

REVIEW

PPAR control: it's SIRTainly as easy as PGC

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Abstract

This review describes recent advances in our knowledge of the regulatory interactions influencing the expression of peroxisome proliferator-activated receptor (PPAR)-regulated genes. We address recent advances highlighting the role of PPAR γ (PPARG) coactivator-1 (PGC-1) and lipin-1 in co-ordinating the expression of genes controlling nutrient handling. We evaluate the possibility that SIRT1 lies at the heart of a regulatory loop involving PPAR α , PGC-1 α (PPARA, PPARGC1A as given in the HUGO

Database), and lipin-1 (LPIN1 as listed in the HUGO Database) that ultimately controls the metabolic response to varying nutrient and physiological signals via a common mechanism mediated by post-translation modifications (deacetylation) of both PPAR α and PGC-1s. Finally, we comment on the potential of pharmaceutical manipulation of these targets as well as the possible problems associated with this strategy.

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Introduction

Nuclear receptors (NRs) are members of a superfamily of ligand-regulated and orphan transcription factors that regulate gene expression in response to nutritional and physiological stimuli. NRs are separated into distinct classes. First, there are classic hormone receptors that bind specific hormones, such as the glucocorticoids (GCs), thyroid hormones, and estrogen. The GCs and tri-iodothyronine, acting via the glucocorticoid receptor (GR) and thyroid hormone receptor (TR) respectively, are important regulators of genes involved in metabolic fuel homeostasis during development and in response to metabolic stress. Estrogen-related receptors (ERRs) also play critical roles in the regulation of cellular energy metabolism. Secondly, there are NRs that function as metabolic sensors, binding to substrate and end-product component molecules of metabolic pathways such as lipids and fatty acids (FA). This second class of NRs includes the peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXR α), the farnesoid X receptor (FXR), and hepatocyte nuclear factor 4 α (HNF-4 α or HNF4A as listed in the HUGO Database) all of which function, together with the retinoid X receptor (RXR), to regulate lipid and glucose homeostasis in response to nutritional and physiological stimuli.

Importantly, cross-talk can occur between these NRs, for example between ERR and the PPARs, via the common inducible coactivators such as PPAR γ coactivator-1 α

(PGC-1 α or PPARGC1A as listed in the HUGO Database). In this review, we focus on how PGC-1s coordinate the regulation of metabolite-responsive NRs and therefore the expression of genes controlling nutrient handling. In particular, we comment on emerging data supporting a common mechanism mediated by post-translation modifications (deacetylation catalyzed by the NAD⁺-regulated protein deacetylase SIRT) of both PPAR α (PPARA as listed in the HUGO Database) and the PGC-1s, and propose that SIRT1 may lie at the heart of a regulatory loop involving PPARs, PGC-1s, and lipin-1 that ultimately controls the metabolic response of tissues, including liver and adipose tissue, to varying nutrient and physiological signals.

Regulation of the lipo-oxidative NR PPAR α and its role in lipid handling and insulin sensitivity

Histone acetylation allows *trans*-acting factors to associate with cognate DNA binding sites and activate transcription. Histone acetyltransferases (HATs) function to acetylate and remodel chromatin, leading to increased access to target genes by transcriptional machinery. In the absence of ligand, PPAR α recruits corepressors and histone deacetylases (HDACs), which reverses histone acetylation, resulting in a more compact chromatin environment in which transcription is repressed (Fig. 1). Activation through ligand binding induces a conformational change leading to dissociation of

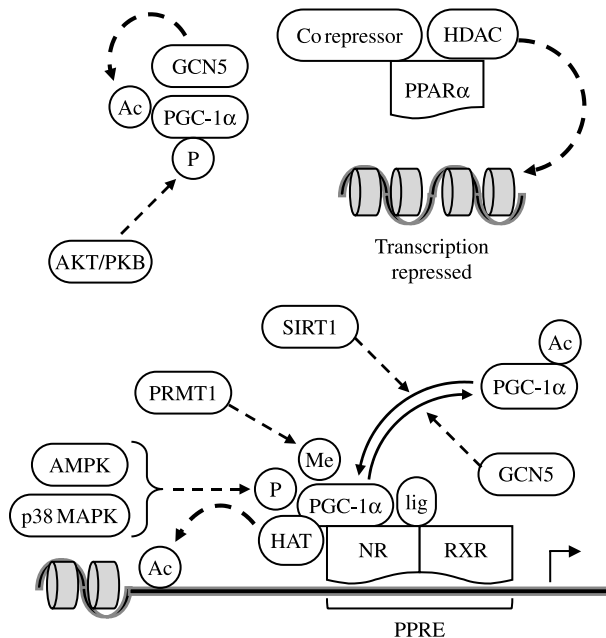


Figure 1 Overview of PGC-1 α post-translational modification. Post-translational modification of PGC-1 α by reversible acetylation, phosphorylation, and methylation are key regulatory factors for PGC-1 α function. SIRT1-mediated deacetylation activates PGC-1 α , while acetylation by GCN5 inhibits PGC-1 α -directed gene expression. In skeletal muscle, phosphorylation by AMPK and p38 MAPK increases stabilization of PGC-1 α . In contrast, AKT/PKB-mediated phosphorylation facilitates degradation of hepatic PGC-1 α . PRMT1 also activates PGC-1 α through methylation at several arginine residues. Ac, acetyl group; AMPK, AMP-dependent protein kinase; HAT, histone acetyl transferase; HDAC, histone deacetylase; MAPK, mitogen-activated protein kinase; Me, methyl group; NR, nuclear receptor; P, phosphate group; PGC-1 α , peroxisome proliferator-activated receptor γ coactivator 1 α ; PPAR α , peroxisome proliferator-activated receptor α ; PPRE, PPAR response element; PRMT1, protein arginine methyltransferase 1; RXR, retinoid X receptor; SIRT1, sirtuin 2 ortholog 1.

corepressors and recruitment of protein complexes containing HAT activity that enhance gene transcription via modification of local chromatin structure (Fig. 1). In addition, ligand binding to PPAR α causes PPAR α to heterodimerize with the RXR and recruit coactivators to activate a program of lipid-induced activation of genes encoding proteins involved in FA uptake, activation, and oxidation. PPAR α target genes include carnitine palmitoyltransferase I (CPT I), involved in the transport of long-chain fatty acyl groups into the mitochondria, medium-chain acyl-CoA dehydrogenase (involved in β -oxidation) and, specifically in liver, mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (the rate limiting enzyme of ketogenesis), peroxisomal acyl-CoA oxidase (peroxisomal β -oxidation), and microsomal cytochrome P450 (CYP) FA ω -hydroxylases. Thus, PPAR α plays a critical role in maintenance of lipid homeostasis (oxidation and production). Exposure of insulin-sensitive tissues (in particular liver and skeletal muscle) to excess nonesterified FA and circulating triglycerides (triacylglycerol, TAG) induces

insulin resistance (Friedman 2002) that can be corrected by the administration of PPAR α activators by actions to promote removal of intracellular lipid through tissue FA oxidation (Ye *et al.* 2001). Induction of PPAR α gene targets requires the interaction of PPAR α and PGC-1, often in complex with other enzymes and coactivators. Formation of these complexes is required for full transcriptional induction of PPAR α targets in a variety of tissues.

Regulation of NRs by PGC-1 α

The PGC-1s are a small family of transcriptional coactivators that play a critical role in the control of glucose, lipid, and energy metabolism. There are three known isoforms of PGC-1: PGC-1 α (PPARGC1A); PGC-1 β (PPARGC1B); PGC-1-related coactivator (PRC or PPRC1 as listed in the HUGO Database). PGC-1 coactivators functionally interact with transcription factors, in particular with members of the NR superfamily such as PPAR γ and PPAR α , ERR, LXR, and HNF-4 α (Puigserver & Spiegelman 2003, Nagai *et al.* 2009, Yang *et al.* 2009), but also with non-NR transcription factors and regulatory elements including cAMP response element-binding protein (CREB), the lipogenic transcription factor sterol regulatory element-binding protein-1c (SREBP-1c or SREBF1 as listed in the HUGO Database), and forkhead box O1 (FOXO1), abnormalities in which have been implicated in the development of diabetes (Yamagata *et al.* 1996, Yoon *et al.* 2001, Nakae *et al.* 2002, Puigserver *et al.* 2003, Gupta *et al.* 2005).

HAT enzymes such as p300, CBP, and SRC-1 bind to the amino terminal of PGC-1, where they function to acetylate and remodel chromatin, leading to modified access to target genes by transcriptional machinery (Fig. 1). The carboxy terminus of PGC-1 contains a Ser/Arg-rich region, an RNA binding domain which is involved in RNA processing, and is bound by TRAP/DRIP, a modulating complex involved in transcriptional initiation. NRs including the PPARs, ERR, HNF-4 α and GR commonly bind to LXXLL motifs present in the N-terminal domain, while other transcription factors bind to different regions of the protein. This allows for a coordinated transcriptional response to nutrient and physiological signals.

All three isoforms of PGC-1 play a common role in control of mitochondrial physiology and FA oxidation, but also regulate differing metabolic pathways in an isoform-specific manner. PGC-1 α and PGC-1 β are highly expressed in tissues dependent on aerobic metabolism such as heart, skeletal muscle, and brown adipose tissue, where they coactivate nuclear respiratory factors (NRFs). In turn, the NRFs induce expression of genes that regulate mitochondrial DNA and function and induce mitochondrial biogenesis.

Post-translational modification of PGC-1 α

PGC-1 coactivators have the ability to regulate their own transcription in response to nutrient signaling such as fasting/fed status. However, an extra level of regulation is

exerted through post-translational modifications. In particular, reversible acetylation, phosphorylation, and methylation are key mechanisms by which PGC-1 α function is maintained (Fig. 1). Both PGC-1 α and PGC-1 β are found in complex with GCN5, an acetyl transferase which acetylates PGC-1 at several lysine residues and inhibits its transcriptional activity (Lerin *et al.* 2006; Fig. 1). Conversely, protein deacetylase SIRT1 (the mammalian Sir2 ortholog) deacetylates a number of nonhistone targets including PGC-1 α and PGC-1 β , with activation of both cofactors (Rodgers *et al.* 2005, Kelly *et al.* 2009; Fig. 1). Thus, SIRT1 opposes the action of GCN5 and induces expression of PGC-1 gene targets (Rodgers *et al.* 2005, Kelly *et al.* 2009; Fig. 1). SIRT1, located in the cell nucleus, requires NAD⁺ as a cofactor and is negatively regulated by either NADH or the deacetylation product nicotinamide. SIRT1 consumes one NAD⁺ for every acetyl group removed from a protein substrate. A decrease in the NAD⁺/NADH ratio inhibits SIRT1 activity. This dependency on oxidized NAD may link SIRT1 activity to cellular metabolism.

Another level of complexity is introduced since, in muscle, PGC-1 α is phosphorylated by both p38 MAPK and the energy-sensing enzyme, AMP-activated protein kinase, leading to a more stable and active protein (Puigserver *et al.* 2001, Irrcher *et al.* 2009; Fig. 1). In contrast, phosphorylation of PGC-1 α by AKT/protein kinase B (involved in the insulin signaling cascade) in the liver leads to decreased stability and activity (Li *et al.* 2007a; Fig. 1). Furthermore, PGC-1 α function is induced through methylation at several arginine residues in the C-terminal region by protein arginine methyltransferase I (PRMT1; Fig. 1), which also coactivates NRs (Teyssier *et al.* 2005). Of interest, nonobese diabetic Goto-Kakizaki rats, a rodent model of diabetes, have decreased hepatic PRMT activity associated with impaired arginine methylation, and transfection with PRMT siRNA attenuates insulin signaling to gluconeogenic gene expression (Iwasaki 2009). Thus, control of PPAR α -PGC-1 α gene transcription is emerging as a complex regulatory platform consisting of other NRs, various factors that amplify the signal and confer stability on the key transcription factors and cofactors, all of which appear to be necessary for full transcriptional induction of PPAR α gene targets.

SIRT1 as a regulator of PPAR α -PGC-1 α directed gene expression in liver

Expression of PGC-1 coactivators in the liver is relatively low in the fed state; however, in parallel with effects of fasting to increase PPAR α signaling, hepatic PGC-1 α mRNA expression is elevated after starvation (Herzig *et al.* 2001, Yoon *et al.* 2001) and plays a critical role in the regulation of hepatic gluconeogenesis (Fig. 2) and FA oxidation. Importantly, Pgc-1 α mRNA expression is also increased in three different rodent models of increased hepatic gluconeogenesis (Herzig *et al.* 2001, Yoon *et al.* 2001). Increased expression of PGC-1 α in liver via adenovirus vector enhances hepatic

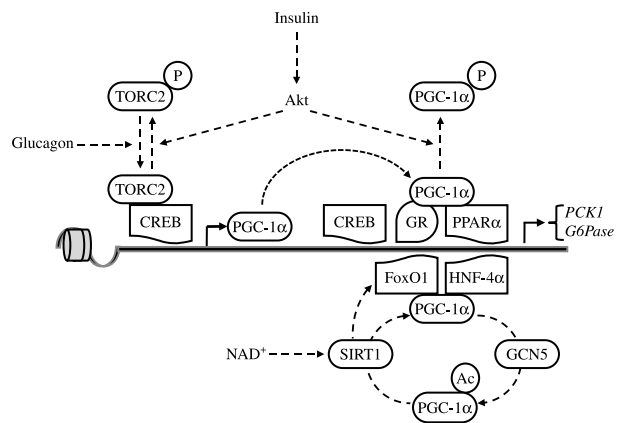


Figure 2 The critical role of PGC-1 α in the regulation of hepatic gluconeogenesis. Glucagon stimulates the dephosphorylation and translocation of the CREB-regulated transcriptional coactivator (TORC2) to the nucleus, where it coactivates CREB leading to induction of PGC-1 α . PGC-1 α subsequently coactivates and forms complexes with FoxO1, the GR and HNF-4 α (as well as PPAR α) and induction of gluconeogenic gene expression. Activation of Akt by insulin phosphorylates TORC2 and PGC-1 α leading to their degradation. PGC-1 α is deacetylated by SIRT1, induction of PGC-1 α being associated with coactivation of FoxO1 and HNF-4 α and induction of gluconeogenic gene expression. This PGC-1 α -directed gluconeogenic gene expression pathway is inhibited by GCN5. Ac, acetyl group; CREB, cAMP response element-binding protein; FoxO1, forkhead box O1; GR, glucocorticoid receptor; HNF-4 α , hepatocyte nuclear factor-4 α ; P, phosphate group; PGC-1 α , peroxisome proliferator-activated receptor γ coactivator 1 α ; PPAR α , peroxisome proliferator-activated receptor α ; SIRT1, sirtuin 2 ortholog 1; TORC2, CREB-regulated transcriptional coactivator 2.

glucose production (Herzig *et al.* 2001; reviewed in Vidal-Puig & O'Rahilly (2001)). The rise in glucagon levels on fasting is associated with the dephosphorylation and translocation of the CREB-regulated transcription coactivator (TORC2 that is listed as CRTC2 in the HUGO Database) to the nucleus, where it coactivates CREB, a transcription factor present on the PGC-1 α gene promoter, leading to induction of PGC-1 α (Fig. 2). PGC-1 α subsequently coactivates and forms complexes with FoxO1, the GR and HNF-4 α , which (as well as PPAR α) are essential for expression of the key gluconeogenic genes PCK1 and/or G6Pase (Fig. 2). Conversely, activation of AKT by insulin elicits phosphorylation of both TORC2 and PGC-1 α leading to their degradation (Dentin *et al.* 2007, Li *et al.* 2007a).

An alternative gluconeogenic pathway has been described, where PGC-1 α is deacetylated by SIRT1, induction of PGC-1 α being associated with coactivation of FOXO1 and HNF-4 α and induction of gluconeogenic gene expression (Rodgers *et al.* 2005; Fig. 2). SIRT1 also opposes phosphorylation-dependent nuclear exclusion of FOXO1 and elicits translocation and restriction of FoxO1 to a nuclear subdomain in hepatocytes (Frescas *et al.* 2005). Interestingly, this pathway was not activated by classical gluconeogenic stimuli, including the GCs and glucagon, and is thought to represent an entirely separate parallel pathway for induction

of gluconeogenic gene expression (Rodgers *et al.* 2005), which may involve a rise in pyruvate and NAD⁺ levels (reviewed in Rodgers *et al.* (2008)). This PGC-1 α -directed gluconeogenic gene expression pathway is inhibited by GCN5 (Lerin *et al.* 2006).

Studies of the role of PGC-1 α on energy metabolism have mainly utilized gain-of-function or complete-loss-of-function models. Total ablation of hepatic PGC-1 α elicits fasting steatosis; however, insulin sensitivity and glucose tolerance are improved concomitant with suppression of gluconeogenesis. However, this phenotype may reflect consequences of loss of PGC-1 α function in nonhepatic tissues, including skeletal muscle, heart, brain, and brown fat that elicit abnormal heart function, muscle performance, and thermogenesis (Lin *et al.* 2004, Leone *et al.* 2005). In contrast, a recent study has examined the long-term metabolic impact of physiological changes in PGC-1 α expression, achieved using a Cre/Lox system to create mice heterozygous for PGC-1 α specifically within the liver (Estall *et al.* 2009). Loss of one allele of hepatic PGC-1 α led to a chronic reduction in hepatic PGC-1 α mRNA and protein (Estall *et al.* 2009). This resulted in impaired FA oxidation and TAG assembly and/or production pathways leading to hypertriglyceridemia (Estall *et al.* 2009). In addition these mice exhibited reduced hepatic insulin sensitivity, which was associated with impaired insulin-stimulated Akt activation (Estall *et al.* 2009). Nevertheless, the long-term decline in PGC-1 α led to only a modest reduction in gluconeogenesis (Estall *et al.* 2009). Interestingly, acute disruption of hepatic PGC-1 expression using an RNAi adenovirus has opposing effects, leading to enhanced insulin sensitivity, in part reflecting reduced expression of the mammalian tribbles homolog TRIB3 (Koo *et al.* 2004), an inhibitor of AKT signaling (Mortensen *et al.* 2006). These mice were characterized by fasting hypoglycemia and reduced expression of PEPCK and G6Pase (Koo *et al.* 2004).

Recently, SIRT1-mediated deacetylation of PGC-1 α has been reported to play a critical role in regulation of hepatic FA oxidation. Hepatic deletion of SIRT1 leads to impaired PPAR α signaling, while overexpression of SIRT1 activates PPAR α , increasing expression of PPAR α gene targets. SIRT1 induces PPAR α signaling through deacetylation of PGC-1 α (Purushotham *et al.* 2009; Fig. 3). Interestingly, SIRT1 does not affect the formation of the PPAR α -PGC-1 α complex, since in SIRT1 knockdown hepatocytes PGC-1 α is still recruited to the PPAR response element (PPRE) of FA oxidation genes. However, PGC-1 α remains acetylated when SIRT1 is not present so it is unable to induce transcription of PPAR α gene targets. There is a potential inhibitory role for GCN5 in this system. As noted above, GCN5 counters the effect of SIRT1 by acetylating PGC1 α , inhibiting its transcriptional activity (Lerin *et al.* 2006, Gerhart-Hines *et al.* 2007; Fig. 3). Hence, the balance between relative levels and activity of SIRT1 and GCN5 could provide regulatory convergence point for induction of PPAR α gene targets. In agreement, PGC-1 α target genes for FA oxidation are induced in skeletal muscle by SIRT1 and inhibited by GCN5 (Gerhart-Hines *et al.* 2007).

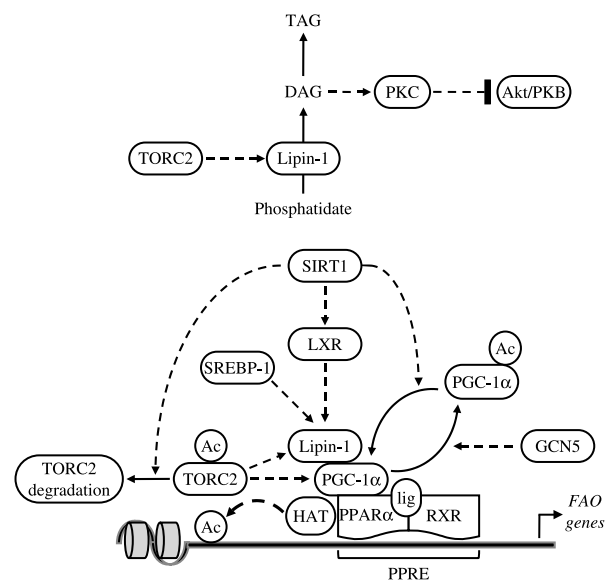


Figure 3 Overview of lipin-1 regulation of PGC1 α -PPAR α -directed gene expression. Lipin-1 is reported to enhance PPAR α -PGC-1 α -directed gene expression through induction of PPAR α transcription and by forming a complex with PGC-1 α and PPAR α , leading to increased FA oxidation. In contrast, TORC2-mediated induction of lipin-1 leads to increased DAG and TAG synthesis. Ac, acetyl group; AMPK, AMP-dependent protein kinase; DAG, diacylglycerol; FAO, fatty acid oxidation; HAT, histone acetyl transferase; LXR, liver X receptor; PGC-1 α , peroxisome proliferator-activated receptor γ coactivator 1 α ; PKC, protein kinase C; PPAR α , peroxisome proliferator-activated receptor α ; PPRE, PPAR response element; RXR, retinoid X receptor; SIRT1, sirtuin 2 ortholog 1; SREBP-1, sterol regulatory element binding protein 1; TAG, triacylglycerol; TORC2, CREB-regulated transcriptional coactivator 2.

While this study did not examine GCN5 or PPAR α directly, it seems likely that both GCN5 and SIRT1 are part of the same regulatory platform of PPAR α -PGC1 α induction of FA oxidation in skeletal muscle, liver, and other metabolically active tissues. These may include pancreatic islets, linking insulin secretion with insulin action in liver and skeletal muscle. This seems particularly likely since both PPAR α and SIRT1 have been separately reported to repress a common gene target, uncoupling protein 2 (UCP2) that plays an important role in regulation of insulin secretion (Bordone *et al.* 2006, Ramsey *et al.* 2008).

Lipin-1 as a coordinator of PPAR α -PGC-1 α -directed gene expression

Lipin-1 (listed as in LPIN1 in the HUGO Database) is another regulator of PPAR α -PGC-1 α -directed gene expression. In the cytoplasm, lipin-1 promotes TAG accumulation and phospholipid synthesis by functioning as a Mg²⁺-dependent phosphatidate phosphatase (phosphatidic acid phosphatase-1 (PAP-1); Reue & Zhang 2008; Fig. 3). PAP-1 converts phosphatidate to diacylglycerol (DAG), the immediate precursor of TAG and neutral phospholipids.

The expression level and compartmentalization of lipin-1 controls the assembly and secretion of hepatic very low-density lipoprotein (VLDL; Bou Khalil *et al.* 2009). Overexpression of lipin-1 in cultured hepatocytes leads to increased TAG synthesis (Bou Khalil *et al.* 2009). In the nucleus, lipin-1 acts as a transcriptional coactivator linked to FA oxidation (Fig. 3). The role of lipin-1 in transcriptional activation was discovered in a mouse model of PGC-1 α deficiency, in which fasting failed to induce the hepatic expression of lipin-1, PPAR α , and PPAR α target genes involved in upregulation of FA oxidation (Finck *et al.* 2006). Subsequently, lipin-1 has emerged as an important regulatory factor for induction of PPAR α -PGC-1 α gene targets. Lipin-1 induces PPAR α gene expression as well as forming an interactive complex with PPAR α and PGC-1 α (Fig. 3) leading to induction of FA oxidation genes including CPT1 (Finck *et al.* 2006). Conversely, a mutation in lipin-1 is responsible for the fatty liver dystrophic (*fld*) mouse phenotype, which includes hepatic steatosis, impaired FA oxidation, and hyperlipidemia (Reue 2009). Lipin-1 can also interact with other hepatic transcription factors such as HNF-4 α , PPAR δ and PPAR γ , indicating that lipin-1 and PGC-1 α may act as a regulatory link between PPAR α and other NRs. Of interest, it has been reported recently that the lipogenic transcription factor SREBP-1 is involved in the regulation of lipin-1 expression (Fig. 3) and that lipin-1 protein is induced by sterol depletion (Ishimoto *et al.* 2009). In addition, lipin-1 gene expression is induced by T0901317, an activating ligand for the LXR (Ishimoto *et al.* 2009).

A further layer of complexity in lipin-1 function is highlighted by recent studies detailing a role of lipin-1 in the development of insulin resistance that conflicts with the beneficial effects of lipin-1 through amplification of the PPAR α -PGC-1 α signaling pathway. Lipin-1 is induced by TORC2 (Ryu *et al.* 2009), a key coactivator of gluconeogenic gene expression (Koo *et al.* 2005; Fig. 3), which leads to increased levels of DAG and consequent activation of protein kinase C. This, in turn, leads to inhibition of Akt signaling and insulin resistance (Fig. 3). TORC2 also induces PGC-1 α (Koo *et al.* 2005; Fig. 3), while knockdown of lipin-1 decreases PGC-1 α mRNA levels (Ryu *et al.* 2009). Interestingly, SIRT1 has been reported to deacetylate TORC2 leading to its ubiquitin-mediated degradation and inhibition of gluconeogenic gene expression (Liu *et al.* 2008; Fig. 3). However, the impact of SIRT1 on TORC2-mediated lipin induction has yet to be characterized.

Given that SIRT1 is able to induce degradation of TORC2 as well as activating PGC-1 α , it seems possible that SIRT1 lies at the heart of a regulatory loop involving PPAR α , PGC-1 α , lipin-1, and TORC2 (Fig. 3) that ultimately controls the response of lipid metabolism in the liver, and potentially other tissues, to different nutrient and physiological signals. Further credence is added to this hypothesis given reports that SIRT1 acts on targets in a signal-specific manner, deacetylating PGC-1 α only in response to nutrient signaling but not glucagon (Rodgers *et al.* 2005, 2008). Hence, in healthy

individuals, in response to a high-fat diet, SIRT1 may stimulate FA oxidation through PPAR α -PGC-1 α -lipin-1. This process may be countered by GCN5-directed acetylation of PGC-1 α . In contrast, when the body requires synthesis of TAG an alternative signaling mechanism would induce a TORC2-mediated increase in lipin-1, leading to increased TAG production.

The SIRT1-PGC-1 α axis and lipin-1 signaling to glucose-stimulated insulin secretion

Normal pancreatic islets express both PGC-1 α (Yoon *et al.* 2003) and SIRT1 (Moynihan *et al.* 2005) at low levels. As in liver, fasting for 24 h increases PGC-1 α mRNA expression in islets, an effect reversed by 24 h of refeeding (Zhang *et al.* 2005). More importantly, PGC-1 α mRNA and protein expression have been reported to be elevated in islets from animal models of diabetes, including the *ob/ob* mouse and ZDF rats (Yoon *et al.* 2003). Overexpression of PGC-1 α in islets substantially reduces the expression of the β -cell glucose sensors for glucose-stimulated insulin secretion (GSIS), GLUT2, and glucokinase, and also impairs GSIS, suggesting it can precipitate β -cell dysfunction (Yoon *et al.* 2003). Chronic hyperlipidemia and hyperglycemia, which together cause adverse effects on β -cell function via 'glucolipotoxicity' (reviewed in Nolan & Prentki (2008)), also affect PGC-1 α gene expression. Islets incubated with oleate/palmitate for 72 h show a dose-dependent increase in PGC-1 α mRNA expression, whereas inhibition of PGC-1 α by siRNA improves the impairment of GSIS induced by chronic exposure to FA (De Souza *et al.* 2003, 2005, Zhang *et al.* 2005). This suggests that enhanced PGC-1 α expression participates in chronic hyperlipidemia-induced β -cell failure. However, exposure to high (25 mM) glucose (which also impairs insulin secretion) suppresses PGC-1 α mRNA expression (Zhang *et al.* 2005). When exposed to high glucose and FA in combination, the effect of hyperglycemia to lower PGC-1 α in islets was dominant (Zhang *et al.* 2005). If PGC-1 expression limits PPAR α transcriptional activity, this might explain why PPAR α null mice maintained on standard low-carbohydrate diet have no obvious phenotype, including unaltered GSIS (Bihan *et al.* 2005). Suppression of PGC-1 α expression by hyperglycemia could become maladaptive if the islets are simultaneously exposed to high lipids or where increased dietary lipid delivery is sustained over a long period.

Analogues of the incretin GLP-1 (listed as ZGLP1 in the HUGO Database) have been proposed as a possible means to enhance islet function in type 2 diabetes (Nielsen 2005). However, GLP-1 increases islet PGC-1 α mRNA expression (Zhang *et al.* 2005) which, as noted above, leads to repression of genes involved in β -cell glucose sensing with a marked inhibition of GSIS (Yoon *et al.* 2003). Increased SIRT1 expression specifically in pancreatic β cells (BESTO transgenic mice), which would be predicted to induce PPAR α signaling through deacetylation and induction of PGC-1 α improves glucose tolerance and enhances insulin secretion, in particular

first-phase insulin secretion, in response to glucose and the plasma membrane-depolarizing agent KCl (Moynihan *et al.* 2005). Microarray analyses of MIN6 cells overexpressing SIRT1 identified 41 downregulated and 24 upregulated transcripts, while analysis of MIN6 cell lines constitutively expressing siRNAs against the *Sirt1* gene revealed 24 upregulated and 18 downregulated transcripts (Moynihan *et al.* 2005). In particular, the expression of *Ucp2* and the prolactin receptor gene (*Prlr*), both of which significantly influence β -cell function, were downregulated by SIRT1 overexpression (Moynihan *et al.* 2005). Downregulation of UCPs is proposed to reduce uncoupling and allow a more efficient ATP production under circumstances of limited access to nutrients, which could be explained by a more efficient oxidative phosphorylation, lowered production of ROS, and reduced oxidative damage.

GCs induce lipin-1 in differentiating adipocytes, and a GC response element (GRE) has been identified in the *Lpin1* promoter (Zhang *et al.* 2008). We demonstrated that excessive exposure to the synthetic GC dexamethasone during the last third of pregnancy both causes insulin resistance and impairs islet adaptations to insulin resistance with a complex interaction between GC and PPAR α signaling (Holness & Sugden 2001, Holness *et al.* 2006). Thus, the strong possibility exists that lipin-1, if expressed and functional in islets, may exert a coactivator function whereby, via its physical interactions with PPAR α and the GC receptor, is very likely to impact GSIS. The potential importance of the GC in regulating lipin-1 expression in adipose tissue may therefore extend to regulating lipin-1 expression or function in the pancreatic islet.

The lipogenic NRs (the LXR and PGC-1 β , PPAR γ)

LXR's roles in liver and white adipose tissue: a role for SIRT1

LXRs α and β , like the PPARs, are a second family of nutrient-responsive NRs that heterodimerize with RXR to influence gene expression. LXR β (NR1H2) is ubiquitously expressed. LXR α (NR1H3) is abundant in liver and also in adipose tissue, intestine, kidney, and spleen. LXR activation is thought to be predominantly insulin-sensitizing (Cao *et al.* 2003, Dalen *et al.* 2003, Laffitte *et al.* 2003) due to suppression of hepatic glucose output secondary to an LXR-led reduction in gluconeogenic capacity (Stulnig *et al.* 2002a,b). However, the LXRs also promote hepatic lipid synthesis and can elicit dramatic increases in hepatic TAG production (Tobin *et al.* 2002, Chen *et al.* 2004). Thus, as well as acting as sensors of cellular cholesterol and modulating the expression of genes concerned with cellular cholesterol handling, the LXRs enhance expression of genes involved in FA biosynthesis and TAG secretion.

As in liver, LXR activation in adipocytes stimulates lipid accumulation (Juvet *et al.* 2003). *LXR α* gene expression is increased in adipose tissue from obese human subjects (Dahlman *et al.* 2006), whereas LXR-deficient mice show

increased FA synthesis and energy consumption (Kalaany *et al.* 2005). In addition to their conventional role in storing TAG, adipocytes contain large amounts of free cholesterol, and constitute the body's largest pool of free cholesterol (Krause & Hartman 1984). It has been proposed that adipose tissue acts as a cholesterol sink and cholesterol acts to signal a requirement for adipocyte hypertrophy and/or serve as a sensor of adipocyte TAG storage (Le Lay *et al.* 2001, 2003). PPAR α null mice have a markedly higher plasma cholesterol content (Patel *et al.* 2001, Knight *et al.* 2003), suggesting that, although expressed at relatively low level in adipose tissue, PPAR α is involved in the regulation of adipocyte cholesterol 'buffering'.

LXR increases the synthesis of FA and TAG by upregulating SREBP-1c (Repa *et al.* 2000). A carbohydrate response element-binding protein (ChREBP that is listed as MLXIPL in the HUGO Database), a glucose-sensitive transcription factor that enhances hepatic conversion of excess carbohydrate to lipid (Yamashita *et al.* 2001), is a hepatic LXR target which stimulates lipogenic genes independent of SREBP-1c (Cha & Repa 2007). It has been proposed that, in liver, glucose at physiological concentrations is a high-affinity LXR ligand (Mitro *et al.* 2007). This may explain why both low-fat and high-carbohydrate diets can induce hypertriglyceridemia. The lipogenic actions of the LXRs directly oppose the action of PPAR α , which promotes FA oxidation (reviewed in Mandard *et al.* (2004)). It has been suggested that PPARs suppress SREBP-1c promoter activity through inhibition of LXR signaling (Yoshikawa *et al.* 2003).

LXRs are acetylated at Lys⁴³² in LXR α and Lys⁴³³ in LXR β , and deacetylation regulates LXR transcriptional activity (Li *et al.* 2007b). LXR agonists trigger deacetylation as SIRT1 interacts with LXR in a ligand-dependent manner (Li *et al.* 2007b). It appears that, as acetylation of Lys⁴³² prevents LXR ubiquitination, LXR is hypo-ubiquitinated (and therefore stabilized) in the absence of SIRT. This stabilization of LXR lowers its transcriptional activity, which explains why LXR activity is lower in the absence of SIRT1. SIRT1 deacetylates and thus positively regulates LXR (Fig. 3).

Regulation of hepatic lipid synthesis and secretion by PGC-1 β

Although PGC-1 was originally reported to combine with the lipogenic PPAR, PPAR γ , it is now clear that PGC-1 β (PPARGC1B) can influence lipid synthesis by acting on a range of transcription factors. Thus, PGC-1 β plays a critical role in stimulating the expression of genes involved in hepatic lipogenesis and TAG secretion. Adenoviral-mediated overexpression of hepatic PGC-1 β in rats leads to increased TAG synthesis and VLDL secretion and consequent hypertriglyceridemia and hypercholesterolemia (Lin *et al.* 2005). PGC-1 β induces hepatic lipogenesis through coactivation of both LXR and SREBP-1 (Lin *et al.* 2005). This leads to increased expression of the lipogenic genes FA synthase (*FAS*), stearoyl-CoA desaturase (*SCD1*) and HMG-CoA reductase (*HMGCR*; Fig. 4). Both PGC-1 β and SREBP-1c, but not

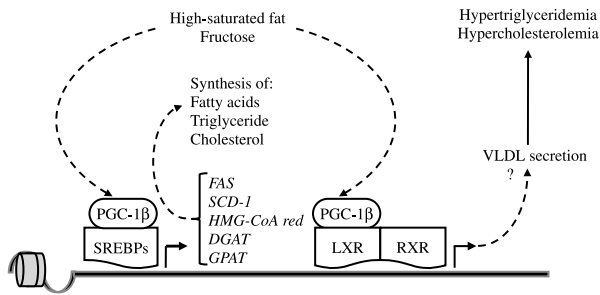


Figure 4 The critical role of PGC-1 β in stimulating hepatic lipid synthesis and secretion. PGC-1 β is induced in liver in response to high dietary saturated fat and fructose. PGC-1 β coactivates SREBP-1c and increases the expression of a range of genes involved in the synthesis of FA, TAG and cholesterol, including *FAS*, *SCD-1*, *HMG-CoA reductase*, *DGAT* and *GPAT*. PGC-1 β also stimulates VLDL secretion, possibly via augmenting activation of LXR α , leading to hypertriglyceridemia and accumulation of cholesterol in VLDL, the precursor to LDL cholesterol. LXR, liver X receptor; PGC-1 β , peroxisome proliferator-activated receptor γ coactivator 1 β ; RXR, retinoid X receptor; SREBP, sterol regulatory element-binding protein; VLDL, very low-density lipoprotein; ?, indicates potential mechanism.

PGC-1 α , are induced in liver in response to acute (24–48 h) high (58%) dietary saturated fat (mainly hydrogenated coconut oil; Fig. 4). Interestingly, the increases in PGC-1 β and SREBP-1c in response to dietary saturated fat were specific to liver and not replicated in skeletal muscle or white adipose tissue, while dietary cholesterol intake had little impact on hepatic PGC-1 β expression (Lin *et al.* 2005). PGC-1 β coactivates SREBP-1c and increases the expression of a range of genes involved in the synthesis of FA, TAG and cholesterol, including *FAS*, *SCD-1*, *HMGCR*, *DGAT*, *GPAT*, and microsomal triglyceride transfer protein (*MTTP*; Lin *et al.* 2005; Fig. 4). While SREBP overexpression alone increases lipogenic gene expression and hepatic lipid levels (Shimano *et al.* 1996, Horton *et al.* 1998), hypertriglyceridemia does not occur, probably as a result of parallel upregulation of hepatic low-density lipoprotein receptor (LDLR) levels (Shimano *et al.* 1997). In contrast, PGC-1 β fails to stimulate LDLR expression, but does stimulate VLDL secretion, possibly via augmenting activation of LXR α , leading to hypertriglyceridemia and accumulation of cholesterol in VLDL, the precursor to LDL cholesterol (Lin *et al.* 2005; Fig. 4).

More recently, antisense oligonucleotide-mediated knock-down of hepatic PGC-1 β has been demonstrated to oppose the lipogenic impact of a high-fructose diet (Nagai *et al.* 2009). Knockdown of PGC-1 β was associated with attenuation of fructose-induced increases in SREBP-1c, LXR, and *FAS* expression (Nagai *et al.* 2009). Thus, PGC-1 β has been suggested as a novel mechanism linking the consumption of saturated fat to hypertriglyceridemia and hypercholesterolemia (Lin *et al.* 2005; Fig. 4). Upregulation of PGC-1 β may represent the mechanism linking excessive intake of saturated fat or fructose to hyperlipidemia, insulin resistance and atherosclerosis.

PPAR γ and adipocyte function: interactions with SIRT1 and lipin-1

PPAR γ activation promotes lipid synthesis and storage in white adipose tissue (Kubota *et al.* 1999), as well as preadipocyte differentiation to mature adipocytes (Park *et al.* 2008). Wnt/ β -catenin signaling maintains preadipocytes in an undifferentiated state in part through inhibition of PPAR γ (Prestwich & Macdougald 2007). Rev-erb α acts downstream of PPAR γ by facilitating gene expression of PPAR γ target genes, including that encoding C/EBP α (important for the acquisition of insulin sensitivity; Wu *et al.* 1999, Rosen *et al.* 2000) and acts as a repressor of anti-adipogenic genes. PPAR δ , also expressed in adipose tissue, is not involved in preadipocyte differentiation directly, but is implicated in the control of preadipocyte proliferation and PPAR γ gene expression (reviewed in Grimaldi (2001)).

Certain PPAR γ target genes that are normally expressed only at low levels in mature adipocytes are dramatically upregulated by thiazolidinediones (TZDs), among these the enzyme glycerol kinase. Glycerol kinase allows glycerol 3-phosphate production from glycerol, thereby enhancing the capacity for FA esterification to TAG. Unlike classic PPAR γ -target genes such as aP2 (which is constitutively associated with coactivators), the glycerol kinase gene is targeted by NR corepressors. TZDs trigger the dismissal of corepressor HDAC complexes and the recruitment of coactivators to the glycerol kinase gene. They also induce PGC-1 α , whose recruitment to the glycerol kinase gene is sufficient to release the corepressors (Guan *et al.* 2005). Ectopic expression of PGC-1 α in white adipocytes increases the expression of UCP1, genes encoding respiratory chain proteins (cytochrome *c*-oxidase subunits COX II and IV) and enzymes of FA oxidation and causes white adipocytes to acquire features of brown adipocytes (Puigserver *et al.* 1998, Tiraby *et al.* 2003). In *ob/ob* mice, the expression of transcripts encoding mitochondrial proteins decreases with the development of obesity. TZD treatment in *ob/ob* mice increases PGC-1 α expression and increases mitochondrial mass and energy expenditure. In mature adipocytes, SIRT1 binds and represses PPAR γ in association with mobilization of fat stores during food deprivation (Picard *et al.* 2004). In contrast, lipin-1 promotes adipocyte TAG storage (see above). Lipin-1 physically interacts with PPAR γ and is recruited to PPAR γ response element upstream of the PEP carboxykinase (PEPCK) gene (Koh *et al.* 2008). PEPCK is involved in glycogenesis in white adipose tissue (Franckhauser *et al.* 2002).

Lipin-1 deficiency in *fld* mice causes lipodystrophy characterized by impaired adipose tissue development (Reue *et al.* 2000). Lipin-1 overexpression in adipocytes promotes increased TAG content and obesity (Phan & Reue 2005). In the mouse, lipin-1 deficiency is associated with insulin resistance, whereas transgenic overexpression of lipin-1 in adipose tissue promotes insulin sensitivity, even though the mice have increased adiposity (Phan & Reue 2005).

High adipose tissue lipin-1 expression is also associated with enhanced insulin sensitivity in man (Yao-Borengasser *et al.* 2006, Miranda *et al.* 2007, Donkor *et al.* 2008). This enhanced insulin sensitivity may reflect an increased ability of adipose tissue to act as a sink for lipid, preventing excessive lipid deposition in liver and skeletal muscles which impairs insulin action.

Clinical implications

Targetting PPAR α -activated genes has been proposed to be beneficial for countering fatty liver (Purushotham *et al.* 2009), while increasing PGC-1 α protects against the development of insulin resistance in skeletal muscle through induction of GLUT4, increased FA oxidation and mitochondrial biogenesis (Michael *et al.* 2001, Lagouge *et al.* 2006, Gerhart-Hines *et al.* 2007, Kelly *et al.* 2009). Thus, PPAR α agonists are under investigation as potential therapies for patients with metabolic and cardiovascular disease (Buse *et al.* 2005, Henry *et al.* 2009). Despite this, it is unclear whether activation of individual components of the PPAR α regulatory circuit provides a benefit to patients with metabolic disease, particularly in the liver. In particular, hepatic PGC-1 α is increased in rodent models of type 2 diabetes mellitus (T2DM; Herzig *et al.* 2001, Yoon *et al.* 2001) which may lead to induction of gluconeogenesis and hyperglycemia, while at least two clinical studies have identified a correlation between mutations of the *PPARGC1A* gene (previously known as the PGC-1 α gene) and insulin resistance or diabetes (Ek *et al.* 2001, Hara *et al.* 2002). Overexpression of PGC-1 α in cultures of primary rat skeletal muscle cells induces increased expression of the mammalian tribbles homolog TRB3, an inhibitor of AKT signaling (Mortensen *et al.* 2006), highlighting the potential of PGC-1 α to cause insulin resistance. Moreover, PGC-1 $^{-/-}$ mice are protected against high-fat diet induced insulin resistance (Leone *et al.* 2005). Acute disruption of hepatic PGC-1 expression enhances insulin sensitivity, in part reflecting reduced expression of TRIB3 (Koo *et al.* 2004). The observation that, in liver, TRIB3 is a target for PPAR α and that knockdown of hepatic TRIB3 expression improves glucose tolerance, whereas hepatic overexpression of TRIB3 reverses the insulin-sensitive phenotype of PGC-1-deficient mice has led to the suggestion that TRIB3 inhibitors may have a potential role in the treatment of T2DM (Koo *et al.* 2004). However, more recently, chronic reduction of hepatic PGC-1 α expression has been shown to impair hepatic insulin sensitivity (Estall *et al.* 2009).

Epigenetic modification, including DNA methylation, represents a molecular mechanism linking environmental events to altered gene expression and the development of disease states, including T2DM (see e.g. (Pembrey *et al.* 2006)). A recent study undertook a genome-wide promoter analysis of DNA methylation, screening for genes

differentially methylated in T2DM, which identified cytosine hypermethylation of PGC-1 α in diabetic subjects (Barres *et al.* 2009). Hypermethylation of the PGC-1 α promoter was associated with reduced PGC-1 α expression (Barres *et al.* 2009). Using human myotubes, a link between the DNA methyltransferase (DNMT3B) and acute non-CpG methylation of the PGC-1 α promoter by FA was identified (Barres *et al.* 2009). The full therapeutic significance of this observation has yet to be established.

Overexpression in liver of the long form of lipin-1 (lipin 1 β , the predominant form in liver; Huffman *et al.* 2002, Peterfy *et al.* 2005) increases the expression of PPAR α and PPAR α target genes involved in FA uptake and utilization (Finck *et al.* 2006). Thus, lipin-1 may be a promising target for therapeutic intervention for metabolic disorders such as fatty liver and resolution of insulin resistance. Lipin-1 is also required for the maintenance of the mature adipocyte phenotype both through its PAP activity in relation to TAG synthesis and via its action to amplify the transcriptional activity of PPAR γ and the expression of PPAR γ target genes, such as PEPCCK and glycerol kinase (Koh *et al.* 2008). Alterations in lipin-1 function in adipose tissue are therefore likely to impact the efficacy of the TZDs in the treatment of insulin resistance. In addition, the expression of the lipin-1 isoform found in mature adipocytes (lipin-1 β) increases following TZD treatment, which causes weight gain (Yao-Borengasser *et al.* 2006).

A recent study on nondiabetic Chinese females demonstrated that *LPIN1* mRNA levels in abdominal visceral adipose tissue negatively correlated with body mass index, body fat percentage and plasma TAG and leptin levels (Chang *et al.* 2009). However, no single nucleotide polymorphism of the *LPIN1* gene was associated with type 2 diabetes in the population investigated in this study, leading the authors to conclude that the *LPIN1* gene was not a major susceptibility gene for T2DM (Chang *et al.* 2009). Furthermore, the suitability of agonists of lipin-1 as pharmaceutical candidates is confounded given its links with PGC-1 α and its reported ability to induce synthesis of DAG, TAG, and VLDL. It seems likely that the opposing actions of lipin-1 occur in response to different physiological stimuli and therefore further studies are required to establish which lipin-1-directed pathway is dysregulated during the onset of metabolic disease. This will provide important information with respect to development of therapeutic strategies for modulation of this pathway.

Resveratrol, a polyphenol found in red wine, activates SIRT1s (Howitz *et al.* 2003). Treatment of high-fat-fed mice with resveratrol elicits PGC-1 α deacetylation and activation, opposes weight gain, and enhances insulin sensitivity (Baur *et al.* 2006, Lagouge *et al.* 2006). More recently small molecular weight molecules, including SRT1460 and SRT1720, that selectively activate SIRT1 and are 1000-fold more potent activators than (and structurally unrelated to) resveratrol have been identified (Milne *et al.* 2007). The therapeutic potential of SIRT1 activators to treat

insulin resistance and diabetes has been examined *in vivo* in models of T2DM. SRT1720 opposes hyperinsulinemia and the impairment in glucose tolerance introduced by high-fat feeding in mice to an extent similar to that achieved with rosiglitazone (Milne *et al.* 2007). SRT1720 treatment of Zucker *fa/fa* rats also improves glucose and insulin responses during an oral glucose tolerance test (Milne *et al.* 2007). In addition, the recent identification of four unique low-molecular-weight inhibitor scaffolds that inhibit the human sirtuins, including SIRT1, by binding reversibly and noncompetitively with respect to both acetyl-lysine and NAD⁺ binding highlights further potential therapeutic tools (Sanders *et al.* 2009).

The consumption of saturated fat has been linked with the development of a number of disease states, including T2DM, cardiovascular disease and atherosclerosis. Modest SIRT1 overexpression protects against hepatic steatosis and glucose intolerance induced by high-fat feeding (Banks *et al.* 2008, Pfluger *et al.* 2008). Hepatic deletion of SIRT1 impairs PPAR α activity, resulting in decreased FA oxidation, and results in hepatic steatosis and inflammation in response to high-fat feeding, leading to the suggestion that therapeutic modulation of SIRT1 activity may be beneficial for the treatment of hepatic diseases as well as obesity-associated metabolic syndrome (Purushotham *et al.* 2009). Antisense oligonucleotide knockdown of hepatic SIRT1 reduced fasting hyperglycemia by normalizing basal hepatic glucose production, increasing hepatic insulin sensitivity in a rat model of T2DM (streptozotocin injection followed by 4 weeks of fructose and high-fat feeding), which led to the suggestion that novel SIRT1 inhibitors targeted to the liver could prove beneficial in the treatment of T2DM (Erion *et al.* 2009). Thus, consideration must be given to these potential pitfalls of strategies for mitigation of metabolic disorders involving modulation of SIRT1 activity.

PGC-1 β is induced by saturated-fat feeding and results in upregulation of genes involved in FA, TAG and cholesterol synthesis and increases VLDL secretion and accumulation of cholesterol in VLDL, potentially increasing LDL cholesterol (Lin *et al.* 2005). This has led to the suggestion that upregulation of PGC-1 β may link the consumption of saturated fat to hypertriglyceridemia and hypercholesterolemia (Lin *et al.* 2005). Knockdown of PGC-1 β in liver and adipose tissue reverses hepatic insulin resistance induced by fructose feeding and increases whole-body glucose disposal due to increased adipose tissue glucose uptake (Nagai *et al.* 2009). PGC-1 β therefore represents an attractive target for therapeutic intervention in atherosclerosis, insulin resistance and hypertriglyceridemia as well as nonalcoholic fatty liver disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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