PGC-1α, glucose metabolism and type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by glucose metabolic disturbance. A number of transcription factors and coactivators are involved in this process. Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) is an important transcription coactivator regulating cellular energy metabolism. Accumulating evidence has indicated that PGC-1α is involved in the regulation of T2DM. Therefore, a better understanding of the roles of PGC-1α may shed light on more efficient therapeutic strategies. Here, we review the most recent progress on PGC-1α and discuss its regulatory network in major glucose metabolic tissues such as the liver, skeletal muscle, pancreas and kidney. The significant associations between PGC-1α polymorphisms and T2DM are also discussed in this review.

Key Words
- PGC-1α
- type 2 diabetes mellitus
- glucose metabolism
- polymorphism

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic isorder characterized by hyperglycemia in the context of insulin resistance (IR) and insulin secretion deficiency due to β-cell dysfunction. The global prevalence of T2DM is continuously rising, being held responsible for about 90% of all the 347 million diabetes cases worldwide (Yang *et al.* 2015). T2DM can cause serious microvascular and macrovascular complications, such as diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, ischemic heart disease and cerebrovascular disease. These complications predominantly account for the increased mortality and economic burden. Many novel medicines are available, though the undesirable side effects (hypoglycemia, weight gain, gastrointestinal effects and cardiovascular complications) and imperfect glycemic control limit their use in long-term treatment. Therefore, the development of safe and effective drugs for T2DM is imperative, for which the molecular-level target therapy represents a promising approach.

Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), also known as PPARGC1A or PGC-1, is a multifunctional regulatory factor originally identified as a coactivator of peroxisome proliferator-activated receptor gamma (PPARγ) in 1998 (Puigserver *et al.* 1998). The *PGC-1α* gene is located on chromosome 4p15.1 in humans, a region associated with basal insulin levels in Pima Indians (Pratley *et al.* 1998). This gene encodes a 91 kDa protein, which is predominantly expressed in

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tissues with high energy demands, such as the heart, skeletal muscle and kidney (Esterbauer *et al*. 1999). As a coactivator, PGC-1α protein does not bind to DNA directly but is recruited to the template through interactions with a wide range of transcription factors involved in cellular energy metabolism. By regulating the activities of these transcription factors, PGC-1α acts as a molecular switch for multiple cellular processes, including mitochondrial biogenesis and respiration, gluconeogenesis and glucose transport, glycogenolysis, fatty acid oxidation, peroxisomal remodeling, muscle fiber-type switching, and oxidative phosphorylation (Corona & Duchen 2015). As such, PGC-1α is a very attractive target for antidiabetic therapy.

In this review, we summarize the major findings on the function of PGC-1α in glucose metabolism and discuss its potential therapeutic applications for T2DM. The close correlation between PGC-1α polymorphisms and T2DM is also discussed in this review.

PGC-1α and the liver

The liver is a vital organ responsible for glucose homeostasis. Normally, blood glucose concentration is stably maintained within a narrow range in both well-fed and fasting states. This is mainly determined by three factors: (i) glucose absorption by the intestine, (ii) gluconeogenesis by the liver and (iii) glucose utilization by skeletal muscle. In this process, the liver acts as a glucose reservoir that balances the glucose storage and release. In the well-fed state, the liver uptakes glucose from the blood and stores it in the form of glycogen (glycogenesis). In the fasting state, the liver synthesizes glucose through glycogenolysis and gluconeogenesis and releases it into the bloodstream. Impaired hepatic glucose uptake and excessive hepatic glucose production are partially responsible for hyperglycemia in T2DM. Especially, previous studies indicated that PGC-1α plays a central role in the regulatory network of glucose metabolism in the liver.

PGC-1α is a downstream sensor of metabolic, hormonal and inflammatory signals that is responsible for the balance of hepatic gluconeogenesis, fatty acid β-oxidation and mitochondrial biogenesis. The process has been reviewed elsewhere (Sugden *et al*. 2010). Briefly, in the fasting state, the pancreatic alpha cells synthesize and release glucagon to maintain a normal blood glucose level. Glucagon binds to its receptor present on hepatocytes and subsequently triggers the conformational change of G protein, which results in the dissociation of α-subunit from the G-protein complex. Free α-subunits subsequently bind to adenylate cyclase, thereby catalyzing the conversion of adenosine triphosphate (ATP) into adenosine 3′,5′-monophosphate (cAMP). Two cAMP molecules bind to each regulatory subunit of protein kinase (PKA), releasing its catalytic subunit, which translocates into the nucleus and phosphorylates the cAMP response element (CRE)-binding protein (CREB) at Ser133. The phosphorylated CREB recruits CREB-binding protein (CBP) to the PGC-1α promoter and regulates its expression. PGC-1α can coactivate several transcriptional factors, including hepatocyte nuclear factor-4α (HNF-4α) and forkhead box O (FOXO) 1, and therefore control the transcription of the rate-limiting gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase isoenzyme 4 (PDHK4) and glucose-6-phosphatase (G6Pase). However, after a meal, pancreatic beta cells synthesize and release insulin which binds to its receptor and triggers the phosphorylation of Akt, which in turn phosphorylates PGC-1α and inhibits its activity. This results in the stimulation of glycogen synthesis and inhibition of gluconeogenesis in the liver (Fig. 1).

Moreover, accumulating evidence suggests an important role for PGC-1α in the regulation of lipid and bile acid metabolism that could contribute to gluconeogenesis (Hashidume *et al*. 2011, Li *et al*. 2011). Recent studies have demonstrated that several signaling

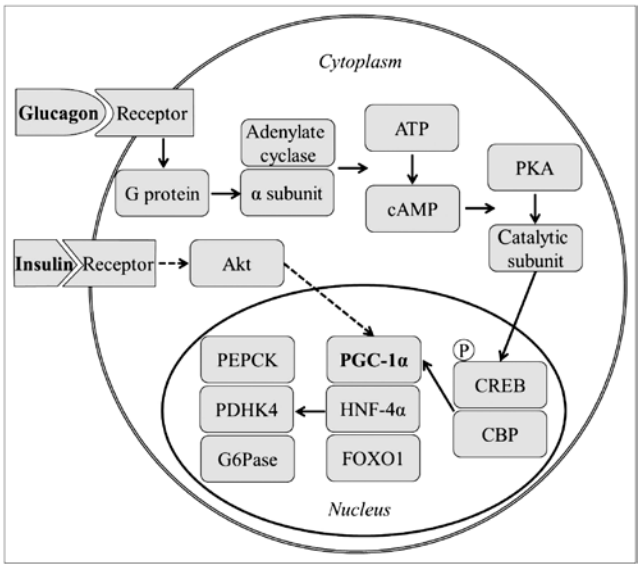

Figure 1
Signaling pathways of PGC-1α-regulated glucose metabolism in the liver.

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pathways, transcription factors and coactivators contribute to these processes through the regulation of PGC-1α expression and activity (Fig. 2). Abnormal activation of these glucose metabolic processes is closely implicated in the pathogenesis of hepatic IR and T2DM.

AMP-activated protein kinase

AMP-activated protein kinase (AMPK) is a highly conservative serine/threonine protein kinase. It acts as a sensor of cellular energy status critical to the regulation of glucose and lipid metabolism in various organs, especially the skeletal muscle and liver. Activation of hepatic AMPK was reported to decrease glucose production and increase fatty acid oxidation (Viollet *et al*. 2009). Thus, AMPK is now recognized as a promising drug target for the treatment of T2DM. There is a strong correlation between AMPK/PGC-1α signaling pathway and T2DM (Weickert & Pfeiffer 2006). For instance, metformin, one of the most widely prescribed drugs for T2DM, exerts a strong antihyperglycemic effect partly though the increasing of PGC-1α expression, via its upstream kinase AMPK (Aatsinki *et al*. 2014). These results are consistent with the previous study showing that AMPK activator metformin and adenoviral overexpression of AMPK increase PGC-1α transcriptional activity in a phosphorylation-dependent manner (Buler *et al*. 2012*b*). In addition, several Chinese herbal medicines for diabetes mellitus recover glucose homeostasis by regulating the AMPK/PGC-1α signaling pathway. Yuan and Piao (2011) reported that an active ingredient from *Artemisia sacrorum* Ledeb. decreased PGC-1α, G6Pase and PEPCK gene expression through AMPK-mediated inhibitory phosphorylation of glycogen synthase kinase-3β (pGSK-3β) and CREB in human HepG2 cells. In 2012, Yuan and coworkers subsequently reported that ginsenoside Rg2 also suppresses hepatic gluconeogenesis through AMPK/PGC-1α signaling pathway (Yuan *et al*. 2012). The phosphorylation of AMPK induced by Rg2 decreases the phosphorylation of CREB via pGSK-3β and disrupts the interaction of CREB and CREB-regulated transcription coactivator 2 (CRTC2) via induction of Src homology region 2 (SH2) domain-containing phosphatase (SHP) expression, which subsequently inhibits PGC-1α-dependent gluconeogenic enzyme gene expression. In a recent study, the same research team reported the effects of eugenol on hepatic glucose production in hepatocytes and C57BL/6J mice and obtained analogous results (Jeong *et al*. 2014). Moreover, berberine, an isoquinoline alkaloid isolated from genera *Berberis* and *Coptis*, can increase the phosphorylation of AMPK (Thr172) and reduce the expression of PGC-1α, resulting in a significant improvement in glucose tolerance in diabetic rats (Zhang *et al*. 2012). The effect of above-mentioned herbal medicines on gluconeogenesis can be abolished by the compound C (an AMPK inhibitor).

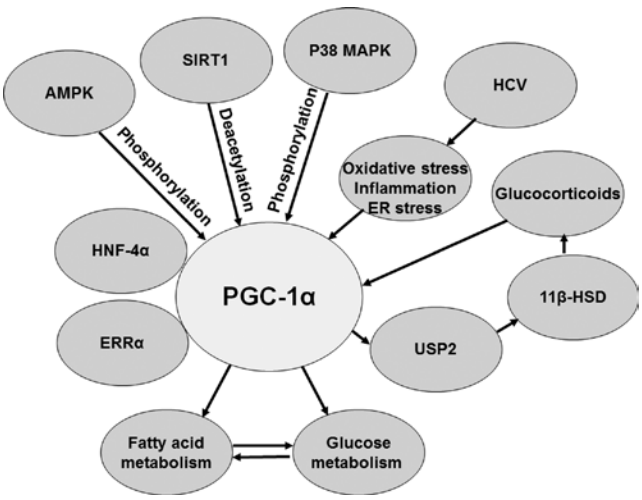

Figure 2
Interactions of PGC-1α with the main factors involved in hepatic glucose metabolism.

In addition, AMPK/PGC-1α signaling pathway alleviates IR and T2DM by modulating hepatic lipogenesis and fatty acid synthesis. For instance, deletion of the mammalian homolog of *Drosophila Indy* in mice attenuates hepatic lipogenesis and IR through the regulation of AMPK/PGC-1α signaling pathway (Birkenfeld *et al*. 2011). Recent research has indicated that monascin and ankaflavin can prevent fatty acid accumulation partly mediated by the activation of AMPK and subsequent promotion of fatty acid oxidation by PGC-1α (Hsu *et al*. 2014). Furthermore, it is also reported that interference of AMPK/PGC-1α pathway by metformin triggers the expression of anti-inflammatory interleukin 1 receptor antagonist (IL1RA) (Buler *et al*. 2012*b*). IL1RA is a naturally occurring anti-inflammatory antagonist of IL-1, IL-6, leptin, TNF-α, and several other IL-1-dependent cytokines and chemokines, and improves β-cell function and reduces hepatic lipogenic gene expression (Tack *et al*. 2012, Negrin *et al*. 2014).

Estrogen-related receptors

Estrogen-related receptors (ERRα, ERRβ and ERRγ) are orphan nuclear receptors. Notably, through interaction with PGC-1α, ERRα and ERRγ are involved in the

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regulation of mitochondrial biogenesis and fatty acid β-oxidation. Recent study has shown that PGC-1α can coactivate ERRα to induce the expression of glucokinase, a key enzyme of glucose metabolism in the liver (Zhu *et al*. 2010). Especially, a study reported that ERRα acted as a repressor of gluconeogenesis by directly binding to the glucocorticoid accessory factor 3 (gAF3) site of the PEPCK promoter, which in turn inhibited the recruitment of PGC-1α to the PEPCK gene promoter (Herzog *et al*. 2006). Taken together, PGC-1α/ERRα-negative feedback loop participates in the regulation of hepatic glucose metabolism by repressing gluconeogenesis and increasing glucose utilization. Moreover, it was also demonstrated that ERRγ, along with coactivator PGC-1α, significantly increased the phosphatidic acid phosphatase function of lipins and subsequently diminished insulin-stimulated Akt phosphorylation, resulting in dysregulation of insulin signaling in HepG2 cells (Kim *et al*. 2011). A subsequent study from the same laboratory also found that ERRγ appeared to be an important downstream target of the glucagon signaling pathway. Glucagon-mediated activation of CREB–CRTC2 induces hepatic ERRγ gene expression, which in turn increases G6Pase and PEPCK gene expression along with coactivator PGC-1α (Kim *et al*. 2012*a*). How ERRα and ERRγ differentially affect PGC-1α activity remains largely elusive.

Hepatocyte nuclear factor-4α

Hepatocyte nuclear factor-4α (HNF-4α) is an orphan nuclear receptor as are the ERRs and a liver-enriched transcription factor that regulates the metabolism of glucose, fatty acids, amino acids, cholesterol, lipids, bile acids and drugs, whereas its dysfunction leads to impaired glucose transport and glycolysis. It is coactivated by PGC-1α. Several studies have shown its strong correlation with T2DM (Andrulionyte *et al*. 2006, Jafar-Mohammadi *et al*. 2011). Full transcriptional activation of the PEPCK promoter requires coactivation of the HNF-4α by PGC-1α (Yoon *et al*. 2001). PGC-1α protein contains three LXXLL motifs responsible for the interaction with HNF-4α. These LXXLL motifs synergistically activate HNF-4α-mediated transcription (Rha *et al*. 2009). Additionally, a study carried out in the mouse hepatocytes demonstrated that the region between –298 and –180 of the G6Pase promoter contained several HNF-4α-binding sites responsible for the activation of G6Pase by PGC-1α (Rhee *et al*. 2003). Interestingly, in the same year, HNF-4α was reported to mediate this activation by binding to the region between –76 and –64 of the mouse G6Pase promoter (Boustead *et al*. 2003). In addition to the HNF-4α-binding site located between –76 and –64, a 3 bp sequence discovered by the same team was found to be a crucial site for HNF-4α-binding activity (Schilling *et al*. 2008). In addition, many other transcription factors and coactivator proteins, such as DAX-1 (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1), sterol regulatory element-binding proteins (SREBPs), vanin-1, cAMP, xenobiotic-metabolizing cytochrome P450 (CYP) 2A5 enzyme, HNF-6, and FOXO1, also contribute to the PGC-1α/HNF-4α-mediated transcriptional regulation of the gluconeogenic genes (Yamamoto *et al*. 2004, Beaudry *et al*. 2006, Arpiainen *et al*. 2008, Schilling *et al*. 2008, Nedumaran *et al*. 2009, Dankel *et al*. 2010, Chen *et al*. 2014).

Sirtuins (SIRTs)

The mammalian SIRTs (SIRT1–7), a family of NAD(+)-dependent deacetylases, are implicated in a variety of cellular processes, including aging, gene transcription, DNA repair, cellular stress, apoptosis, energy metabolism, cancer and inflammation. SIRT1 is the most studied SIRT that regulates the expression of gluconeogenic and glycolytic enzymes and promotes the hepatic glucose output. These effects are mediated, at least in part, by interacting with PGC-1α and deacetylating it (Ghiraldini *et al*. 2013). Consistently, treatment with the specific SIRT1 activator SRT1720 increases mitochondrial membrane potential and cellular ATP content in HepG2 cells, and this effect was blocked by PGC-1α knockdown (Minor *et al*. 2011). This result was subsequently confirmed by other groups using liver-specific SIRT1 knockout mice (Rodgers & Puigserver 2007). Taken together, the SIRT1 deacetylates PGC-1α and increases its activity, and thus plays a pivotal role in the hepatic glucose metabolism and diabetes, both *in vitro* and *in vivo*. SIRT1/PGC-1α axis also affects fatty acid and cholesterol metabolism in the liver. For example, silencing SIRT1 in the liver by adenovirus-delivered SIRT1 small hairpin RNA reduces the gene expression of enzymes involved in fatty acids and triglyceride metabolism. These effects are partly dependent on PGC-1α (Rodgers & Puigserver 2007). It is then further revealed using liver-specific SIRT1 knockout mice that reduced SIRT1 expression impaired PPARα-mediated fatty acid metabolism through PGC-1α, a key coactivator of PPARα (Purushotham *et al*. 2009). Indeed, in a genome-wide coactivation study, PGC-1α was found to enhance the recruitment of 60 kDa BRG-1/Brm-associated factor subunit A (BAF60A) to the PPARα-binding sites (PPREs),

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which further activated PPARα-mediated peroxisomal and mitochondrial fat oxidation genes in the liver (Li *et al.* 2008). Recently, resistin has been reported to weaken the interaction between SIRT1 and PPARα as well as PGC-1α (Yu *et al.* 2013). Given that resistin was initially described as an adipokine increasing hepatic IR and glucose metabolism through an AMPK-dependent pathway, it is plausible that the activity of PGC-1α in the liver may be governed by a complex network of interactions among SIRT1, AMPK and PPARα. This is in accordance with another study that indicates a critical role of PGC-1α in cholesterol synthesis (Rodrigue-Way *et al.* 2014). In addition, it is also reported that SIRT1/PGC-1α axis regulated glucose and lipid metabolism through a PPARα-independent pathway (Peeters *et al.* 2011, Alberdi *et al.* 2013). Moreover, several lines of evidence have indicated that PGC-1α activated by SIRT1 also modulates the effects of thyroid hormone on lipid and glucose homeostasis (Suh *et al.* 2013, Thakran *et al.* 2013). These findings suggest certain connections between hormonal signaling and SIRT1/PGC-1α axis in the regulation of energy metabolism.

Moreover, recent studies have shed light on the relationship between other SIRTs and PGC-1α in hepatic metabolism. For instance, it has been demonstrated that PGC-1α can strongly promote SIRT3 gene expression and is mediated by coactivation of ERRα (Buler *et al.* 2012*a*). Further study has illuminated the complex relationship between these transcription factors. Recent research on ubiquinol-10 has indicated that SIRT3 is under the control of cAMP/AMPK/SIRT1/PGC-1α signaling (Tian *et al.* 2014), whereas SIRT5 is reported to increase ATP synthesis and oxygen consumption in HepG2 cells, which is antagonized by PGC-1α and AMPK (Buler *et al.* 2014). Surprisingly, recent study suggests that the deacetylase SIRT6 can suppress hepatic glucose production by acting as a positive regulator of general control non-derepressible 5 (GCN5)-mediated acetylation of PGC-1α (Dominy *et al.* 2012). These findings expand the spectrum of SIRTs/PGC-1α axis and provide new therapeutic strategies for T2DM.

p38 mitogen-activated protein kinase (p38 MAPK) and other post-translational modulators

The serine/threonine protein kinase p38 mitogen-activated protein kinase (p38 MAPK) is a member of the MAPK family (also including JNK, ERK1/2 and ERK5), which is specifically activated by phosphorylation in response to a variety of extracellular stimuli. It plays an important role in pathological conditions, such as diabetes. p38 MAPK can regulate hepatic glucose, under the control of free fatty acids (FFAs), glucagon and insulin. PGC-1α is directly phosphorylated and activated by p38 MAPK, and then mediates FFA-induced gluconeogenesis in primary hepatocytes (Collins *et al.* 2006). This is consistent with a previous report showing that inhibition of p38 MAPK by SB203580 or siRNA can attenuate the stimulatory effect of glucagon on PGC-1α promoter activation (Cao *et al.* 2005). Similarly, the control of PGC-1α by p38 MAPK appears to be also involved in fatty acid metabolism. Acetyl-coenzyme A carboxylase-α (ACCα) is the rate-limiting enzyme for fatty acid synthesis. Inhibiting p38 MAPK with SB203580 upregulates ACCα gene expression by modulating the expression of PGC-1α (Talukdar *et al.* 2007). Interestingly, ACC is also regulated by thyroid hormone and AMPK (Huang & Freake 1998, Chang *et al.* 2013), suggesting a complex crosstalk among these signaling pathways. In addition to acetylation and phosphorylation, the activity of PGC-1α is also strongly modulated by O-GlcNAcylation and ubiquitination. For example, O-GlcNAcylated PGC-1α has increased affinity to the deubiquitinase BAP1. This recruitment subsequently decreases ubiquitination of PGC-1α, thereby enhancing PGC-1α stability and promoting hepatic gluconeogenesis (Ruan *et al.* 2012).

Hepatitis C virus

Hepatitis C virus (HCV) infection is a global health problem affecting about 130–150 million people. It predisposes the infected to both type 1 diabetes mellitus (T1DM) and T2DM (Antonelli *et al.* 2014). PGC-1α expression is dramatically elevated in HCV-infected cells, accompanied by an upregulated expression of PEPCK and G6Pase (Qadri *et al.* 2012, Shlomai *et al.* 2012). In addition, the HCV nonstructural protein 5A induces metabolic dysregulation and IR in human hepatoma cells, in which PGC-1α could be involved (Parvaiz *et al.* 2014). These results emphasize the important role of PGC-1α in bridging the HCV infection to hepatic IR and diabetes mellitus. In addition, oxidative stress and endoplasmic reticulum (ER) stress are also responsible for the association of HCV with diabetes mellitus. Treatment of HCV replicon cells with the antioxidant *N*-acetylcysteine can attenuate the PGC-1α expression induced by HCV, suggesting that HCV-promoted PGC-1α induction is mediated by oxidative stress and inflammation (Shlomai *et al.* 2012). In addition, a recent study has reported that HCV infection induces PGC-1α expression and ER stress. Moreover, pharmacological induction of ER stress upregulates PGC-1α expression, and pharmacological

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inhibition of HCV-induced ER stress impairs PGC-1α upregulation (Yao *et al*. 2014).

Glucocorticoids

Glucocorticoids (GCs), such as dexamethasone, prednisone and hydrocortisone, are often prescribed as anti-inflammatory agents. Recently, they have been gradually recognized as the important regulators of diabetes mellitus because of their critical roles in peripheral IR and β-cell insulin secretion. In the liver, the function of GCs is ultimately complex and partly mediated by PGC-1α. First, overexpression of PGC-1α can strongly potentiate the activity of PEPCK promoter in response to dexamethasone (Herzig *et al*. 2001), which can be explained by the following facts. Synergistic with cAMP, GCs significantly induced the expression of PGC-1α in hepatocytes (Felder *et al*. 2011). PGC-1α has the ability to physically interact with glucocorticoid receptor (GR) and increase its activity (Knutti *et al*. 2000). Subsequently, GR interacts with the glucocorticoid response unit in the PEPCK promoter and promotes its transcriptional activation (Herzig *et al*. 2001). Secondly, ubiquitin-specific protease 2 (USP2) is another downstream target of hepatic GCs/PGC-1α signaling to stimulate hepatic gluconeogenesis and glucose output (Molusky *et al*. 2012*b*). Intriguingly, USP2 is reported to induce 11β-hydroxysteroid dehydrogenase (11β-HSD) expression, which subsequently converts GCs into active forms (Molusky *et al*. 2012*a*). Finally, microRNA-29a-c ameliorates forskolin/dexamethasone-induced hepatic glucose production by reducing PGC-1α and G6Pase gene expression (Liang *et al*. 2013), indicating an alternative strategy for alleviating glucocorticoid-induced IR. Collectively, GCs interact with PGC-1α signaling in a positive feedback loop to regulate glucose homeostasis.

PGC-1α and skeletal muscle

The skeletal muscle is a major site of glucose and fatty acid utilization. It is generally accepted that glucose uptake and disposal are the most important limiting factors in fuel metabolism and energy homeostasis of skeletal muscle. Thus, a widespread opinion holds that IR in obesity and T2DM are primarily due to the defects in one or both of these factors. These defects are always accompanied by oxidative stress, ER stress, mitochondrial insufficiency and chronic low-grade inflammation. In contrast to the liver and islets, the expression of PGC-1α is downregulated in human diabetic muscle. Notably, researchers have successfully established a causal relationship between PGC-1α dysregulation in skeletal muscle and abnormal energy homeostasis, as well as IR and T2DM. Furthermore, PGC-1α is also involved in the regulation of muscle fiber-type switching (Wang *et al*. 2013) and autophagy (Yu & Long 2015).

Glucose uptake

The skeletal muscle accounts for about 80% of insulin-stimulated glucose disposal. Glucose transporter 4 (GLUT4) is a major glucose transporter expressed in the skeletal muscle, adipocyte and cardiac muscle. Insulin facilitates glucose uptake in skeletal muscle by promoting GLUT4 translocation from intracellular compartments to the plasma membrane. Therefore, impairment of insulin-stimulated GLUT4 translocation results in reduced glucose disposal and peripheral IR in T2DM. It has been reported that overexpression of PGC-1α significantly activates GLUT4 expression and increases glucose uptake (Wende *et al*. 2007). Overexpression of PGC-1α-related coactivator (PRC) exerts a similar effect (Philp *et al*. 2011). These findings highlight the importance of PGC-1α in the regulation of GLUT4 expression and translocation in muscle. At least two mechanisms are involved in this process. (1) Pessin and his colleagues (Thai *et al*. 1998, Mora & Pessin 2000) have reported that myocyte enhancer factor 2A (MEF2A) binds to the GLUT4 promoter and mediates GLUT4 transcription in skeletal muscles. PGC-1α can increase the expression of MEF2A by activating nuclear respiratory factor 1 (NRF1) (Ramachandran *et al*. 2008). Moreover, PGC-1 also binds to MEF2C and coactivates it to increase GLUT4 expression (Michael *et al*. 2001). However, the overexpression of MEF2C alone is necessary but not sufficient to drive GLUT4 transcription (Handschin *et al*. 2003), suggesting that PGC-1α may mediate GLUT4 expression via a MEF2-independent signaling pathway. (2) AMPK activator (AICAR), alone or in combination with insulin, increases Akt substrate of 160 kDa (AS160) phosphorylation in skeletal muscle (Kramer *et al*. 2006). Phosphorylation of AS160 can activate Rab proteins in GLUT4 vesicles and promote its translocation to the plasma membrane (Satoh 2014). Two recent reports have reported that PGC-1α is essential for AICAR-induced expression of GLUT4 (Leick *et al*. 2010, Suwa *et al*. 2015). These results are consistent with the previous report that modest PGC-1α overexpression in obese Zucker rat muscles can increase insulin-induced AS160 phosphorylation (Benton *et al*. 2010). Several

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transcription factors and coactivators are implicated in PGC-1α-induced translocation and activation of GLUT4, either dependent on or independent of insulin, including AMPK (Jager *et al*. 2007), SIRT1 (Zhang *et al*. 2011), p38 MAPK (Wright 2007), ERR (Cho *et al*. 2013), and PPARγ (Kang *et al*. 2013). Specifically, some antidiabetic and antioxidative agents, such as lipoic acid, oligomannuronate, metformin and selenium-enriched exopolysaccharides, can improve skeletal muscle glucose uptake through AMPK/PGC-1α/GLUT4 pathway (Wang *et al*. 2010, Hao *et al*. 2011, Zhou *et al*. 2014). Consistently, both ER stress and oxidative stress are reported to impair GLUT4 production and glucose uptake via a PGC-1α-dependent signaling pathway (Raciti *et al*. 2010, Aoi *et al*. 2013). Moreover, aberrant DNA methylation in the PGC-1α promoter sequence also contributes to impaired glucose tolerance by influencing the expression of PGC-1α and GLUT4 in skeletal muscle (Zeng *et al*. 2013). In addition, PGC-1α has been shown to directly induce angiogenesis in skeletal muscle by enhancing the delivery of oxygen and glucose (Arany *et al*. 2008, Rowe *et al*. 2014), although not in all studies (Sawada *et al*. 2014). Thus, PGC-1α-mediated increase in skeletal muscle glucose uptake is probably due to the modulation of blood flow. Taken together, these findings reveal a significant association between PGC-1α and glucose uptake.

Glucose disposal

Impaired glucose disposal in skeletal muscle reduces insulin sensitivity and contributes to the development of T2DM. PGC-1α sets a strict control on glucose disposal in skeletal muscle, including suppression of glycolysis and glucose oxidation, inhibition of glycogen degradation, and augmentation of glycogen synthesis and fatty acid oxidation (Wende *et al*. 2007, Mormeneo *et al*. 2012). As described previously, PGC-1α activity is regulated by a variety of posttranslational modifications, especially by phosphorylation and acetylation. PGC-1α is involved in many signaling pathways that are critical to glucose storage and utilization, including AMPK (Li *et al*. 2014), p38 MAPK (Hong *et al*. 2011), and SIRT1 pathways (Gao *et al*. 2014). Furthermore, a series of studies have shed light on the role of posttranslational modifications of PGC-1α in glucose metabolism. For example, Silvestre and coworkers have reported that skeletal muscle-specific AMPKα1/2 knockout mice display impaired glucose tolerance and downregulated SIRT1, in association with decreased PGC-1α gene expression and deacetylation (Silvestre *et al*. 2014). The authors further show that SIRT1 inversely activates AMPK activity through phosphorylation of Thr172. However, as the relationship between p38 MAPK and AMPK pathways is particularly complicated, whether AMPK lies upstream of p38 MAPK is still debated. The mechanisms of how PGC-1α is regulated by p38 MAPK are significantly different. First, p38 MAPK directly phosphorylates PGC-1α at three sites (threonine 262, serine 265 and threonine 298) (Puigserver *et al*. 2001), which disrupts the binding and repression of PGC-1α by repressors such as p160 Myb binding protein (p160MBP), and greatly enhances the transcriptional activity of PGC-1α (Fan *et al*. 2004). These findings provide new insights into the regulation of PGC-1α by p38 MAPK. Second, p38 MAPK can indirectly increase PGC-1α expression. PGC-1α promoter comprises several positive regulatory domains that bind different cooperative transcription factors. Phosphorylation of MEF2 and ATF2 by p38 MAPK stimulates PGC-1α expression by binding to the regulatory domains on the PGC1α promoter, respectively (Fernandez-Marcos & Auwerx 2011). Conversely, angiotensin II stimulates p38 MAPK-dependent PGC-1α serine 570 phosphorylation and the subsequent GCN5-dependent acetylation, repression of PGC-1α cotranscriptional activity, and downregulation of catalase expression in vascular smooth muscle cells. Whether p38 MAPK plays a positive or negative role in PGC-1α gene expression and activity remains controversial.

PGC-1α and pancreas

Pancreatic β cells are responsible for synthesizing and secreting insulin, which helps to maintain blood glucose levels within a normal range. The reduction of pancreatic β cells mass is now widely acknowledged as an important pathophysiological factor implicated in T2DM. To date, several studies have reported the close relationship between PGC-1α and pancreatic β-cell dysfunction. For instance, adenovirus-mediated overexpression of PGC-1α in isolated rat islets results in a decrease in glucose-stimulated insulin secretion (Yoon *et al*. 2003). Although the exact mechanism through which PGC-1α affects the pancreatic islet function is still not completely elucidated, the explanation that follows here seems reasonable.

Pancreatic β-cell apoptosis

PGC-1α is an important regulator of pancreatic β-cell apoptosis. On one hand, PGC-1α is involved in the glucotoxicity-induced pancreatic β cells apoptosis.

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Glucokinase, a key regulatory enzyme that catalyzes glucose to glucose-6-phosphate, plays an important role in the regulation of glucose-stimulated insulin secretion by acting as a 'glucose sensor' in pancreatic islets. It has been reported that YH-GKA, a novel benzamide activator of glucokinase, dramatically reduces the mRNA level of PGC-1α and prevents glucotoxicity-induced INS-1 pancreatic β-cell apoptosis (Oh *et al.* 2014). Interestingly, PGC-1α overexpression in isolated rat islets induces the expression of G6Pase and suppresses glucokinase and glycerol-3-phosphate dehydrogenase, and therefore blunts membrane depolarization and insulin exocytosis in response to glucose (Yoon *et al.* 2003). On the other hand, PGC-1α mediates the FFA-induced pancreatic β-cell apoptosis in the development of T2DM, a process known as 'lipotoxicity'. Zhang and coworkers demonstrated that there is a direct correlation between FFAs and PGC-1α (Zhang *et al.* 2005). After 72-h incubation, elevated FFAs (oleate/palmitate) not only dose-dependently increase PGC-1α expression level in isolated islets but also increase PGC-1α mRNA level in isolated islets and in mouse β-cell-derived bTC3 cell lines. Furthermore, recent data demonstrate that NADH-cytochrome b5 oxidoreductase (Ncb5or)-null mice, characterized by increased intracellular saturated fatty acid accumulation and hyperglycemia, show significantly higher islet transcript level of PGC-1α accompanied by accelerated β-cell injury (Guo *et al.* 2012). Taken together, these results indicate that the effects of PGC-1α on pancreatic β-cell apoptosis may at least in part be mediated by altered FFA metabolism. However, some recent conflicting reports showed that palmitic acid (PA) can extensively reduce the expression of PGC-1α mRNA and increase pancreatic β-cell apoptosis (He *et al.* 2011). The reason for the discrepancy is currently unclear.

Pancreatic β-cell regeneration

The development of T2DM partly depends on the balance between β-cell proliferation and death (apoptosis). Therefore, the regeneration of pancreatic β cells is considered to be a potentially curative treatment for T2DM. A recent study has demonstrated that the increased expression of PGC-1α is closely related to glucocorticoid-suppressed expansion and transdifferentiation of porcine neonatal pancreatic cell clusters into β cells (Kim *et al.* 2012*b*). Subsequently in 2014, the same research team reported that the silencing of PGC-1α by siPGC-1α significantly improved the glucocorticoid-suppressed expansion and transdifferentiation of porcine neonatal pancreatic cell clusters via the FOXO1–PDX1 pathway (Kim *et al.* 2014). These data indicate that PGC-1α is a critical regulator of pancreatic β-cell regeneration.

Insulin secretion

Impaired insulin secretion by pancreatic β cells is a characteristic feature of T2DM. Uncoupling protein 2 (UCP2), a mitochondrial transporter protein, has been reported to participate in the regulation of glucose-stimulated insulin secretion from pancreatic β cells (Sun *et al.* 2011). In cold-exposed rats, inhibition of islet PGC-1α expression by antisense oligonucleotide corrects UCP2 expression level and partially normalizes insulin secretion in pancreatic islets (De Souza *et al.* 2003). Oberkofler and coworkers subsequently characterize the underlying mechanism that PGC-1α can enhance the expression of sterol regulatory element-binding protein isoforms (SREBP)-1c via coactivation of the liver X receptor and upregulate the expression of SREBP2 via coactivation of the GR, resulting in an increase in UCP2 expression in INS-1E β cells (Oberkofler *et al.* 2006).

Mitochondrial dysfunction

In pancreatic β cells, mitochondrial metabolism is responsible for the generation of metabolic signals and coupling glucose recognition with insulin secretion. Mitochondrial dysfunction is known to produce excessive reactive oxygen species (ROS), eventually leading to oxidative stress and pancreatic β-cell dysfunction. PGC-1α, as a crucial factor responsible for mitochondrial biogenesis, is closely associated with oxidative stress-induced pancreatic β-cell dysfunction. For instance, transient exposure of INS-1E β cells to oxidative stress results in increased mitochondrial ROS formation, decreased PGC-1α expression, and reduced 15 mM glucose-stimulated insulin secretion (Li *et al.* 2009). GW501516, a specific PPARδ agonist, decreases basal insulin secretion, but not glucose-stimulated insulin secretion (GSIS) in palmitate-exposed HIT-T15 pancreatic β cells (Jiang *et al.* 2010). These changes correlate with improved mitochondrial energy metabolism and increased mRNA expression of PGC-1α. Recently, mitochondrial dysfunction in pancreatic islets of congenitally malnourished offspring has also been studied. Prenatal malnutrition leads to a reduction of insulin secretion in 3-month-old male and female offsprings, due to mitochondrial dysfunction and higher PGC-1α expression (Theys *et al.* 2011). Glutathione peroxidase (GPX) is a major antioxidant enzyme that converts hydrogen peroxide into water and protects cells

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against oxidative stress. Thus, a recent study shows that GPX mimic ebselen enhances GSIS in islets of GPX1 knockout mice, and knockdown of PGC-1α by siRNA can largely eliminate this effect (Wang *et al*. 2014).

PGC-1α and diabetic nephropathy

Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus and the leading cause of end-stage renal disease, affecting approximately one-third of diabetic patients, with no effective treatment available so far. Several studies, both in human beings and in animal models, have provided important clues to its etiology and pathogenesis. Considering the key role of mitochondrial dysfunction in DN, many researchers have focused their attention on PGC-1α. The mRNA and protein expression of PGC-1α are markedly downregulated in renal tubular cells of streptozotocin-induced diabetic rats. Rap1, a member of the RAS-like small GTP-binding protein superfamily, can significantly ameliorate renal tubular mitochondrial dysfunction, oxidative stress and apoptosis concomitant with the increased expression of PGC-1α and ameliorated tubular injury (Xiao *et al*. 2014). In two other diabetic models, transgenic OVE26 and Akt2-KO mouse, PGC-1α expression is also markedly downregulated, associated with significant changes in several glucose metabolism-related regulators (Sun *et al*. 2014). The pathogenesis of DN may, at least in part, be due to PGC-1α-mediated mitochondrial biogenesis.

The AMPK/SIRT1/PGC-1α pathway is a fundamental signaling system in energy metabolism and mitochondrial biogenesis. Recent studies relate the AMPK/SIRT1/PGC-1α signaling pathway to the progression of DN. For example, resveratrol, a type of natural phenol extracted primarily from the traditional Chinese medicinal herb *Polygonum cuspidatum*, has been reported to prevent DN in *db/db* mice through the phosphorylation of AMPK and the activation of SIRT1/PGC-1α signaling (Kim *et al*. 2013). In 2014, another kind of natural plant polyphenol, the grape seed proanthocyanidin extract, is also reported to ameliorate podocyte injury in low-dose streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats through the activation of AMPK/SIRT1/PGC-1α signaling pathway (Bao *et al*. 2014). Moreover, several studies have evaluated the therapeutic efficacy of PGC-1α on DN. For instance, both telmisartan and fenofibrate exert their renoprotective effects in animal models of DN by activating PGC-1α expression and reducing oxidative stress (Lakshmanan *et al*. 2011, Hong *et al*. 2014), indicating the therapeutic potential of PGC-1α in the treatment of DN. Nonetheless, researchers from Korea have shown conflicting results, reporting that PGC-1α is increased in response to high-glucose (25 mM) or IL-6 treatment. PGC-1α overexpression contributes to high glucose-induced apoptosis and growth arrest of renal podocytes (Kim & Park 2013). Although the discrepancy is not yet fully explained, it can be hypothesized that sustained activation of PGC-1α may change the energy supply–demand balance and cause different pathogenic outcomes in DN.

PGC-1α, oxidative stress and T2DM

As mentioned previously, PGC-1α is a crucial factor responsible for mitochondrial biogenesis. Mitochondrial dysfunction will produce excessive ROS, eventually leading to oxidative stress. Therefore, PGC-1α and oxidative stress are deeply implicated in T2DM and its complications. First, in the hepatocytes, it has been indicated that elevated endogenous asymmetric dimethylarginine (ADMA) contributes to the suppression of hepatic mitochondrial biogenesis, PGC-1α transcription and diabetes. These effects of ADMA could be inhibited by treatments with antioxidant (Chen *et al*. 2011). This is consistent with another report showing that the downregulation of GLUT2 and PGC-1α induced by glucose oxidase was evidently inhibited by NAC in rats and in hepatocytes (Wang *et al*. 2012). Secondly, in arsenic-treated mouse adipocytes and myotubes, the expression of SIRT3 and its associated transcription factor, FOXO3a, was dramatically decreased. Arsenic decreased the binding affinity of FOXO3a to the PGC-1α promoter. Overexpression of SIRT3 can stimulate FOXO3a deacetylation and the subsequent PGC-1α and MnSOD upregulation, which facilitates ROS detoxification in response to chronic arsenic exposure (Padmaja Divya *et al*. 2015). Thirdly, in dorsal root ganglion (DRG) neurons, Choi and coworkers reported that adenoviral overexpression of PGC-1α can prevent high glucose-induced oxidative stress (Choi *et al*. 2014). Fourthly, in rat glomerular mesangial cells, high glucose treatment resulted in the downregulation of PGC-1α, accompanied by an increase in ROS generation and mesangial cell hypertrophy. The transfection of pcDNA3–PGC-1α can significantly reverse these pathological changes (Guo *et al*. 2015). Finally, recent study, in cardiac cells, has demonstrated that sulforaphane treatment can increase fatty acid oxidation and prevent cardiomyopathy probably by reversing oxidative stress-induced inhibition

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of LKB1/AMPK/PGC-1α signaling pathway (Zhang *et al.* 2014). Taken together, these findings indicate a significant cooperative role of PGC-1α and oxidative stress in the pathogenesis of diabetes.

PGC-1α polymorphisms and T2DM

Several previous studies have demonstrated a close correlation between polymorphisms in the PGC-1α gene and T2DM. For example, Gly482Ser, the most common polymorphism in the PGC-1α gene, is positively associated with T2DM in different populations, including the Chinese (Lu *et al.* 2007); Danish (Ek *et al.* 2001); Japanese (Hara *et al.* 2002); and Canadian, German, Austrian, Finnish, Norwegian and Spanish (Andrulionyte *et al.* 2004).

The underlying mechanisms are as follows: on the one hand, the Gly482Ser polymorphism of PGC-1α gene is associated with a decreased PGC-1α mRNA expression and reduced insulin secretion (Ling *et al.* 2008). Additionally, an autosomal genomic scan shows that fasting plasma insulin concentration is linked to chromosome 4p15-q12 (Pratley *et al.* 1998). Interestingly, chromosome 4p15-q12 is syntenic to the chromosome 4p15.1, a region where PGC-1α gene has been mapped (Esterbauer *et al.* 1999). On the other hand, several published studies have found significant association between the Gly482Ser variant of PGC-1α gene and IR (Fanelli *et al.* 2005, Goyenechea *et al.* 2008). First, PGC-1α variants with Gly/Gly at the 482nd amino acid impair the transcription of mitochondrial transcriptional factor A (TFAM), resulting in mitochondrial dysfunction and IR (Choi *et al.* 2006). TFAM is a DNA-binding protein with high-mobility group (HMG)-box domains and acts as a link between the nucleus and the mitochondria during mitochondrial DNA (mtDNA) replication, transcription and inheritance. Recently, some studies have suggested that the expression of *Tfam* is significantly downregulated in the liver (Kim *et al.* 2015) and muscle cells (Taheripak *et al.* 2013) of *db/db* type 2 diabetic mice and DRG neurons (Choi *et al.* 2014) of streptozotocin-induced type 1 diabetic mice. Collectively, these findings strongly suggest that the TFAM may be closely associated with diabetes mellitus. Further investigations subsequently elucidate the underlying mechanism. PGC-1α can induce NRF-1 expression, which, in turn, activates *Tfam* to directly regulate mitochondrial biogenesis (Hickey *et al.* 2011, Agrawal *et al.* 2014). This association has been confirmed by the *in vivo* (Choi *et al.* 2014) and *in vitro* (Yan *et al.* 2013) results. Secondly, PGC-1α participates in insulin-stimulated glucose uptake in muscle cells by binding with the muscle-selective transcription factor MEF2C and coactivating it, thus controlling the level of GLUT4 expression (Michael *et al.* 2001). The Gly482Ser polymorphism can weaken the binding of PGC-1α and MEF2C, thereby increasing the risk of T2DM in Chinese Han population (Lu *et al.* 2007). In a recently published study, Zhang and coworkers further propose the following molecular mechanism (Zhang *et al.* 2010): the region at 400–500 amino acids of PGC-1α harbors a tetrapeptide. The region just distal to this tetrapeptide is required for coactivation of the GLUT4 via MEF2C. Hence, mutations in this region may decrease the transcription of GLUT4 and dysregulate insulin-dependent glucose transportation in skeletal muscle cells, contributing to IR. Thirdly, plasma adiponectin concentration is inversely related to the risk of developing T2DM, IR, obesity, atherosclerosis and gastrointestinal malignancies. Recently, a decreased plasma adiponectin level has been associated with Gly482Ser polymorphism of the PGC-1α gene in Japanese type 2 diabetic men but not women (Okauchi *et al.* 2008). However, the mechanism behind the linkage disequilibrium is still not fully understood. Finally, Ha and coworkers report that lifestyle factors, including PA and body fat, may modulate the genetic effects of the PGC-1α Gly482Ser polymorphism on IR in Korean children (Ha *et al.* 2015). Despite some limitations, this cross-sectional study strongly suggests the association between PGC-1α polymorphisms and diabetes.

Several other polymorphisms in PGC-1α gene are also reported to be associated with IR and T2DM. For example, the relationship between Thr394Thr variant and T2DM as well as its related mechanism is investigated in several populations. In Asian Indian population, the A allele of Thr394Thr (ACG→ACA) polymorphism is significantly associated with T2DM, and the XA genotype confers 1.6 times higher risk for T2DM compared with the GG genotype in this population (Vimaleswaran *et al.* 2005). Subsequently in 2007, a replicate case–control study reported the effect of PGC-1α Thr394Thr and Gly482Ser variants on T2DM in two North Indian populations, obtaining the same results (Bhat *et al.* 2007). In addition, the PGC-1α Thr394Thr polymorphism can affect the therapeutic effect of rosiglitazone, an oral antidiabetic medicine that directly binds with PPARγ and activates it to reduce hepatic glucose output and to increase peripheral glucose disposal. A recent study reported that the Chinese T2DM patients with Thr394Thr polymorphism experienced a decreased therapeutic response than

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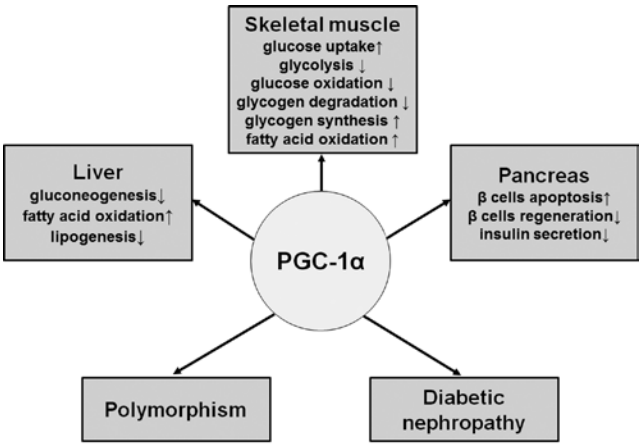

Figure 3
The main functions of PGC-1α in different tissues.

patients with the wild-type genotype (Zhang *et al.* 2010). In order to elucidate the underlying mechanism of Thr394Thr variants, the bacterial two-hybrid system has been used in a study carried out in southern Chinese population. The results indicate that the 482Ser variant is less efficient than the 482Gly variant in binding with MEF2C, whereas the 394Thr (A) has a synergistic effect on the interaction between 482Ser variant and MEF2C (Zhang *et al.* 2007).

However, conflicting findings are reported on the relationship between the PGC-1α polymorphism and the risk of diabetes. For example, the Gly482Ser polymorphism of PGC-1α has no association with diabetes in French Caucasians and non-diabetic German and Dutch and Northern Chinese Han populations (Lacquemant *et al.* 2002, Chen *et al.* 2004, Stumvoll *et al.* 2004). It is also shown that Gly482Ser, Thr528Thr and Thr612Met polymorphisms in the PGC-1α gene are not associated with T2DM or body mass index among Hispanics and Non-Hispanic Whites from Colorado (Nelson *et al.* 2007). Explanations for these discrepancies may include differences in ethnic, genetic and environmental heterogeneity; gene pools; and sample size. In any case, further investigation is needed.

Conclusions and future perspectives

In summary, the current findings highlight the central role of PGC-1α in the regulatory network of glucose metabolism. Obviously, the expression and activity of PGC-1α are regulated by various cytokines, transcription factors, and other external stimuli via multiple intracellular signaling pathways. This complex pathway should be considered as a novel therapeutic strategy and potential pharmacological agent for T2DM treatment. However, it should be noted that PGC-1α not only is differentially expressed in different tissues but also has distinct and even opposite functions in different cells (Fig. 3). In addition, most of studies did not take into account the complex crosstalk between different signaling pathways. Further investigation is needed to determine the precise role of PGC-1α pathway in the T2DM, and it largely relies on the development of novel PGC-1α-targeting reagents and tissue-specific transgenic or knockout animal models.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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