Peroxisome proliferator-activated receptor γ coactivator-1α in heart disease (Review)

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Abstract. Heart disease (HD) is a general term for various diseases affecting the heart. An increasing body of evidence suggests that the pathogenesis of HD is closely related to mitochondrial dysfunction. Peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) is a transcriptional coactivator that plays an important role in mitochondrial function by regulating mitochondrial biogenesis, energy metabolism and oxidative stress. The present review shows that PGC-1α expression and activity in the heart are controlled by multiple signaling pathways, including adenosine monophosphate-activated protein kinase, sirtuin 1/3 and nuclear factor κB. These can mediate the activation or inhibition of transcription and post-translational modifications (such as phosphorylation and acetylation) of PGC-1α. Furthermore, it highlighted the recent progress of PGC-1α in HD, including heart failure, coronary heart disease, diabetic cardiomyopathy, drug-induced cardiotoxicity and arrhythmia. Understanding the mechanisms underlying PGC-1α in response to pathological stimulation may prove to be beneficial in developing new ideas and strategies for preventing and treating HDs. Meanwhile, the present review explored why the opposite results occurred when PGC-1α was used as a target therapy.

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Abbreviations: AMP, adenosine monophosphate; AMPK, adenosine monophosphate (AMP)-activated protein kinase; APN, adiponectin; AS, atherosclerosis; ATP, adenosine triphosphate; CHD, coronary heart disease; DCM, diabetic cardiomyopathy; DIC, drug-induced cardiotoxicity; HDs, heart diseases; HF, heart failure; I/R, infarct/reperfusion; MI, myocardial infarct; NF-κB, nuclear factor κB; NRF1/2, nuclear respiratory factor1/2; Nrf2, nuclear factor, erythroid 2 like-2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; ROS, reactive oxygen species

Key words: peroxisome proliferator-activated receptor γ coactivator-1α, heart disease, mitochondrial, energy metabolism, oxidative stress

Contents

1. Introduction

Heart disease (HD) is a general term for various diseases affecting the heart, such as heart failure (HF), coronary heart disease (CHD) and cardiomyopathy. The heart is a highly energy-efficient organ. Mitochondria play an important role in the maintenance of myocardial cell bioenergetics via adenosine triphosphate (ATP) production. Mitochondrial dysfunction can promote oxidative stress, calcium imbalance, metabolic reprogramming, abnormal intracellular signal transduction and apoptosis in cardiomyocytes (1). Therefore, mitochondrial-dependent pathways may represent attractive therapeutic targets for human HD.

Peroxisome proliferator-activated receptor (PPAR) γ coactivator-1α (PGC-1α) is encoded by the *PPAGC1A* gene situated on chromosome 4p15.2, which is expressed in most cells and is recognized as a coactivator transcription factor for maintaining the transcriptional activation of target genes related to mitochondrial biosynthesis, energy metabolism and oxidative stress (2). The heart is a very efficient tissue where ATP and PGC-1α are highly expressed. HDs caused by changing PGC-1α comprise genetic or pathological stimuli factors (such as hyperglycemia or hyperlipidemia). Gly482Ser (rs8192678) polymorphism is the most frequently studied *PPARGC1A* polymorphism. Genetic evidence suggests that the PGC-1α Gly482Ser mutant variant increases the risk of type II diabetes, coronary artery disease and hypertension

induced-left ventricular hypertrophy and diastolic dysfunction (3-5). PGC-1α can also serve as an oxidative stress regulator or energy receptor to respond to stimuli in the heart. For example, PGC-1α mediates the elimination of reactive oxygen species (ROS) by binding to and co-activating the nuclear factor erythroid 2 like-2 (Nrf2) and its downstream antioxidant genes (6). A heart-specific PGC-1α deficiency can result in HF and is considered a model of energy-related HF, which leads to the compromised utilization of both glucose and fatty acids as well as reduced mitochondrial function (7). This suggests that mutations or changes in PGC-1α may contribute to the pathogenesis of HD.

The present review elucidated recent research on the roles of PGC-1α signaling pathways in various HDs, including cardiac hypertrophy and HF, CHD, myocardial infarct (MI), infarct/reperfusion (I/R), diabetic cardiomyopathy (DCM), drug-induced cardiotoxicity (DIC) and arrhythmia. It focused on the interaction between PGC-1α and HD, specifically examining the upstream of PGC-1α and its post-translational modifications in HD pathogenesis. In addition, it discussed the therapeutic potential of PGC-1α in HD and its role as a diagnostic biomarker.

2. Structure of PGC-1α

PGC-1α is highly conserved and located on the reverse strand of human chromosome 4 (mouse chromosome 5). Although variants have been reported, the most well-studied PGC-1α is expressed from a proximal promoter and encodes a protein containing 797 amino acids. PGC-1α contains an amino terminal activation domain with LXXLL/LXXLL/LLXXL motifs that mediate binding and coactivation of several nuclear receptors and transcription factors, such as PPARs or NRF1/2. This complex can serve as a docking scaffold for histone-modifying enzymes, mediator complex and RNA splicing machinery (2,8).

3. Upstream of PGC-1α

Adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling pathway. AMPK acts as a cellular energy receptor and regulates lipid metabolism and glucose metabolism. Under stress, such as hypoglycemia or hypoxia, the AMPK signaling pathway in cells is activated in response to changes in the AMP/ATP ratio, while the catabolic process of ATP production is promoted to restore the energy balance (9). The role of AMPK in HD is currently controversial. Certain studies have found that AMPK is activated as an adaptive and protective response in a number of models of cardiac injury such as pressure overload-induced cardiac hypertrophy or ischemia (10,11). However, mice with HF with preserved ejection fraction (HFpEF) show a significant reduction in AMPK activity (12). Cardiomyocyte-specific AMPK knockout mice can also develop left atrium (LA) remodeling and atrial fibrillation (12). Regardless of whether AMPK is activated or inhibited in HD, activating AMPK is considered a beneficial effect (13).

AMPK increases ATP production by promoting mitochondrial biogenesis (9). PGC-1α is the main regulatory factor for mitochondrial biogenesis (2). Further research has revealed that AMPK directly enhances the activity of PGC-1α by phosphorylating the threonine-177 and serine-538 sites of PGC-1α (14). When cells are subjected to oxidative stress, activation of the AMPK/PGC-1α signaling pathway promotes transcription of genes related to mitochondrial biogenesis and fatty acid oxidation to meet energy demands (15). In addition, AMPK promotes the activation of transcription factor EB to directly activate the promoter of the gene encoding PGC-1α (16). Therefore, the AMPK/PGC-1α signaling pathway plays important roles in metabolism homeostasis and HD.

Sirtuin (SIRT)1/3 signaling pathway. Sirtuins (SIRT1-SIRT7), a family of NAD^+-dependent protein-modifying enzymes, play an important role in cardiovascular diseases such as atherosclerosis, myocardial infarction, DIC and HF by regulating glucolipid metabolism, oxidative stress and inflammatory response (17). SIRT1, a major member of the SIRT family, is responsible for the deacetylation of PGC-1α in the nucleus. PGC-1α deacetylation can enhance binding ability using transcription factors, such as nuclear respiratory factor1/2 (NRF1/2), estrogen-related receptors or PPARs. Moreover, it can enhance cellular energy metabolism and oxidative stress capacity, adapting to different physiological conditions (18). SIRT1 can cause deacetylation and activation of liver kinase B1 to increase AMPK activation. AMPK activation increases SIRT1 activity through upregulation of NAD^+ level (19). The interaction between AMPK and SIRT1 plays an important role in regulating physiological and pathological processes of the heart by regulating PGC-1α or other genes (13,20). In addition, SIRT3 can promote AMPK phosphorylation and increase PGC-1α activity (21). Ultimately, changes in PGC-1α activity will affect cardiac function.

Nuclear factor κB (NF-κB) pathway. The NF-κB signaling pathway is a central regulator of immunity and inflammation (22), which has recently emerged as important factors in a wide variety of HDs including atherosclerosis, cardiac remodeling and HF (23). Recent research has revealed that NF-κB and PGC-1α exert mutual regulatory effects. During inflammation, NF-κB signaling is activated and p65 binding to the PGC-1α promoter reduces PGC-1α expression and activity in a dose-dependent manner (24). This ultimately leads to downregulation of antioxidant target genes and the oxidative stress response. Simultaneously, oxidative stress will promote inhibitor kappa B alpha (IκBα) phosphorylation and subsequently increase p65 nuclear translocation, thereby exacerbating inflammatory factor release (25). Therefore, cross interaction between NF-κB and PGC-1α regulates the inflammatory response and HD.

Calcium (Ca^{2+}) homeostasis. Cardiac Ca^{2+} homeostasis is a key regulator of excitation-contraction coupling. Impaired Ca^{2+} homeostasis damages mitochondria and heart function, causing HF or other HDs (26). Ca^{2+}-induced elevations in PGC-1α expression via the following mechanisms: i) p38 MAPK activation (27) and ii) AMPK phosphorylation activation (28). More direct evidence shows that cardiac-specific kinase-dead calcium/calmodulin-dependent protein kinase kinase-β mice leads to cardiac remodeling and HF through phosphorylation

of AMPK and by upregulation of PGC-1α (29). Meanwhile, PGC-1α affects Ca^{2+} homeostasis by regulating Ca^{2+} release from the sarcoplasmic reticulum (SR) (30). Therefore, cross interaction between Ca^{2+} homeostasis and PGC-1α plays an important role in HD.

4. Roles of PGC-1α in heart-related processes

PGC-1α is a key regulatory factor for the development and maturation of myocardial cells with functions in energy metabolism, inflammation, oxidative stress and contraction reaction. Therefore, the regulation of PGC-1α is crucial for cardiac homeostasis and PGC-1α signal transduction disorders are associated with various HDs. Specifically, PGC-1α deactivation will lead to the occurrence and development of cardiac hypertrophy, HF, CHD, DCM, DIC and arrhythmia.

Cardiac hypertrophy and HF

Cardiac hypertrophy. Myocardial hypertrophy is widely defined as an increase in heart mass and volume to cope with various factors, such as a continuous increase in blood pressure and blood volume, including hypertrophy of myocardial cells, proliferation of myocardial interstitial cells and changes in the extra-myocardial matrix. Myocardial hypertrophy is divided into physiological and pathological myocardial hypertrophy (31). Previous studies have demonstrated that cardiac hypertrophy and HF are associated with the suppression of PGC-1α (32,33). The inhibition of PGC-1α is regulated by multiple factors. On one hand, the inactivation of AMPK or AKT/Forkhead box protein O1 (FOXO1) and the activation of STAT3 or NF-κB inhibit the promoter activity of PGC-1α, reducing its mRNA and protein expression (33-36). On other hand, post-translational modifications of PGC-1a affect its ability. For example, SIRT1 repression led to PGC-1α acetylation in a phenylephrine (PE)-induced cardiomyocyte hypertrophy model (37). Meanwhile, PE-induced cardiomyocyte hypertrophy also suppresses PGC-1α expression by enhanced O-glycosylation (31). PGC-1α downregulation, or its activity reduction, inhibits mitochondrial biogenesis, fatty acid metabolism, mitochondrial oxidative phosphorylation, angiogenesis and nuclear factor of activated T cell 4 dephosphorylation (promoting the transcription of hypertrophic genes, in particular, BNP), which are involved in the process of myocardial hypertrophy (2,38,39).

HF. Pathological myocardial hypertrophy is the main predictive factor of the progression and poor prognosis of HD, usually related to HF. As expected, a heart-specific PGC-1α deficiency can result in HF and is considered a model of energy-related HF, which leads to the compromised utilization of both glucose and fatty acids as well as reduced mitochondrial function (7). PGC-1α dysregulation can also inhibit the recruitment of RNA polymerase II to metabolic gene promoters in HF, which might be another mechanism underlying a metabolic imbalance (7,40). Further research has shown that PGC-1α is associated with dilated HF, including changes in dyssynchronous local calcium release resulting from the disruption of t-tubular structures of cardiomyocytes, depending on energy metabolism (41). In addition, PGC-1α can mediate the control of mitochondrial quality and, thereby, the occurrence and development of HF by modulating mitochondrial dynamics, mitochondrial biogenesis and mitophagy (42). Fig. 1 shows a schematic diagram of the involvement of PGC-1α in pathological hypertrophy and HF.

CHD. CHD, also called ischemic heart disease, is one of the most common HDs. Its pathogenesis is mainly coronary artery stenosis or blockage caused by atherosclerosis (AS), which leads to long ischemic hypoxia or MI (43). Studies have demonstrated that PGC-1α plays a key role in endothelial damage, macrophage function and smooth muscle cell proliferation and migration by affecting oxidative stress, energy metabolism and inflammation (44-47). In addition, PGC-1α regulates MI or I/R injury via effects on ROS production, mitochondrial biogenesis, mitophagy and energy metabolism (48,49). Given the complex role of PGC-1α in CHD, fully understanding its function in different cells will provide a basis for the future application of PGC-1α agonists. A promising advantage of PGC-1α agonists is the ability to improve multiple pathological pathways in CHD.

AS. The pathological mechanism underlying AS relies on an imbalance between blood flow and energy expenditure, leading to the impairment of endothelial function, mononuclear macrophage infiltration and vascular smooth muscle cell (VSMC) proliferation and migration (50). Research shows that the overexpression of PGC-1α in coronary artery disease (CAD) vessels increases vascular intraluminal pressure and exerts a therapeutic effect in patients with CAD via a shift from mitochondria-derived hydrogen peroxide to nitric oxide (NO)-mediated vasodilation (51). These results indicate that PGC-1α is a promising target for treating AS. Fig. 2 shows a summary of the aforementioned data.

Endothelial dysfunction is considered a gatekeeper of vascular diseases and one of the signs of AS (52). PGC-1α participates in the regulation of endothelial function by maintaining vascular tension and via antioxidant and anti-inflammatory factors. For example, PGC-1α can activate the phosphatidylinositol 3-kinase/AKT signaling pathway, leading to the decrease of endothelial nitric oxide synthase (eNOS) serine 1177 phosphorylation and NO production; this maintains vascular tension (53). Additionally, PGC-1α can combine with Nrf2 to form a complex that exerts antioxidant effects and inhibits endothelial dysfunction caused by high glucose/oxidation low lipoprotein (oxLDL) (45). PGC-1α can inhibit NF-κB signaling and reduce monocyte chemoattractant protein 1 and vascular cellular adhesion molecule-1 (VCAM-1) expression in endothelial cells, which can lead to a decrease in monocyte aggregation and slow the progression of AS. Meanwhile, PGC-1α inhibits ROS production by regulating the NF-κB and VEGFA signaling pathways and alleviating oxidative stress and inflammatory responses (46,54).

The presence of macrophages is an obvious sign of atherosclerotic plaque. Increased levels of inflammatory factors, such as vascular VCAM-1 and intercellular adhesion molecules, can mediate the adhesion between the surface of monocytes and the endothelium, leading to the recruitment of monocyte-derived cells under the endothelium and differentiation into macrophages. Macrophages engulf excessive oxidized lipoproteins under the endothelium and eventually become foam cells, a sign of 'fat streaks' and early atherosclerotic plaques (55). A study

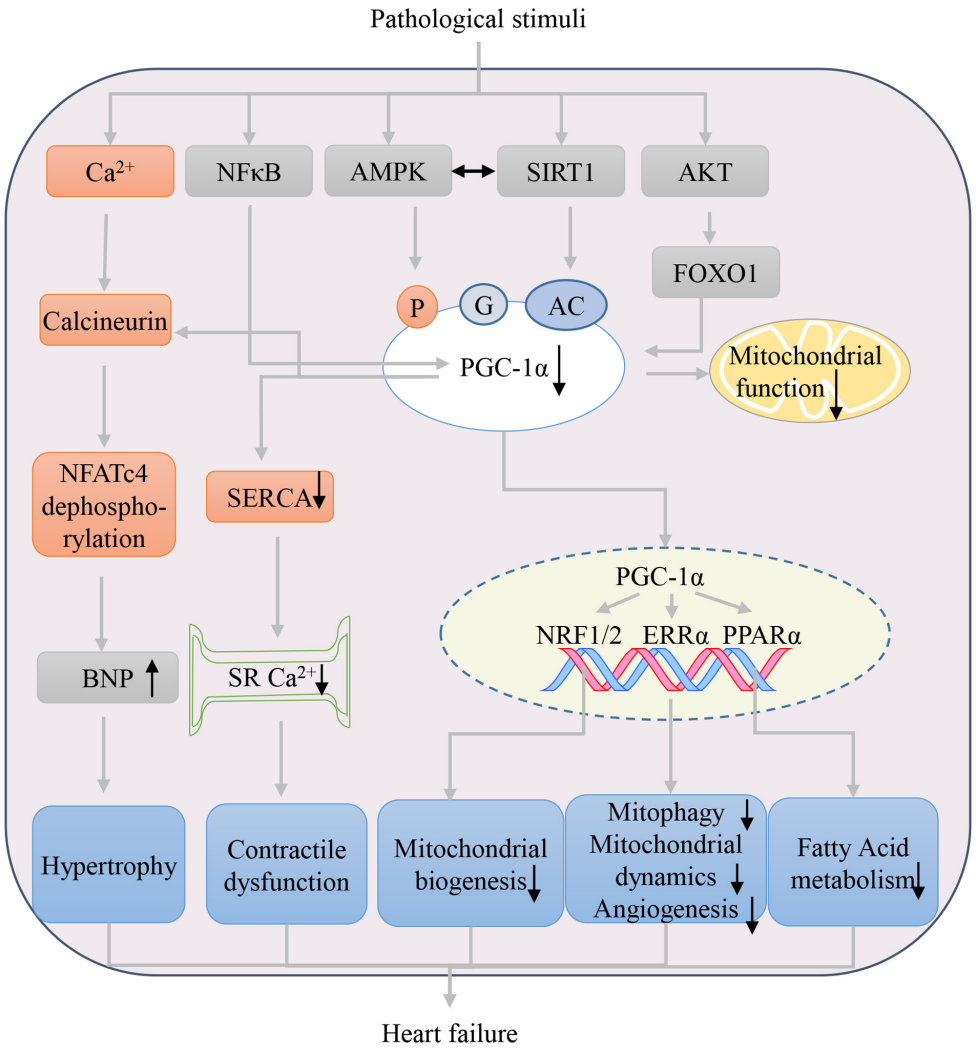

Figure 1. Schematic diagram of the involvement of PGC-1α in pathological hypertrophy and HF. AMPK, NF-κB and AKT/FOXO1 regulate the promoter activity of PGC-1α. SIRT1 regulates PGC-1α acetylation. The decreased PGC-1α activity lead to downregulated mitochondrial biogenesis, mitophagy, mitochondrial dynamics, angiogenesis and fatty acid metabolism via the regulation of its co-activated transcription factors NRF1/2, ERRα and PPARα. In addition, PGC-1α regulates calcineurin and SERCA expression and affects myocardial hypertrophy and systolic function. PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; HF, heart failure; AMPK, Adenosine monophosphate (AMP)-activated protein kinase; NF-κB, nuclear factor κB; FOXO1, Forkhead box protein O1; SIRT, sirtuin; NRF1/2, nuclear respiratory factor1/2; ERRα, estrogen-related receptor α; PPAR, peroxisome proliferator-activated receptor; SERCA, sarco/endoplasmic reticulum Ca(2+)-ATPase; NFATc4, nuclear factor of activated T cell 4; AC, acetylation; P, phosphorylation; G, O-GlcNAc.

has shown that PGC-1α inhibits adhesion molecule gene expression and cell adhesion (56). Furthermore, the overexpression of PGC-1α inhibits oxLDL uptake in macrophages. By contrast, the macrophage-specific deletion of PGC-1α accelerates atherosclerosis in $LDLR^{-/-}$ mice by promoting foam cell formation (47).

In addition to endothelial cells and macrophages, VSMC proliferation and migration play important roles in vascular homeostasis. Reports show that PGC-1α inhibits VSMC proliferation and migration by attenuating NOX1 or upregulating the antioxidant enzyme superoxide dismutase (SOD)2 to mediate the generation of ROS and prevent extracellular signal-regulated kinase 1/2 phosphorylation (57-59).

MI and I/R. The damage caused to the myocardium during MI is the result of two processes: Ischemia and subsequent reperfusion. Cardiac tissue will go through two phases after MI: Inflammatory phase (3 h to 7 days) and repair phase (7-21 days) (60). When subjected to hypoxic pressure, the mitochondrial function of myocardial cells is impaired and NF-κB p65 activation increases, thereby silencing PGC-1α promoter activity (24). Transcriptomics analysis has shown that the enrichment of PPAR/retinoid X receptor binding sites is decreased and levels of the target gene PGC-1α are lower in post-MI border zone tissues than they are in the healthy left ventricle 7 days after infarction (61). In animal models of I/R, PGC-1α expression is reduced at 3 days but partially recovers at 16 days in the infarcted area, with no changes in remote areas (62). Lou *et al* (63) discovered that infarct-remodeled hearts (6 weeks after infarction) show activation of fatty acid β-oxidation and mobilization of fatty acids from the endogenous triglycerides store via increased PPARα/PGC-1α signaling. These results suggest that the activation of NF-κB may inhibit the expression of PGC-1α during the inflammatory phase of MI. PGC-1α expression gradually recovers after inflammation disappears. To maintain the energy required by the heart, it is hypothesized that PGC-1α expression may be elevated in infarct-remodeled hearts. More evidence is needed to verify this hypothesis.

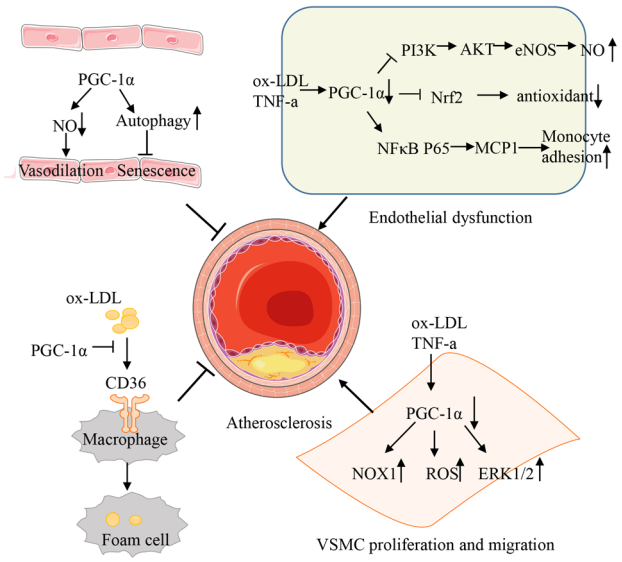

Figure 2. Schematic diagram of the involvement of PGC-1α in the process of AS. PGC-1α affects AS by regulating vascular vasodilation and senescence, endothelial dysfunction, foam cell formation and VSMC proliferation and migration. PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; AS, atherosclerosis; VSMC, vascular smooth muscle cell; NF-κB, nuclear factor κB; Nrf2, nuclear factor, erythroid 2 like-2; eNOS, endothelial nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; NOX1, NADPH oxidase 1; ERK1/2, extracellular signal-regulated kinase 1/2; ox-LDL, oxidation low lipoprotein; ROS, reactive oxygen species.

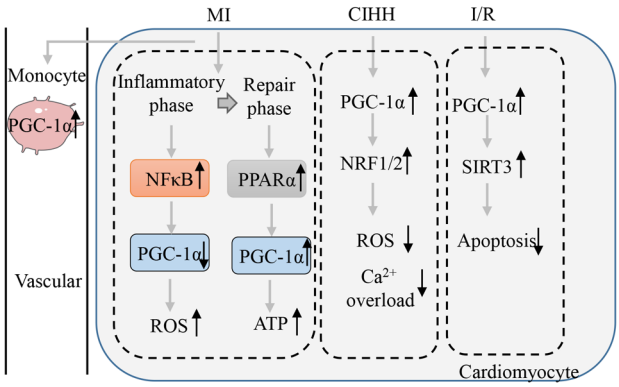

Figure 3. Schematic diagram of the involvement of PGC-1α in the process of MI and I/R. During the inflammatory phase of MI, NF-κB activation inhibits the expression of PGC-1α. During the repair phase of MI, PGC-1α expression is gradually recovered and becomes elevated in infarct-remodeled hearts to provide sufficient energy. Prior to I/R, CIHH treatment reduces the Ca^{2+} overload and ROS production by binding to NRF1/2. PGC-1α also inhibits myocardial apoptosis by promoting SIRT3 expression in I/R. MI can cause upregulation of PGC-1α in monocytes. PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; MI, myocardial infarct; I/R, infarct/reperfusion; CIHH, chronic intermittent hypobaric hypoxia; ROS, reactive oxygen species; SIRT, sirtuin; NF-κB, nuclear factor κB.

Mitochondrial ROS (mROS) and Ca^{2+} overload are particular drivers of I/R injury, resulting in mitochondrial permeability transition pore opening, cell death and ventricular remodeling (64). Ischemic preconditioning is the most powerful intervention for reducing MI size before reperfusion. Chronic intermittent hypobaric hypoxia (CIHH) treatment can reduce the calcium overload and hypoxia/reoxygenation injury in cardiomyocytes by upregulating the expression of PGC-1α and regulating glucose and lipid metabolism (65). Meanwhile, PGC-1α mediates the elimination of ROS by binding to and co-activating NRF1/2 and its downstream genes (66). In addition, PGC-1α inhibits myocardial apoptosis by promoting SIRT3 expression (67). Overall, PGC-1α prevents IR damage by reducing mROS production and cell apoptosis.

PGC-1α participates in the regulation of MI risk factors, including low adiponectin (APN) levels and an increased risk of type 2 diabetes in patients with MI (68). APN activates AMPK-PGC-1α signaling in cardiomyocytes and reduces apoptosis to protect against post-MI remodeling and dysfunction (69). PGC-1α expression is increased in blood mononuclear cells of patients with st-elevated myocardial infarction and the expression level was correlated with the infarct size (70). These results indicate that PGC-1α plays an important role in MI or I/R and may serve as a blood marker for MI. Fig. 3. shows a schematic diagram of the involvement of PGC-1α in the process of MI and I/R.

DCM. DCM refers to myocardial disease that occurs in patients with diabetes and cannot be explained by hypertensive heart disease, coronary atherosclerotic heart disease, heart valve disease and other HDs. The PPARα/PGC-1α pathway plays an important role in the occurrence and development of DCM by promoting metabolic inflexibility. In the early diabetic heart, PPARα and PGC-1α are activated to increase fatty acid oxidation and lipid uptake rates, instead of glucose oxidation (71). This leads to increased ATP generation and a decreased AMP/ATP ratio, which leads to AMPK inactivation and subsequent PGC-1α inhibition, ultimately resulting in an excessive supply of fatty acids and lipid accumulation in the DCM heart (9,72). Cardiac lipotoxicity will lead to increased total ceramide levels. The accumulation of ceramides in the heart leads to oxidative stress and mitochondrial dysfunction by inhibiting PGC-1α, PPARα and CD36 expression (72,73).

PGC-1α also participates in the pathological mechanism of DCM by regulating ROS production, inflammatory response and Ca^{2+} homeostasis. On one hand, PGC-1α can interact with heme-oxygenase-1 to improve antioxidant defense by ROS clearance (74). The anti-DCM effect has been validated in caloric restriction and exercise models by activating the AMPK/SIRT1/PGC-1α signaling pathway (75,76). Moreover, moderate overexpression of PGC-1α maintains Ca^{2+} homeostasis by increasing the expression of sarcoplasmic/endoplasmic reticulum Ca^{2+} transporting ATPase 2 (77). Fig. 4 shows a schematic diagram of the involvement of PGC-1α in DCM.

DIC. Cardiotoxicity caused by drugs is essentially a harmful reaction in the heart that occurs during drug use. For example, the cardiotoxicity produced by the anti-cancer agent doxorubicin limits its wide clinical applications. Energy homeostasis, oxidative stress, apoptosis and mitophagy disorders are considered the main factors associated with cardiotoxicity (78,79). PGC-1α mainly functions in the myocardium by participating in energy metabolism and mitochondrial oxidative stress. PGC-1α can also affect the production of ROS, mitochondrial biogenesis, mitochondrial autophagy and ultimately cell apoptosis through NRF2 (80). A recently discovered function of PGC-1α is the ability to promote autophagy and inhibit apoptosis by binding to nucleolin (81). At present, certain drugs have shown protective effects in DIC by upregulating PGC-1α,

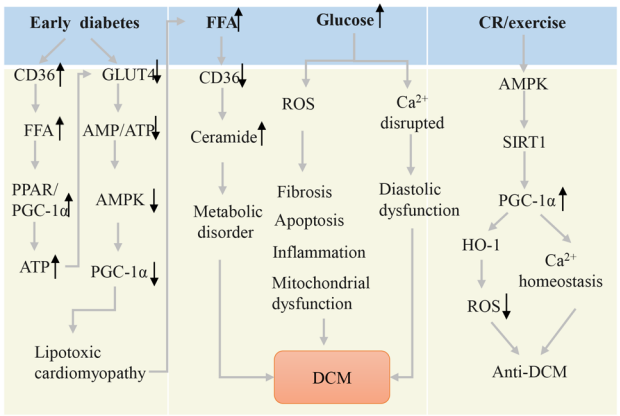

Figure 4. Schematic diagram of the involvement of PGC-1α in DCM. PGC-1α plays a dual role in the formation of lipotoxic cardiomyopathy in early diabetes. CR/exercise reduces DCM by upregulating PGC-1α expression. PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; CR, caloric restriction; DCM, diabetic cardiomyopathy; FFA, free fatty acids; ROS, reactive oxygen species; AMP, Adenosine monophosphate; AMPK, AMP-activated protein kinase; SIRT, sirtuin; PPAR, peroxisome proliferator-activated receptor; HO-1, heme oxygenase-1.

such as hydropersulfides and the hydroethanolic extract of Cirsium (80,82). In the future, the aim will be to identify drugs for treating DIC by upregulating PGC-1α.

Arrhythmia. Cardiac rhythm is controlled by various ion channels and electrogenic ion transporters. Intracellular sarcoplasmic reticulum and mitochondria regulate these channel and transporter changes (83). Recent research has shown that PGC-1α participates in the occurrence and development of arrhythmia. A transcription profiling analysis of PGC-1α$^{-/-}$ mouse atrial tissues showed that genes related to Na^+-K^+-ATPase activity, hyperpolarized activation of cyclic nucleotide gated ion channels, Na^+ channel-dependent action potential activation and propagation, Ca^{2+} current generation and Ca^{2+} homeostasis were downregulated. Compared with the levels in wild-type mice, $Na_v1.5$ channel protein expression is reduced, while the gap junction protein expression remains unchanged (84). In PGC-1α$^{-/-}$ mouse ventricular tissues, genes related to Na^+-/K^+- ATPase activity, Ca^{2+} influx, action potential repolarization, autonomous function and morphological characteristics are also downregulated. The expression of $Na_v1.5$ decreases and tissue fibrosis increases (85). Naumenko *et al* (41) specifically knocked out myocardial PGC-1α and found that mice exhibit dilated HF and myocardial electrophysiological remodeling related to energy metabolism inhibition, with abnormal SR absorption and release of Ca^{2+}. The findings of previous research confirm that PGC-1α participates in cardiac electrophysiology, provides substrates for the occurrence of arrhythmia and may be related to Na^+/Ca^{2+} homeostasis (84-86).

5. Summary and future directions

The present review systematically analyzed the role of PGC-1α in the development of HD. Various HDs are closely related to energy metabolism, calcium signaling and antioxidant capacity. PGC-1α is involved in these processes. Summarizing the pathogenesis of different types of HDs clearly reveals that impaired heart function can lead to the downregulation of PGC-1α at different times and to varying degrees, leading to oxidative stress reactions. This result provides a basis for PGC-1α as a therapeutic target. However, the mechanisms underlying the effects of PGC-1α in HD are extremely complex and remain to be elucidated. Based on this review, future studies should focus on the following.

First, the mechanism by which PGC-1α genetic variations lead to HD is unclear. Although studies have been published proving PGC-1α genetic variation is closely related to diabetes and CAD disease, most existing studies are focused on the effect of PGC-1α genetic variation on diabetes in different ethnic groups (3-5). More detailed analysis, such as considering the differences between diabetes cardiomyopathy or coronary heart disease caused by diabetes, is lacking. However, these studies are helpful for using PGC-1α genetic variations as biomarkers.

Second, the role of PGC-1α in HDs has not been fully explored. The post transcriptional translation and promoter of PGC-1α are regulated by multiple factors. The effects of multiple signaling pathways on PGC-1α when myocardial cells are stimulated need to be simultaneously studied. Concurrently, different reasons for the decrease in PGC-1α were discovered among different stimuli. Similarly, PGC-1α plays a dual role in the formation of lipotoxic cardiomyopathy in early diabetes. Although the role of PGC-1α in DCM has been clarified, studying it in human DCM is difficult. As there are no clear indicators for categorizing diabetes, the use of PGC-1α agonists or inhibitors is challenging.

Third, controlling the amount of PGC-1α overexpression is difficult. Previous studies show that overexpression of PGC-1α can cause cardiomyopathy (87). Whitehead *et al* (77) found that moderate overexpression of PGC-1α improves cardiac function and fibrosis in aged mice hearts. These results indicate that the dosage of PGC-1α is critical. Moreover, they are inconsistent with our expectations, thereby limiting PGC-1α as a therapeutic target for HDs.

6. Conclusion

Overall, the present study showed that PGC-1α plays a crucial role in HDs and is one of the key targets for treating HDs. Clarifying the mechanism of PGC-1α in HDs will promote the precision of HD treatment.

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Availability of data and materials

Not applicable.

Authors' contributions

SS was responsible for conceptualization, literature research, writing the original draft and funding acquisition. HG was responsible for writing, review and editing. GC and ZZ were responsible for acquisition, analysis and interpretation of data. HZ drafted the manuscript and created the figures. DL, XL and XW were responsible for the acquisition of funding and revised the manuscript for critically for important intellectual content. GZ and FL were responsible for project administration, conceptualization and the designing the method for writing the review. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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