacological therapeutics, there appears to be a therapeutic window for the use of PPARγ agonists, such as thiazolidinediones (TZDs),

for type 2 diabetes at concentrations that have little if any direct effects on the heart (Zhu et al., 2013).

Interestingly, PPARα is in turn capable of activating the *PGC-1α* promoter in certain cell types, indicating that an autoregulatory loop exists between PPARα and PGC-1α (Duncan et al., 2010). Moreover, as the *PPARα* promoter contains a functional ERRE, PPARα expression can be activated by ERRα, which provides an additional site of cross-regulation (Huss et al., 2004). Furthermore, the presence of PPARα is required for the ERRα-mediated regulation of a series of FAO targets in MEFs (Giguere, 2008). Thus, these data underscore the existence of multiple positive feedback loops that drive metabolic gene expression pathways in the heart.

2.3.3. NRFs

Two NRF isoforms, termed NRF-1 and NRF-2 (also known as GABP), are the first vertebrate regulatory factors implicated in the global expression of genes involved in multiple mitochondrial functions (Virbasius et al., 1993; Virbasius et al., 1993). NRFs regulate the expression of nuclear genes required for mitochondrial OXPHOS. Mitochondria are composed of over 1,500 proteins that are encoded by both mtDNA and nuclear DNA (nDNA). The mitochondrial genome contains 37 genes encoding 22 transfer RNAs (tRNAs), 2 ribosomal RNAs (rRNAs), and 13 subunits present in complexes I, III, IV, and V. Apart from these, all the other mitochondrial proteins are encoded by nDNA. Notably, crosstalk occurs between mtDNA and nDNA via nuclear-encoded proteins, including mitochondrial transcription factor A (TFAM) and mitochondrial transcription factor B (TFBM), both of which are induced by PGC-1α-activated NRFs (Pohjoismaki et al., 2012; Villena, 2015). Once NRFs are activated, TFAM subsequently binds to both strands of mtDNA, and it is essential for mtDNA replication, transcription, and maintenance (Kukat et al., 2013). Both an impaired mitochondrial membrane potential and a decreased mtDNA content have been observed in a *NRF-1* knockout model, implying that NRF-1 has a role in stabilizing mitochondrial function as a coactivated effector of PGC-1 activation (Huo et al., 2001). Additional studies have shown that *TFAM* deletion in cardiac tissue results in a significant decrease in the electron transport capacity and mtDNA content, which further causes cardiomyopathy and heart failure (Wang et al., 1999). Conversely, increased TFAM expression in cardiac tissue plays a protective role against heart failure induced by MI (Ikeuchi et al., 2005). These results indicate that stimulation of the PGC-1α signaling pathway may protect against cardiac diseases via the activation of NRFs. On the other hand, NRFs also control the expression of nuclear genes encoding respiratory chain subunits and other proteins required for mitochondrial function. For instance, NRF-1 can induce MEF2 to coordinate the expression of mitochondrial respiratory chain subunits (Ramachandran et al., 2008). Along with the direct regulation of PGC-1α by MEF2A, this network provides a positive feedback loop through NRF-1, MEF2A, and PGC-1α to control mitochondrial function and content in cardiac myocytes (Aubert et al., 2013).

3. Role of PGC-1 in cardiac metabolism

3.1. Mitochondrial biogenesis

Both PGC-1α and PGC-1β are highly expressed in cardiac myocytes and have been confirmed to be key factors for myocardial mitochondrial biogenesis. Cardiac PGC-1α potently induces mitochondrial biogenesis in both cell culture and transgenic animals (Patten et al., 2012). PGC-1α expression in the heart increases significantly at birth, consistent with the metabolic switch from glycolysis to OXPHOS in cardiac myocytes and the burst of mitochondrial oxidative capacity (Martin et al., 2014). However, mitochondrial biogenesis is decreased with aging (Russell et al., 2004). Both PGC-1α and PGC-1β can coactivate a set of transcription factors, including ERRs, PPARs, NRFs, and likely others, which robustly induce the expression of a large number of nuclear genes that encode almost all mitochondrial proteins involved in FAO, the TCA cycle, and the electron transport chain (ETC). For instance, PGC-1s induce the expression of CD36 and FA transport proteins (FATPs) mainly by co-activating PPARs, which increase FA uptake in cardiac myocytes (Patten et al., 2012). Moreover, PGC-1s regulate FA flux and storage in the process of lipolysis of cellular triglycerides by adipose triglyceride lipase (ATGL) (Haemmerle et al., 2011). FAO in mitochondria generates reducing equivalents and acetyl-CoA, which subsequently enters the TCA cycle and generates additional reducing equivalents to fuel the ETC and ATP synthesis. In addition to nuclear-encoded genes, mitochondrial biogenesis requires the replication and transcription of the mitochondrial genome itself. The activation of TFAM, TFBM, and mitochondrial polymerases by the PGC-1 coactivators may participate in the process. Thus, PGC-1s regulate mitochondrial biogenesis by

coordinating the expression of mitochondrial proteins encoded by both the nuclear and mitochondrial genomes.

Accumulating loss-of-function studies have shown that *PGC-1α* deletion results in the impaired expression of genes involved in OXPHOS and FAO, which leads to a reduced ability to maintain body temperature upon cold exposure. In addition, *PGC-1α*-deficient mice display decreased cardiac energy reserves, a reduced heart rate and contractile function, and impaired inotropic and chronotropic responses. They also respond poorly to physiological and pathophysiologic stresses, such as exercise, fasting, chronic pressure overload, and ischemic insult (Arany et al., 2005; Arany et al., 2006). Moreover, *PGC-1α* knockout contributes to the development of cardiomyopathy mainly as the result of a metabolic switch. The related mechanisms could involve reductions in the maximal capacities for mitochondrial ATP synthesis and FAO and an increase in triglycerides due to reduced consumption (Lehman et al., 2008). Several studies have demonstrated that *PGC-1β* knockout mice have only mildly abnormal cardiac phenotypes, with relatively normal contractile function but impaired chronotropic responses under stressed conditions (Lelliott et al., 2006; Lai et al., 2008). A lack of both *PGC-1α* and *PGC-1β* significantly diminishes the cardiac mitochondrial content, causing mice to die within 24 hours after birth because of heart failure (Lai et al., 2008; Patten et al., 2012). However, the above data came from global *PGC-1* knockout mice, so we must take for consideration that the cardiac phenotype might be a consequence of the systemic alterations induced by *PGC-1* knockout rather than direct cardiac effects. A critical evaluation of the role of PGC-1s in cardiac function in intact animals thus requires the cardiac-specific knockout of *PGC-1s*. Fortunately, a recent study has eliminated systemic alterations such as glucose homeostasis induced by inhibition of PGC-1 and its coactivated targets, as evidenced by a distinctive mitochondrial cristae-stacking abnormality in the model of cardiac-specific inducible *PGC-1α/β* double-deficient mouse (Lai et al., 2014). This suggests that PGC-1α and PGC-1β contribute to mitochondrial structural integrity and function. The integrity and function of mitochondrion in the heart also depend partly on its membrane structure, including cardiolipin. A genetic defect in cardiolipin remodeling leads to modification in mitochondrial ultrastructure and function. Therefore, PGC-1α and PGC-1β regulate mitochondrial structural integrity and function by regulating phospholipid synthesis. These results suggest that PGC-1α and PGC-1β have synergetic functions and collectively support mitochondrial biogenesis in the heart.

Conversely, increasing gain-of-function studies have shown that PGC-1α is a powerful driver of cardiac mitochondrial biogenesis (Villena, 2015) and that the complex effects may vary dramatically between neonatal and adult hearts. PGC-1α overexpression in rat neonatal cardiac myocytes is beneficial, as demonstrated by increases in mitochondrial biogenesis, oxygen consumption, and coupled respiration. However, its overexpression in the adult mouse heart leads to uncontrolled mitochondrial biogenesis, aberrant mitochondrial structures, and reversible dilated cardiomyopathy, which can be completely reversed when PGC-1α expression is knocked out (Lehman et al., 2000; Russell et al., 2004). Although increased mitochondrial biogenesis provides benefits to the heart, it is important to carefully maintain PGC-1α expression at a moderate level to prevent adverse effects. Notably, PGC-1β overexpression in the adult heart does not appear to cause cardiac dysfunction. In fact, PGC-1β overexpression prevents cardiac dysfunction in a model of septic cardiomyopathy (Schilling et al., 2011). Therefore, ectopic expression of PGC-1β seems to be safer.

3.2. Fuel shift

As a self-renewing biological pump, the heart converts chemical energy into mechanical energy by utilizing the most efficient fuel to produce ATP for contraction. The sources of ATP the heart needs are diverse, which come from FAs, glucose, lactate, ketone bodies, and (under extreme circumstances) amino acids. To secure the availability of energy substrates, the heart has developed into a "metabolic omnivore" where the source of ATP production can be changed from one fuel to another (Baskin et al., 2011). During fetal development, the heart primarily consumes glucose and lactate due to relatively hypoxic environment and lower FA levels (Rowe et al., 2010). Soon after birth, heart function significantly improves as exposed to an oxygen-rich environment, consistent with the activation of multiple genes involved in FA transport and FAO by long-chain FAs contained in maternal milk (Janssen et al., 2014); thus, a dramatic shift in fuel utilization occurs from glucose and lactate oxidation toward high reliance on mitochondrial FAO (Lai et al., 2008). Emerging evidence suggests that PGC-1 coactivators play a pivotal role in the shift of substrate utilization. The PGC-1s mainly interact

with PPARα, and further mediate this shift (Taegtmeyer et al., 2010). It has recently been shown that FAs liberated from the triacylglyceride pool by the actions of ATGL are also required to activate PPARα signaling (Carley et al., 2014). Overall, perinatal changes in myocardial metabolism are mainly driven by the activation of the PPARα by long-chain FAs, which are contained in maternal milk.

When subjected to pathological conditions such as myocardial hypertrophy and heart failure, there is a mismatch among FA uptake, triacylglyceride turnover, and PPARα activation (Carley et al., 2014). Increasing studies have indicated that a shift away from FAO and back to glucose oxidation occurs partly due to the downregulation of PGC-1α and its coactivated targets, such as PPARs (Huss et al., 2007; Abel et al., 2011). On the other hand, glucose oversupply results in the activation of mTOR pathway (Kundu et al., 2015). In an effort to maintain a delicate balance between energy transformation and utilization, this fuel shift may initially serve as an adaptive transition and play a compensatory role in meeting the energy demands of contraction by adapting metabolic machinery of heart. However, over a long period of time, this metabolic shift may be maladaptive and ultimately lead to energy starvation and cardiac diseases (Schilling et al., 2011; Kundu et al., 2015). Indeed, studies of animal models and humans have shown that high-energy phosphate reserves are reduced in the hypertrophied and failing hearts. Moreover, increased myocardial glucose uptake precedes the onset of left ventricular hypertrophy and heart failure (Sen et al., 2013). Furthermore, early intervention to attenuate glucose uptake can prevent the maladaptive metabolic response and preserve cardiac function (Kundu et al., 2015). Therefore, glycometabolic disorder is a prominent feature of the maladapted failing heart.

Collectively, the PGC-1 coactivators are important regulators of the fuel shift in the courses of both physiological and pathological conditions. Targeting the fuel shift may offer new opportunities to rebuild the hypertrophied and failing hearts, however, several unresolved questions remain to be more completely answered. For example, is the fuel shift simply a phenomenon accompanying the progression of underlying diseases? Alternatively, does it contribute to pathological remodeling?

3.3. Reactive oxygen species (ROS)

Mitochondrial activity inevitably generates toxic byproducts, such as ROS, which can lead to heart failure, atherosclerosis, and diabetes (Schilling et al., 2011). Excessive production of ROS in the myocardium is a leading cause of oxidative stress, resulting in myocardial damage. The major site of ROS generation in most cells is the mitochondrial ETC (Ma et al., 2017). Electrons exit the ETC and interact with free oxygen, which further yields partially reduced oxygen species that are highly reactive (Patten et al., 2012). The expression of PGC-1 has been demonstrated to increase by physical exercise even in rat cardiac muscle and is restored to control levels by the antioxidant treatment (Venditti et al., 2016). Moreover, several lines of evidence suggest that PGC-1α, which is closely associated with the ETC, transcriptionally modifies pathways involved in ROS production or scavenging in the heart (Lu et al., 2010). PGC-1α can efficiently scavenge ROS by reducing the mitochondrial membrane potential, which decreases oxidative stress in the mitochondria and thus plays a protective role against cardiac diseases such as myocardial ischemia/reperfusion (I/R) injury (McLeod et al., 2005). The related mechanism may involve the expression of several uncoupling proteins (UCPs) partly induced by PGC-1α, which are inner mitochondrial membrane proteins that dissipate the protein gradient across the inner mitochondrial membrane (Girnun, 2012). Furthermore, the PGC-1-NRF signaling pathway mediates antioxidant gene expression. The selective functional incapacity of NRFs has been demonstrated to result in failure to maintain mitochondrial DNA (mtDNA) replication and OXPHOS gene expression, which contributes to increased ROS generation in infected cardiac myocytes (Wan et al., 2012). Moreover, PGC-1 coactivators induce ROS scavengers, such as superoxide dismutase 1 (SOD1), SOD2, catalase, and glutathione peroxidase 1 (GPX1), which counterbalance the release of ROS or transform them into less reactive species upon oxidant stress (Sun et al., 2014). Overall, PGC-1 coactivators modulate oxidative stress generation, suggesting that targeting these coactivators in cardiac myocytes may be a novel therapeutic approach for the prevention and treatment of myocardial damage.

4. Significant treatments that target the PGC-1 signaling pathway

PGC-1α has been reported to play a critical role in cardioprotective therapies. A summary of several significant cardiac disease treatments targeting the PGC-1 signaling pathways, including medications, exercise training, and caloric restriction, are presented in Table 2.

4.1 Treatment with medication

Medications that target PGC-1 signaling pathways may be useful for the alleviation and prevention of cardiac diseases. Losartan is an angiotensin II receptor antagonist with antihypertensive activity. It has been widely accepted that the activity and expression of PGC-1α and left ventricular function are markedly suppressed following acute MI (AMI). Sun and colleagues have found that losartan increases PGC-1α gene expression, which further ameliorates the adverse effects of AMI and preserves left ventricular function (Sun et al., 2007). Additionally, catecholamine, a class of hormones and drugs used for the treatment of end-stage heart failure, might stimulate PGC-1α expression via cAMP-mediated mechanisms (Puigserver et al., 1998). Bezafibrate, a PPAR pan-agonist used clinically to treat hyperlipidemia by increasing FAO, has also been shown to increase PGC-1α expression and mitochondrial biogenesis. Bezafibrate reduces the risks of developing coronary heart disease and MI and the incidence of cardiac mortality in metabolic syndrome patients. However, further studies are needed because bezafibrate has low potency and possible toxic effects (Dillon et al., 2012). Fenofibrate, a non-selective PPAR agonist, can restore cardiac expression of PGC-1α and PGC-1β, which reverse systemic lipid accumulation, normalize oxidative

Table 2. Effects of the regulation of PGC-1 coactivators in cardiac diseases.

Treatment		Diseases	Effects	Reference
Medication	Losartan	MI	Losartan increases PGC-1α expression, reserves the adverse effects of MI, and preserves left ventricular function	(Sun et al., 2007)
	Catecholamine	Heart failure	Catecholamine stimulates PGC-1α expression via cAMP-mediated mechanisms	(Puigserver et al., 1998)
	Bezafibrate	Coronary heart disease and MI	Increased PGC-1α expression, mitochondrial biogenesis, and FAO	(Dillon et al., 2012)
	Fenofibrate	Cardiomyopathy	Activation of the PGC-1-PPARα signaling pathway	(Haemmerle et al., 2011)
	SAL	Myocardial I/R injury	Activation of the PGC-1α-NRF1/NRF2 signaling pathway	(Ping et al., 2015)
	APS	Iso-induced myocardial hypertrophy	TNF-α inhibition, PGC-1α upregulation, improved energy biosynthesis, and amelioration of myocardial hypertrophy	(Luan et al., 2015)
	Pioglitazone	Myocardial I/R injury	Pioglitazone increases PGC-1α expression, suppresses myocardial apoptosis, and decreases infarct size	(Shen et al., 2014)
	Diazoxide	Myocardial I/R injury	Pretreatment with diazoxide protects myocardial mitochondria against I/R injury by mimicking IPC and the mechanism of action may involve the activation and overexpression of PGC-1α	(Han et al., 2010)
	CVB-D	DOX-induced cardiomyopathy	Pretreatment with CVB-D inhibits the repression of PGC-1α, NRF-1, and mtDNA copy number, preserves mitochondrial biogenesis, and attenuates DOX-induced cardiac contractile dysfunction and histological alterations	(Guo et al., 2015)
Exercise training	Aerobic interval training	MI	Increased nuclear PGC-1α expression and amelioration of mitochondrial dysfunction	(Jiang et al., 2014)
	A 3-week swimming training	MI	A 3-week swimming training increases mtDNA replication and transcription, reduces myocardial infarct size, and abolishes MI-induced autophagy and apoptosis via activating the PGC-1α signaling pathways	(Tao et al., 2015)
	Short-term endurance exercise training	DOX-induced cardiomyopathy	Increased PGC-1α expression, decreased FoxO1 and MuRF-1 expression	(Kavazis et al., 2014)
Caloric restriction	Long-term caloric restriction	Ischemic myocardial injury	SIRT1 activates both autophagy, by deacetylating autophagy proteins, and mitochondrial biogenesis, via activation of PGC-1α	(Carreira et al., 2011)

Abbreviations: PGC-1, peroxisome proliferator activated receptor (PPAR)-γ coactivator-1; MI, myocardial infarction; mtDNA, mitochondrial DNA; DOX, doxorubicin; FoxO1, forkhead box O1; MuRF-1, muscle ring finger-1.

function in mitochondria, improve cardiac performance, and prevent lethal cardiomyopathy. Exogenous FAs are activated and then either enter mitochondria for oxidation or become re-esterified and stored within lipid droplets after entering the cell. ATGL-mediated hydrolysis of TG stores provides ligands for functional signaling by the PGC-1-PPARα complex, which activates mitochondrial biogenesis and OXPHOS (Haemmerle et al., 2011). This opens the possibility of clinical application of activating PGC-1-PPARα signaling pathway for the treatment of patients with neutral lipid storage disease with myopathy. Salidroside (SAL), an effective extracted component from *R. crenulata*, is a traditional Chinese medicine that has been recognized as a plant-derived adaptogen capable of maintaining physiological homeostasis upon exposure to stress. Accumulating evidence suggests that SAL has protective effects on many cardiac diseases such as myocardial I/R injury (Xu et al., 2013). Recently, Ping and colleagues have demonstrated that SAL improves myocardial mitochondrial respiratory function by stimulating the expression of PGC-1α-NRF-1/NRF-2 pathway during cardioprotection (Ping et al., 2015). Therefore, SAL may be a novel treatment option for the prevention and treatment of myocardial damage. In conclusion, all these data indicate that activation of the PGC-1 signaling pathways confers benefits to the impaired heart. However, there clearly are limited drugs that activate PGC-1 and all have pleiotropic effects beyond PGC-1 activation; thus, the nature and frequency of safety problems that might occur remain a mystery.

4.2 Exercise training treatment

Accumulating studies suggest that the protective role of exercise training in cardiac diseases may involve the activation of PGC-1α expression. It has been demonstrated that aerobic interval training suppresses pathological remodeling via promotion of nuclear PGC-1α expression, thus inhibiting mitochondrial dysfunction following MI in rats (Jiang et al., 2014). In another study on the effect of exercise training, Tao and colleagues have used a C57BL/6 mouse model of AMI induced by left coronary artery (LCA) ligation, which induces a fuel shift from FAO to glucose metabolism in the myocardium, along with the downregulation of PPARα and PPARγ. They have reported that 3-week swimming training attenuates myocardial infarct size and represses AMI-induced autophagy and apoptosis. The related mechanism may involve adaptive increases in mtDNA replication and transcription during the acute phase of MI promoted via induction of the PGC-1α signaling pathways (Tao et al., 2015). It has also been found that short-term endurance exercise training promotes cardiac PGC-1α expression, protecting against drug-induced cardiomyopathy, such as that caused by DOX, a potent antitumor agent used in cancer treatment. These cardioprotective effects of exercise might be attributable to the suppression of FoxO1 activity by increased PGC-1α expression, which leads to decreased expression of FoxO1 target genes, including MuRF-1 (Kavazis et al., 2014; Xin et al., 2017). These results confirm that exercise training reduces mitochondrial dysfunction in the heart via upregulation of PGC-1 signaling pathways, which provides an emerging approach for the treatment of cardiac diseases. There is no doubt that exercise also activates other pathways that exert PGC-1-independent cardiac protective effect, as evidenced by aerobic interval training that improves myocardial SERCA2a performance. This confers a primary effect on normalization of Ca^{2+} handling and improvement of contractility of cardiac muscle (Kemi et al., 2008). Another typical example is that exercise training normalizes the expression of adiponectin and its receptors in patients with chronic heart failure, reversing disorders in lipid and glucose metabolism and further exerting beneficial effects (Van Berendoncks et al., 2011).

4.3 Caloric restriction treatment

Caloric restriction is also a potential research direction, which improves myocardial ischemic tolerance. Long-term caloric restriction mice exhibit a significant increase in cardiac PGC-1α level, supporting optimal energy metabolism and biochemical adaptation, which is necessary for maintaining energy homeostasis (Ranhotra, 2010). The cardioprotection afforded by long-term caloric restriction seems to occur via a NO-dependent increase in nuclear SIRT1 content. A possible mechanism is that SIRT1 activates PGC-1α expression, which improves mitochondrial biogenesis. In addition, SIRT1 can activate autophagy by deacetylating autophagy proteins (Carreira et al., 2011; Yu et al., 2017). These results suggest that caloric restriction ensures good mitochondrial function by promoting mitochondrial turnover via activation of PGC-1α.

5. Conclusions

This review elaborates upon the emerging roles of PGC-1 coactivators in cardiac metabolism. In summary, multiple upstream signals and protein modifications regulate the activity and expression of

PGC-1 coactivators. Upon activation, these coactivators initiate the expression of a number of coactivated genes, such as those encoding ERRs, PPARs, and NRFs, which regulate virtually all aspects of mitochondrial energy transformation in the heart. In addition to regulating mitochondrial biogenesis, PGC-1 coactivators mediate a dramatic fuel shift from glucose oxidation toward FAO, which is reversed in the course of cardiac diseases via regulation of their coactivated targets, PPARs. Moreover, PGC-1 coactivators influence the expression of anti-oxidative enzymes and efficiently scavenge ROS, thereby decreasing oxidative stress in the mitochondria; thus, they play a protective role against myocardial damage. It is well accepted that the activity and expression of PGC-1α are significantly repressed in the setting of cardiac diseases, accompanied by energetic abnormalities in the heart. The upregulation of PGC-1 signaling pathways appears to be a promising strategy for the alleviation and prevention of cardiac diseases. Moreover, a pre-treatment that targets PGC-1 signaling pathways might effectively protect the myocardium from damage. PGC-1 coactivators, as well as their numerous upstream mediators and coactivated genes, provide researchers with many opportunities to explore therapeutic strategies.

Although enormous evidence has clarified specific underlying mechanisms of cardiac metabolism regarding PGC-1 in cardiac metabolism, the development of successful treatments that target PGC-1 remains in its infancy, and future studies are necessary. Data regarding the pathological implications of PGC-1 coactivators on rodent and human cardiac diseases are restricted, often contradictory and mostly limited to PGC-1α. Future research should focus on illustrating the signaling network of PGC-1 coactivators in cardiac diseases. Moreover, there are still many issues to be resolved. For example, how does the activity and expression of PGC-1 coactivators altered in human cardiac diseases? How could the PGC-1 signaling pathways be controlled in a manner that exerts powerful and highly regulatory effects without causing concurrent adverse side effects? Therefore, prior to the investigation of therapies that target PGC-1 signaling pathway, a more comprehensive and detailed view regarding the role of PGC-1 in cardiac metabolism and cardiac diseases is necessary.

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