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REVIEW ARTICLE

PGC-1α activation: a therapeutic target for type 2 diabetes?

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Abstract
Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) has gained popularity as a very attractive target for diabetic therapies due to its role in lipid and glucose metabolism. Pharmacological activation of PGC-1α is thought to elicit health benefits. However, this notion has been questioned by increasing evidence, which suggests that insulin resistant is exacerbated when PGC-1α expression is far beyond normal physiological limits and is prevented under the condition of PGC-1α deficiency. This narrative review suggests that PGC-1α, as a master metabolic regulator, exerts roles in insulin sensitivity in a tissue-specific manner and in a physical activity/age-dependent fashion. When using PGC-1α as a target for therapeutic strategies against insulin resistance and T2DM, we should take these factors into consideration.
Level of evidence: Level V, narrative review.

Keywords Peroxisome proliferator-activated receptor-γ coactivator-1α · Type 2 diabetes · Insulin resistance · Drug therapy

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic diseases in the world. The pathogenesis has been shown to be associated with insulin resistance in insulin-responsive tissues (e.g., skeletal muscle, liver, and adipose tissues) and reduced insulin secretion by β-cells [1, 2]. Furthermore, T2DM may lead to lots of comorbidities, such as cardiovascular disease and certain cancers [3]. Therefore, there is an increasing need for more effective treatments than medications currently available to help manage T2DM.

Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), originally discovered in brown adipose tissue (BAT) [4], is mainly expressed at high levels in energy-demanding tissues such as skeletal muscle, BAT, pancreas, and liver [5]. It interacts with a wide range of transcription factors (TFs, reviewed in [6]) to modulate multiple cellular processes, including muscle fiber-type switching [7], hepatic gluconeogenesis [8], mitochondrial biogenesis [9], and insulin secretion [10]. It is highly inducible in response to physiological stimuli, including cold exposure, fasting, and exercise [11, 12]. It is dysregulated in pathological states, such as hypergluconeogenesis in the liver and mitochondrial dysfunction in skeletal muscle. Dysregulation of PGC-1α has been implicated in the pathogenesis of insulin resistance and T2DM [6]. On this basis, PGC-1α has been regarded as a promising target for anti-diabetic therapy [12].

However, mounting evidence has recently indicated that when using PGC-1α as a target for therapeutic strategies against insulin resistance and T2DM, we should take the following factors into consideration: PGC-1α's expression level, the target tissues, the patient's age, and the patient's exercise [13, 14]. More importantly, several studies have highlighted the importance of PGC-1α deficiency, but not PGC-1α activation, in the prevention and treatment of insulin resistance and diabetes [15, 16]. In this narrative review, we summarize the major findings on the function of PGC-1α in multiple cellular processes and in different tissues, and then discuss its unlikely therapeutic applications for T2DM.

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Regulation of PGC-1α

PGC-1α expression and activity are modulated by different stimuli in distinct tissues. More especially, PGC-1α expression is markedly induced by exercise and calorie restriction in muscle [17, 18], by fasting in the liver [19], and by cold temperatures in BAT [4], by exercise in white adipose tissue (WAT) [20]. In addition, PGC-1α expression is modulated on both transcriptional and post-translational levels. At the level of gene expression, several signaling cascades (e.g., the cAMP pathway) and proteins (e.g., cAMP response element binding protein (CREB) and activating transcription factor 2 (ATF2)) have been involved in the modulation of PGC-1α. In particular, the cAMP pathway plays central roles in activating PGC-1α transcription via promoting the binding of ATF-2 or CREB to the PGC-1α promoter, hence activating its transcription in many tissues. PGC-1α transcription is activated by β-adrenergic agonists through ATF-2 in BAT. The activation of PGC-1α in the liver by glucagon is mediated by CREB [8, 21], whereas calcium signaling cascades in combination with CREB are involved in the activation of PGC-1α in skeletal muscle by exercise [22, 23]. In addition, well-established post-translational modifications of PGC-1α include methylation [24], acetylation (mediated by the sirtuin (SIRT) family and the histone acetyltransferase GCN5) [25–28], and phosphorylation (by p38 MAPK, AMPK, Akt) [29]. The dynamic modifications of PGC-1α makes it to be implicated in the cellular adaptation to environmental conditions [30].

On the other hand, PGC-1α drives a pleiotropic transcriptional response through binding to and co-activating TFs and nuclear receptors, leading to improved lipid, glucose, and energy homeostasis [6, 31]. These TFs and nuclear receptors include myocyte enhance factor 2 [32], SIRT3 [33], hepatocyte nuclear factor 4α (HNF4α) [8], forkhead box O 1a (FOXO1a) [19], estrogen receptor-related α (ERRα) [34], peroxisome proliferator-activated receptor (PPAR) γ [4], PPARα [35], transcription factor A (TFAM), nuclear respiratory factor 1 (NRF1) [36], NF-κB [37], X-box binding protein 1 (XBP1) [38]. Accordingly, this makes regulation of PGC-1α a promising target for the treatment of insulin resistance and T2DM (Fig. 1).

Dysregulation of PGC-1α in animals and humans with T2DM

Over the past years, people have realized that PGC-1α expression is dysregulated in key metabolic tissues (e.g., skeletal muscle, adipose tissue, and liver) of animals and humans with insulin resistance and T2DM. In particular, in skeletal muscle of humans with T2DM and prediabetic individuals, PGC-1α expression and its co-transcription activity were reduced, in parallel with the reduction of the expression of PGC-1α-responsive genes implicated in mitochondrial biogenesis and oxidative phosphorylation

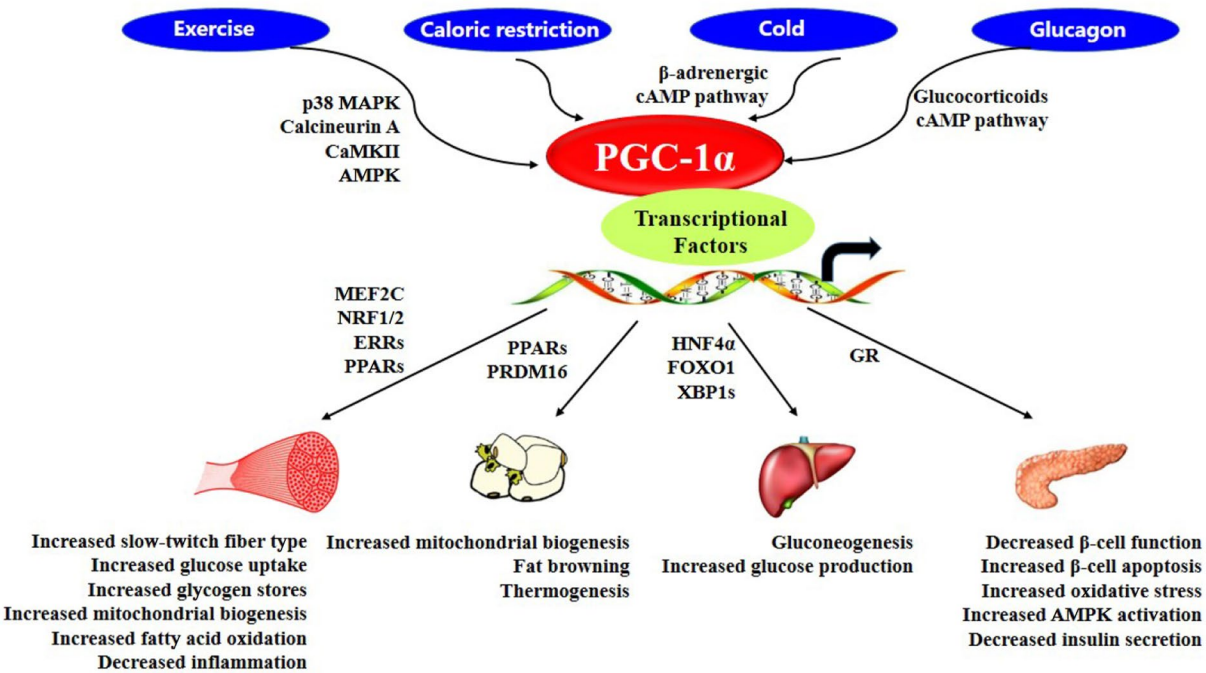

Fig. 1 Regulation and main functions of peroxisome proliferator-activated receptor gamma coactivator-1α

(OXPHOS) [8, 10, 39, 40]. Similarly, in adipose tissue of insulin-resistant subjects, PGC-1α mRNA and protein expression were markedly downregulated [41]. In line with this observation, an high-fat diet (HFD)-fed mice with an adipose tissue-specific deletion of PGC-1α exhibited systemic deregulation of glucose homeostasis, as manifested by the reduction of hepatic insulin sensitivity and elevated levels of blood triglycerides and cholesterol [42]. Moreover, the obesity-associated reduction of adipose PGC-1α has been correlated with obesity-associated inflammation [43]. Therefore, obesity-associated inflammation and the development of systemic insulin resistance may be linked by the down-regulation of adipose PGC-1α. Furthermore, pre-diabetic individuals also exhibit decreased PGC-1α expression in muscle, indicating that PGC-1α inactivation is an early event in the development of this disease [39, 40].

Interestingly, ectopic expression of PGC-1α in muscle cells recovered expression of insulin-sensitive glucose transporter 4 (GLUT4) by coordinating the transcriptional MEF2C on the promoter [32]. Consistent with this in vitro study, muscle overexpression of PGC-1α showed improvement in metabolic responses, as evidenced by increased insulin sensitivity and insulin signaling in aged mice [44]. These results highlight the importance of targeting PGC-1α modulators to specific tissues and its efficacy in metabolic disease models. As a consequence, increasing PGC-1α expression/activity has great potential in the prevention and treatment of insulin resistance and diabetes, which has been extensively reviewed [12, 45, 46].

Paradoxical effects of increased PGC-1α activation on T2DM

These foregoing studies have highlighted the therapeutic potential of increasing PGC-1α activation for T2DM treatment. However, data from tissue-specific transgenic or knockout animal models of PGC-1α have yielded disappointing results. In fact, the effects of PGC-1α activation on insulin sensitivity depend on several key factors, including tissue, physical activity, age, and the level of PGC-1α expression (Fig. 2).

Tissue

Skeletal muscle is a primary site for the utilization of glucose and fatty acids. Defects of these factors in combination with chronic low-grade inflammation, mitochondrial dysfunction, and oxidative stress contribute to the development of T2DM [2]. Evidence is emerging that PGC-1α can regulate the metabolic profile of muscle. First, PGC-1α can modulate the muscle fiber-type switch. Increases in the proportion of type I fibers, which contain more GLUT4 and mitochondria, have been observed in muscle of transgenic mice and pigs as well as exercised humans [7, 17, 47]. Second, PGC-1α regulates glucose metabolism. Increased GLUT4 expression and glucose uptake were observed in the ex vivo muscle with electrotransfection of PGC-1α [48] and in C2C12 and L6 muscle cells that overexpressed PGC-1α [32]. Apart from increasing glucose uptake, PGC-1α may increase fatty acid oxidation and glycogen synthesis and decrease glycolysis and glucose oxidation, resulting in enhanced muscle glycogen stores [49, 50]. These findings are in accordance

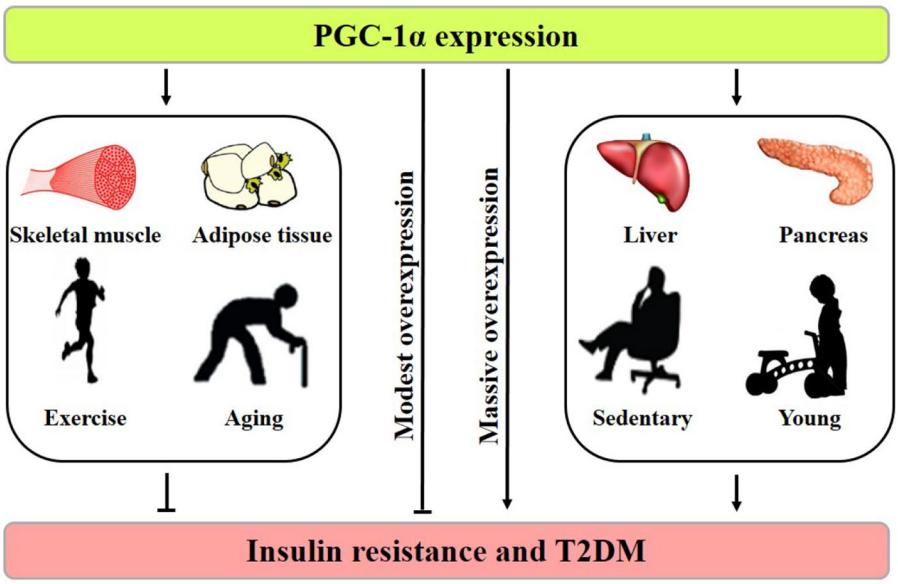

Fig. 2 Whether overexpression of peroxisome proliferator-activated receptor gamma coactivator-1α exerts beneficial or detrimental effects depends on several key factors, including the tissue, activity, age, and the extent of its overexpression

with other studies showing that mice with muscle-specific PGC-1α overexpression displayed elevated muscle glycogen stores [51]. Third, muscle PGC-1α overexpression inhibits the development of inflammation, which has been demonstrated by both gain- and loss-of-function studies [52–54]. Last but not least, PGC-1α mediates OXPHOS and mitochondrial biogenesis in skeletal muscle. For example, forced expression of PGC-1α in cultured cardiac myocytes increased the cellular mitochondrial number and stimulated coupled respiration, as evidenced by the upregulated expression of nuclear and mitochondrial genes including NRF-1/2 and TFAM [55]. Likewise, cardiac-specific induction of PGC-1α resulted in a large increase in cardiac mitochondrial number and size during the neonatal stages [56]. In contrast, PGC-1α knockout mice exhibit a reduction in the expression of genes involved in OXPHOS and impaired mitochondrial function [52, 57, 58]. In cell cultures of human myotubes, PGC-1α overexpression has been demonstrated to increase fatty acid oxidative capacity by improving mitochondrial function [59]. In accord with these findings, recent in vitro and in vivo studies have also reported that the expression of PGC-1α in myotubes and skeletal muscle was elevated by a novel small molecule (ZLN005), exerting promising therapeutic effects for treating T2DM [60]. Overall, these findings highlight the importance of PGC-1α activation in the treatment of T2DM.

Adipose tissue is mainly composed of WAT and BAT. WAT mainly stores energy in form of lipid droplets, whereas BAT possesses non-shivering thermogenic properties due to increased mitochondrial content and expression of uncoupling protein-1 (UCP-1) [2, 61]. In vivo and in vitro studies have shown that PGC-1α increases adaptive thermogenesis [15, 16, 62] and mitochondrial biogenesis in BAT, as evidenced by the activation of transcription of mitochondrial UCP-1 [4]. In contrast, PGC-1α knockout in BAT resulted in dysregulation in lipid turnover, as manifested by a reduced level of lipid metabolizing enzymes and fatty acid transporters [63]. A recent study has identified four compounds with the ability to stabilize PGC-1α1 protein in BAT, setting the foundation for a novel generation of therapeutics based on the activation of PGC-1α1 that could be of use in metabolic disease [64]. Moreover, PGC-1α is implicated in the conversion of white fat into a brown fat-like phenotype. Ectopic expression of PGC-1α in WAT leads to its "browning" while suppression of PGC-1α may favor a white adipocyte phenotype [65–67]. Intriguingly, a brown-like adipose tissue gene programme can also be induced by muscle-specific overexpression of PGC-1α, as evidenced by increased UCP1 and Cidea expression in the subcutaneous fat layer (inguinal). This browning of WAT is stimulated by muscle-derived FNDC5 (a membrane protein that is cleaved and secreted as a myokine, irisin), whose expression is induced by increased muscle PGC-1α [68]. Unlike BAT, PGC-1α mRNA expression in WAT can be induced by exercise [20]. PGC-1α overexpression in WAT promotes mitochondrial biogenesis [69], whereas its deficiency gives rise to reductions in mitochondria [16]. Taken together, these observations highlight the beneficial effects of PGC-1α activation in BAT and WAT.

The liver is an organ that exerts important roles in controlling glucose homeostasis. In both fasting and well-fed states, the glucose concentration in the blood is stably maintained within a narrow range under normal conditions. Gluconeogenesis by the liver, together with glucose absorption by the intestine and glucose utilization by skeletal muscle, determines blood glucose levels [12]. The liver of mice with T2DM exhibits elevated gluconeogenesis, which is the main source of endogenous glucose production [8, 70]. The gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6P) control rates of hepatic glucose production [71]. Interestingly, these gluconeogenic enzymes (PEPCK and G6P) are transcriptionally modulated by PGC-1α. It functions as a co-activator of FOXO1 and HNF-4α and as a co-suppressor of XBP1s, leading to impaired glucose homeostasis in obese and diabetic mice [19, 38, 71]. Furthermore, PGC-1α may decrease inhibition of hepatic glucose production by insulin, contributing to the onset of insulin resistance in liver through PPARα-dependent induction of Tribbles homologue 3 (an Akt inhibitor) [72]. Thus, PGC-1α expression is positively associated with hepatic glucose production [8, 73]. Increased expression of hepatic PGC-1α, as seen in several insulin-resistant animal models, including liver-specific insulin receptor-knockout, ob/ob [8], db/db [74], and HFD-fed [75] mice, has been demonstrated to cause hepatic insulin resistance [73]. Conversely, obese mice with genetically decreased levels of hepatic PGC-1α produced less glucose and were protected against insulin resistance [76]. Thus, in contrast to the induction sought after in tissues like skeletal muscle and adipose tissues, an inhibition of hepatic PGC-1α activity can reduce gluconeogenic activity and hence hold more promise for treating diabetes [77].

The main function of pancreatic β cells is to synthesize and secrete insulin, which contributes to maintain circulating glucose concentrations within a normal range. Normal mitochondrial function and ATP production are required for insulin secretion from pancreatic β cells [78]. The reduction of insulin secretion from β cells have been demonstrated to exacerbate T2DM. Like in the liver, PGC-1α is expressed at abnormally high levels in islets from diabetic rodents. In vitro studies have shown that overexpressing PGC-1α in isolated pancreatic rat islets blocks membrane polarization and induces G6P, thus decreasing insulin secretion [10]. PGC-1α impairs the ability of β-cells to secrete insulin through multiple mechanisms: (1) by impairing β-cell mass and function [79]; (2) by

promoting β-cell apoptosis [80]; (3) by increasing mitochondrial biogenesis, oxidative stress and AMPK activation [81]. Of note, the onset of β-cell dysfunction may be associated with elevated expression of UCP2 [82], whose expression can be increased by PGC-1α in rat pancreatic islets and in INS-1 cells [83, 84]. In contrast, antisense oligonucleotide-induced suppression of rat islet PGC-1α corrects UCP2 expression level and to some extent normalizes insulin secretion by β-cells [83]. Intriguingly, the function of pancreatic islets is also regulated by IL-6, a myokine that is produced and secreted from muscle. In glucose intolerant and type 2 diabetic patients, reduced muscle PGC-1α expression elevated levels of circulating IL-6, leading to a reduction in insulin secretion by β-cells [53]. Therefore, similar to liver, a suppression of PGC-1α activity in pancreatic islets is beneficial for the treatment of diabetes.

Overall, PGC-1α affects lipid and glucose metabolism in a tissue-specific manner. In particular, increased PGC-1α expression is beneficial in skeletal muscle and adipose tissues, where it induces a change of muscle fiber phenotype towards oxidative metabolism and promotes thermogenesis and fat browning in adipose tissue, changes that inhibit diabetes. In contrast, its role is obviously deleterious in the liver and pancreas, in which it increases hepatic glucose production and suppresses insulin secretion, leading to the development of diabetes. Of note, the health benefits of increased PGC-1α expression in muscle go beyond the muscle tissue itself. PGC-1α induces the production and secretion of myokines (such as IL-6 and irisin) from skeletal muscle that influence the function of other tissues such as adipose tissue and pancreatic β cells (Fig. 3).

Physical activity

In response to exercise training, insulin sensitivity is enhanced and circulating levels of free fatty acids and insulin are reduced [85, 86]. PGC-1α expression can be increased in skeletal muscle (especially, the high-oxidative fast type) after prolonged exercise in humans [87, 88] and rodents [11, 86, 89]. Increased muscle PGC-1α promotes the production and secretion of certain myokines, mediating many of the beneficial effects of exercise locally and systemically. Once exposed to these myokines, muscle resident macrophages are polarized towards anti-inflammatory M2 phenotype, leading to increased secretion of anti-inflammatory cytokines (Fig. 2) [90]. Moreover, increased PGC-1α induces a coordinated program of increased fatty acid uptake, mitochondrial biogenesis, and fatty acid oxidation to meet the increased energy demands of working skeletal muscle [14, 91]. The activation and upregulation of PGC-1α have been demonstrated to be partially responsible for the beneficial effects exerted by exercise on skeletal muscle oxidative metabolism and insulin sensitivity, making it an attractive target for the development of antiobesity and/or antidiabetic drugs [11, 92–95]. Of note, increased physical activity does not upregulate the PGC-1α protein expression in the liver, suggesting

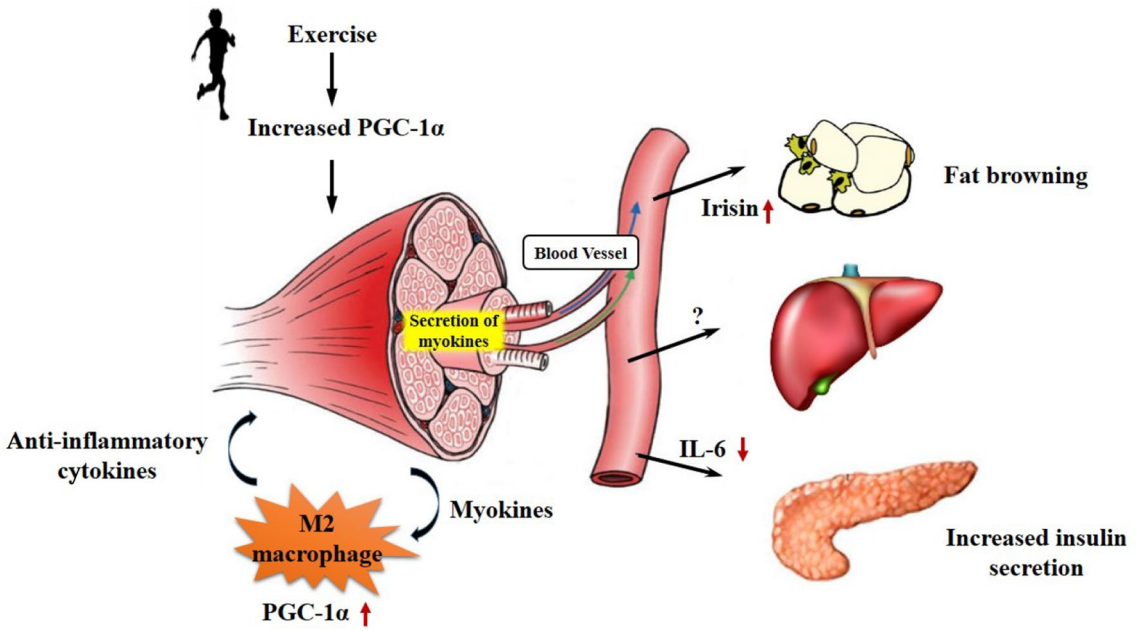

Fig. 3 Beneficial effects exerted by increased peroxisome proliferator-activated receptor gamma coactivator-1α are partially mediated by myokines

that PGC-1α may be not involved in the action of exercise in improving hepatic insulin sensitivity [86].

Paradoxically, in sedentary state, elevated PGC-1α expression was not followed by improved glucose and insulin levels, and instead contributed to insulin resistance in mice fed HFDs [13, 14]. This increased insulin resistance may be due to an elevated provision of lipid, which exceeded the energetic demand of β-oxidation, thus causing a net elevation of intramyocellular fat and diacylglycerol content and insulin resistance [13, 96, 97]. Importantly, however, these detrimental effects could be reversed when these HFD-fed mice received a continuous exercise intervention [13]. These findings suggest that the effects of PGC-1α overexpression, as a monotherapy, depend on physical activity. In particular, elevation of PGC-1α is beneficial in exercised animals and is detrimental in sedentary animals who consume a HFD.

Age

Diabetes risk elevates greatly with age and is related to lower muscle oxidative capacity. Intriguingly, PGC-1α expression/activity in skeletal muscle also decreases with age [98, 99]. Using muscle-specific PGC-1α knockout mice, recent studies have demonstrated that a decline in PGC-1α and reduced mitochondrial oxidative capacity potentiate the development of glucose intolerance and insulin resistance associated with aging [100]. More importantly, when PGC-1α is lacking, age-associated decreases in mitochondrial proteins in skeletal muscle cannot be prevented by exercise training [101]. Consistent with these observations, gain-of-function studies have suggested that mildly increased muscle PGC-1α protects against age-related obesity and diabetes [44]. Overall, these observations highlight the importance of increasing PGC-1α expression in the prevention and treatment of age-induced diabetes.

Paradoxically, muscle PGC-1α overexpression led to insulin resistance in young mice fed HFDs [14]. In contrast, young muscle-specific PGC-1α knockout mice showed modestly improved glucose homeostasis [100]. These mice are capable of elevating mitochondrial protein expression in response to exercise training [102]. Therefore, PGC-1α is mandatory for the beneficial effects of moderate exercise training in elderly but not in young subjects to maintain mitochondrial metabolic and anti-oxidant capacity.

The level of PGC-1α expression

The extent of PGC-1α increases also influences its effects. For instance, in transgenic mice that overexpressed PGC-1α mRNA 10–13-fold, the GLUT4 mRNA and whole-body insulin sensitivity were reduced [103]. Limiting PGC-1α overexpression to skeletal muscle also yielded undesirable pathological effects, exacerbating fat-induced muscle insulin resistance despite an increase in mitochondrial density and mitochondrial activity [14]. PGC-1α overexpression in these models may have been far too large to be physiologically beneficial, since the increase in PGC-1α protein (5–30-fold) in genetically altered mice is considerably higher than those in rodent muscle stimulated by exercise training (1.5–2.5 fold) [89, 104] or cold exposure (1.5–2.8 fold) [105]. Excessive PGC-1α production leads to intramuscular lipid accumulation, contributing to insulin resistance in humans and animals [14, 48]. Therefore, these findings suggest that massively overexpression of PGC-1α leads to deleterious effects, calling into question the therapeutic potential of PGC-1α activation.

Paradoxically, upregulation of PGC-1α in vivo, similar to those that can be induced by physiological stimuli (< 100%), can protect against obesity and T2DM. In rat tibialis anterior muscle, overexpression of PGC-1α within physiological limits via an electrotransfection procedure, such as is observed with exercise, led to increased mitochondrial biogenesis and insulin sensitivity [48]. Beneficial effects of a modest elevation in PGC-1α levels have also been obtained in insulin-resistant muscle of obese Zucker rats, in which intramuscular lipids were reduced [106]. Therefore, modest upregulation of PGC-1α within physiological limits may be sufficient to reprogram the metabolic capacity of skeletal muscle. However, these observations should be subjected to a clinical trial.

PGC-1α deficiency prevents the development of insulin resistance and diabetes

Several loss-of-function studies have provided evidence of the contribution of PGC-1α to the pathogenesis of insulin resistance and diabetes. For instance, data from two models of PGC-1α-null mice have shown that these mice were protected from diet-induced obesity and insulin resistance [15, 16]. Moreover, these findings show that PGC-1α is dispensable for mitochondrial biogenesis and muscle fiber-type transformation [15, 16, 107]. Like whole body PGC-1α-null mice, muscle-specific PGC-1α-null mice have preserved mitochondrial content and displayed normal peripheral insulin sensitivity [53, 108]. More importantly, when challenged with a HFD, glucose intolerance or insulin resistance was not observed in these mice with total muscle PGC-1 deficiency, although mitochondrial structural derangements and impaired muscle oxidative capacity were observed [109]. Interestingly, normal glucose tolerance was also observed in β-cell-specific PGC-1α-null mice, despite disruption of insulin secretion [110]. Further evidence comes from the finding that adipose tissue-specific PGC-1α-null mice did not exhibit impaired mitochondria biogenesis, manifested

by no alterations in the expression levels of mitochondrial genes. Consistent with these in vivo observations, PGC-1α knockdown in cultured 3T3-L1 adipocytes did not impact the mitochondrial gene expression and the adipocytes' respiratory capacity [111]. Overall, these observations present evidence that PGC-1α deficiency may exert beneficial effects on insulin resistance and consequently diabetes. Although in that loss of function models one would expect to observe worsening of the metabolic profile, in most cases these mice show no effects. This could be the results of compensatory effects occurring in the transgenic animals, masking the real functional role of the transcription factor.

Concluding remarks

The prevalence of T2DM is increasing rapidly in both developed and developing countries. Effective therapeutic measures are urgently needed to reduce the current epidemic and to control this disease. PGC-1α, a transcription co-activator, has been regarded as a potential therapeutic target of antidiabetic therapy and pharmacological activation of PGC-1α is thought to elicit health benefits. However, this notion remains contentious, with studies failing to provide consensus evidence of a benefit from PGC-1α activation. Insulin resistant occurs when PGC-1α overexpression is far beyond normal physiological limits. In addition, PGC-1α activation exacerbates insulin resistance when PGC-1α expression is increased in tissues such as liver and pancreas, in young insulin-resistant subjects, and in animals and humans in sedentary state. More importantly, increasing studies have highlighted the contribution of PGC-1α deficiency to T2DM prevention and treatment. Thus, the literature reviewed here suggests that PGC-1α is differentially expressed in different tissues and has distinct and even opposite functions in different cells. When using PGC-1α as a target for therapeutic strategies against insulin resistance and T2DM, we should take the following factors into consideration: its expression level, the target tissues, the patient's age, and the patient's exercise.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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