Effect of sitagliptin on expression of skeletal muscle peroxisome proliferator-activated receptor γ coactivator-1α and irisin in a rat model of type 2 diabetes mellitus

Yuntao Liu[1],* ⓘ**, Feng Xu[2],* and Pan Jiang[1]**

Abstract

Objective: To evaluate the effect of sitagliptin on skeletal muscle expression of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), irisin, and phosphoadenylated adenylate activated protein kinase (p-AMPK) in a rat model of type 2 diabetes mellitus (T2DM).

Methods: A high-fat diet/streptozotocin T2DM rat model was established. Rats were divided into T2DM, low-dose sitagliptin (ST1), high-dose sitagliptin (ST2), and normal control groups (NC). PGC-1α, irisin, and p-AMPK protein levels in skeletal muscle were measured by western blot, and PCG-1α and Fndc5 mRNA levels were assessed by reverse transcription-polymerase chain reaction.

Results: Fasting plasma glucose (FPG), fasting insulin (FIns), homeostatic model assessment-insulin resistance (HOMA-IR), and tumor necrosis factor-α (TNF-α) were significantly up-regulated in the T2DM compared with the other groups, and FPG, FIns, total cholesterol, triglycerides, TNF-α, and HOMA-IR were significantly down-regulated in the ST2 compared with the ST1 group. PGC-1α, irisin, and p-AMPK expression levels decreased successively in the ST2, ST1, and DM groups compared with the NC, and were all significantly up-regulated in the ST2 compared with the ST1 group.

[1]Department of Endocrinology, Affiliated Renhe Hospital of China Three Gorges University, The Second Clinical Medical College of China Three Gorges University, Yichang, China
[2]Yichang Hospital of Traditional Chinese Medicine, Clinical Medical College of Traditional Chinese Medicine, China Three Gorges University, Yichang, China

*These authors contributed equally to this work.

Corresponding author:
Yuntao Liu, Department of Endocrinology, Affiliated Renhe Hospital of China Three Gorges University, Yichang 443000, China.
Email: liuyuntao@yandex.com

Conclusion: Down-regulation of PGC-1α and irisin in skeletal muscle may be involved in T2DM. Sitagliptin can dose-dependently up-regulate PCG-1α and irisin, potentially improving insulin resistance and glycolipid metabolism and inhibiting inflammation.

Introduction

Skeletal muscle has recently become recognized as an active endocrine organ with a vital role in regulating metabolism and the inflammatory response via the secretion of myokines.[1] These myokines are capable of interacting with brain, liver, adipose tissue, and other organs in a series of physical processes.[2] Furthermore, many skeletal muscle-derived proteins such as interleukin (IL)-6, IL-13, IL-15, fibroblast growth factor-21, brain-derived neurotrophic factor, and irisin have been screened, and some have been shown to affect glucose and fatty acid metabolism, insulin resistance, and chronic inflammatory reactions.[3–5]

Boström et al.[1] identified irisin as a novel type of myokine in both mice and humans. Irisin is primarily expressed as the type I membrane precursor protein fibronectin type III domain-containing 5 (FNDC5) in muscle, which is subsequently secreted into the circulation system. Irisin levels can be enhanced by overexpression of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and by aerobic exercise training. Irisin is secreted by skeletal muscle. Previous studies[1,2] demonstrated that exercise up-regulated PGC-1α expression in skeletal muscle cells. PGC-1α is enhanced by up-regulating the expression of FNDC5, whereas irisin is mainly generated by cleavage of FNDC5.[1] Irisin can improve glucose metabolism and insulin resistance.[2,3] Furthermore, previous studies found that dipeptidyl peptidase 4 (DPP-4) inhibitors were capable of up-regulating PGC-1α expression levels in the liver of rats fed a high-fat diet.[4]

Sitagliptin is a DPP-4 inhibitor that prevents DPP-4 from hydrolyzing intestinal islet-stimulating hormone, thereby increasing plasma concentrations of the active forms of glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide. By up-regulating the level of active incretin, sitagliptin can increase insulin release and reduce glucagon levels in a glucose-dependent manner.[1–3]

In this investigation, we established a rat model of type 2 diabetes mellitus (T2DM) and evaluated the effects of sitagliptin on skeletal muscle expression of PGC-1α and irisin, and on markers of insulin resistance, glycolipid metabolism, and inflammation.

Materials and methods

Animals and reagents

Streptozotocin (STZ) was purchased from Sigma (St. Louis, MO, USA). PGC-1α, irisin, and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) primers were designed and synthesized by Wuhan Boster Biological Technology Co., Ltd.

(Wuhan, Hubei, China). Primary and secondary antibodies to PGC-1α were purchased from Wuhan Proteintech Group (Wuhan, Hubei, China) and Wuhan Boster Biological Technology Co., Ltd. (Wuhan, Hubie, China), respectively. The reverse-transcription kit was purchased from Invitrogen (Carlsbad, CA, USA). Fasting plasma glucose (FPG) was detected using a blood glucose meter (Johnson & Johnson, New Brunswick, NJ, USA). High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG) were detected using a C8000 automatic biochemical analyzer (Abbott, Abbott Park, IL, USA). Insulin was detected with a Cobase411 automatic electrochemiluminescence analyzer (Roche, Basel, Switzerland). The rat tumor necrosis factor-α (TNF-α) enzyme-linked immunosorbent assay kit was purchased from Beijing Neobioscience (Beijing, China). Male Sprague-Dawley rats (specific-pathogen-free grade; weight 190–210 g, age 8 weeks) were purchased from the Experimental Animal Center of Wuhan University (SCXK (Hubei) 2017-0012) and reared in the Experimental Animal Center of Affiliated Renhe Hospital of China Three Gorges University for 7 days.

T2DM rat model establishment and grouping

Forty-two rats were divided randomly into normal control (NC; n = 10) and experimental groups (n = 32). NC rats were fed a normal diet and rats in the experimental group were fed a high-fat diet (carbohydrate 30.01%, fat 53.75%, protein 16.24%, total calories 486 kcal/100 g; Wuhan Boster Biological Technology). After feeding for 4 weeks, STZ 40 mg/kg was injected intraperitoneally and blood glucose levels in the tail vein were measured 72 hours later. The rat T2DM model was considered to have been established successfully if the blood glucose was $\geq$16.7 mmol.[5] T2DM was successfully established in 30 rats. After feeding with a high-fat diet for 4 weeks, the rats were divided randomly into T2DM low-dose sitagliptin (ST1, sitagliptin 5 mg/kg/day via intragastric administration) and high-dose sitagliptin groups (ST2, 10 mg/kg/day sitagliptin) for 8 weeks. The NC and T2DM groups received an equivalent volume of normal saline via intragastric administration. Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated as follows: $\mathrm{HOMA\text{-}IR} = \mathrm{FPG\,(mmol/L)} \times \mathrm{fasting\ insulin\,(FIns)\,(mIU/L)}/22.5$. All animal experiments were approved by the local Ethics Committee or Institutional Review Board of Affiliated Renhe Hospital of China Three Gorges University (EF201900011).

Sample collection

At the end of the 16th week, all rats were fasted for 12 hours and then sacrificed under pentobarbital anesthesia. Blood samples were taken from the abdominal aorta and stored at $-80°C$ for subsequent use. Gastrocnemius muscle samples were obtained immediately after blood sampling, marked, and maintained in a refrigerator at $-80°C$.

Reverse transcription-polymerase chain reaction (RT-PCR)

PGC-1α and Fndc5 mRNA levels in muscle tissues from the T2DM model rats were measured quantitatively by RT-PCR. Approximately 100 mg fresh frozen gastrocnemius tissues stored at $-80°C$ were prepared, RNA was extracted according to the TRIzol one-step method,[5] and the concentration and purity of the RNA were measured as described previously.[5] cDNA was obtained by reverse

transcription of the extracted RNA and amplified using the following primers: PGC-1α forward primer: 5′-AAGGTCC CCAGGCAGTAGAT-3′, reverse primer: 5′-TTCAGACTCCCGCTTCTCAT-3′; irisin forward primer: 5′-GATCATCGTC GTGGTCCTCTT-3′, reverse primer 5′-AT GCACTCTTGGTTTTTTCCTT-3′.

Western blot

Muscle tissue (0.2 g) was placed in a 1- to 2-mL homogenizer and cut into pieces using clean scissors. Single detergent lysate (400 μL, containing phenylmethylsulfonyl fluoride; Sigma) was added to homogenize the tissue pieces and then placed on ice. After 5 minutes, the tissues were ground again and placed on ice, and this process was repeated three times. After lysis in RIPA solution for 30 minutes, the lysate was transferred to a 1.5-mL centrifuge tube with a pipette, and then centrifuged at $15,000 \times g$ for 5 minutes at $4°C$. The supernatant was removed and divided into 0.5-mL centrifuge tubes, stored at $−20°C$, and then incubated with goat anti-rabbit irisin antibody (1:10,000 dilution; Sigma). The signal generated by the horseradish peroxidase-coupled anti-p-AMPK and anti-GAPDH antibodies (Sigma) was exposed on Kodak X-film (Kodak, Tokyo, Japan) and detected using an enhanced chemiluminescence detection system (Sigma). Signal densities were analyzed using Bandscan 4.3 software (Glyko Inc., Novato, CA, USA) to determine the protein levels, corrected to the value of the GAPDH band.

Statistical analysis

Statistical analysis was conducted using SPSS for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). All data were expressed as mean ± standard deviation. Differences among multiple groups were analyzed by one-way ANOVA, and comparisons between two groups by least significant difference t-tests. A P value <0.05 was considered significant.

Results

Comparison of metabolism-related parameters

The metabolic parameters in the different groups are shown in Table 1. FPG, FIns, TNF-α, and TG were all significantly higher in the T2DM compared with the NC, ST1, and ST2 groups (all P < 0.05), while FPG, FIns, TNF-α, TC, TG, and HOMA-IR were all significantly lower in the ST2 compared with the ST1 group (all $P < 0.05$).

Comparison of PGC-1α, irisin, and phosphoadenylated adenylate activated protein kinase (p-AMPK) protein expression profiles

The protein expression levels of PGC-1α, irisin, and p-AMPK were significantly higher in the NC compared with the DM, ST1, and ST2 groups (all $P < 0.05$). The expression levels of these biomarkers were significantly up-regulated in both the ST1 and ST2 groups compared with the T2DM group (all $P < 0.05$), and were significantly higher in the SR2 compared with the ST1 group (all $P < 0.05$) (Figure 1).

Comparison of mRNA expression profiles of PGC-1α and Fndc5

PGC-1α and Fndc5 mRNA levels were significantly higher in the NC group compared with the T2DM, ST1, and ST2 groups. All the markers were also significantly higher in both the ST1 and ST2 groups compared with the T2DM group (all P < 0.05), and were significantly up-regulated in the ST2

Table 1. Metabolism-related parameters in rats with type 2 diabetes mellitus, with or without sitagliptin.

Group	n	FPG (mmol/L)	FIns (mmol/L)	TNF-α (ng/ml)	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	HOMA-IR
NC group	10	4.66 ± 1.05	9.89 ± 1.37	14.26 ± 2.37	1.51 ± 0.17	0.58 ± 0.34	0.88 ± 0.37	0.42 ± 0.12	3.40 ± 0.31
DM group	10	18.93 ± 1.9#	20.22 ± 2.0#	36.81 ± 8.5#	1.88 ± 0.19*	1.37 ± 0.40*	0.65 ± 0.39*	0.68 ± 0.10*	9.90 ± 0.3#
ST1 group	10	10.93 ± 1.5*	16.89 ± 2.0*△	30.03 ± 3.1#△	1.89 ± 0.17*	1.35 ± 0.37	0.69 ± 0.38	0.66 ± 0.11	7.80 ± 0.3*△
ST2 group	10	6.93 ± 1.38*☆☆	12.97 ± 2.08*☆	22.27 ± 3.75*☆☆	1.78 ± 0.16*☆	0.89 ± 0.40*☆	0.72 ± 0.38	0.62 ± 0.13	5.60 ± 0.37*☆☆

Values presented as mean ± standard deviation. *$P < 0.05$, and #$P < 0.01$ compared with NC group; △$P < 0.05$ compared with DM group; ☆$P < 0.05$ compared with ST1 group. NC, normal control; DM, type 2 diabetes mellitus; ST1, low-dose sitagliptin; ST2, high-dose sitagliptin; FPG, fasting plasma glucose; FIns, fasting insulin; TNF-α, tumor necrosis factor-α; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model of assessment insulin resistance.

compared with the ST1 group (both $P < 0.05$) (Figure 2).

Discussion

PGC-1α has been shown to up-regulate GLUT4 and GLUT2 expression in skeletal muscle and to increase glucose uptake.[6,7] Furthermore, insulin resistance and glucose metabolism were enhanced by up-regulating the expression of PGC-1α in skeletal muscle,[8,9] while recent studies demonstrated that insulin sensitivity was reduced by down-regulation of PGC-1α expression in rats,[10] and Kleiner et al.[11] found that insulin resistance was increased in PGC-1α-knockout mice. Metformin improved insulin resistance and glucose metabolism by up-regulating the expression levels of PGC-1α, p-AMPK, and p-ERK in C2C12 cells and skeletal muscle in ob/ob rats.[12] However, down-regulation of PGC-1α expression by small interfering RNA reduced p-AMPK and p-ERK expression, and this effect was not reversed by metformin, suggesting that PGC-1α plays a key role in glucose metabolism and insulin resistance. Clinical studies have indicated that placental PGC-1α expression is down-regulated in patients with gestational diabetes mellitus, contributing to abnormal fetal glucose metabolism,[13] and indicating a close association between PGC-1α and glucose metabolism. Down-regulation of PGC-1α thus participates in the occurrence of insulin resistance and diabetes mellitus, and PGC-1α is closely correlated with glucose metabolism and plays a protective role in the occurrence of T2DM.[14] PGC-1α expression levels were shown to be down-regulated the plantar muscle in T2DM rats.[15] Skeletal muscle PGC-1α was also down-regulated in diabetic rats in the current study, suggesting that decreased expression of PGC-1α in skeletal muscle may be involved in the occurrence of T2DM. Aroor et al.[4] found that
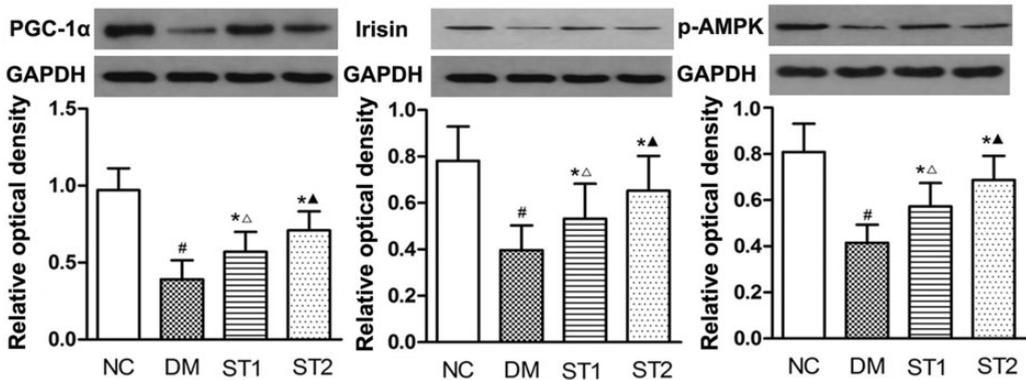
Figure 1. Expression profiles of PGC-1α, irisin, and p-AMPK proteins in skeletal muscle from rats with type 2 diabetes mellitus, with or without sitagliptin. *$P < 0.05$ and #$P < 0.01$ compared with NC group; △$P < 0.05$ compared with DM group; ▲$P < 0.05$ compared with ST1 group. Size markers for PGC-1α, irisin, p-AMPK, and GADPH were 140, 22, 65, and 37 kD, respectively. PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; p-AMPK, phosphoadenylated adenylate activated protein kinase; NC, normal control; DM, type 2 diabetes mellitus; ST1, low-dose sitagliptin; ST2, high-dose sitagliptin, GAPDH, glyceraldehyde 3-phosphate dehydrogenase.
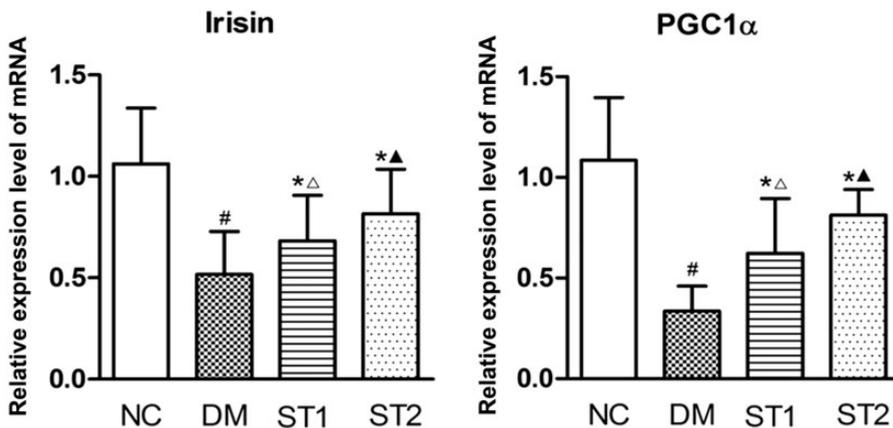

Figure 2. Expression profiles of PGC-1α, irisin, and p-AMPK mRNA in skeletal muscle from rats with type 2 diabetes mellitus, with or without sitagliptin. *$P < 0.05$ and #$P < 0.01$ compared with NC group; △$P < 0.05$ compared with DM group; ▲$P < 0.05$ compared with ST1 group. PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; NC, normal control; DM, type 2 diabetes mellitus; ST1, low-dose sitagliptin; ST2, high-dose sitagliptin.

administration of the DPP4 inhibitor MK0626 up-regulated PGC-1α expression in the liver in rats fed a high-fat diet and reduced insulin resistance. In the present experiment, the DPP4 inhibitor sitagliptin up-regulated the expression of PGC-1α in skeletal muscle of diabetic rats and decreased HOMA-IR, suggesting that it improved insulin resistance partially by up-regulation of PGC-1α. PGC-1α can regulate the expression of irisin.[1] We considered that the up-regulation of irisin by

sitagliptin in the current study was achieved by regulating the expression of PGC-1α. Intraperitoneal injection of recombinant irisin was previously shown to reduce blood glucose in diabetic rats,[16] correlated with increased phosphorylation of AMPK in skeletal muscle and glucose uptake.[17] Up-regulated expression levels of PGC-1α and irisin in rats fed a high-fat diet were accompanied by increased AMPK phosphorylation,[18] and sitagliptin was previously shown to increase the levels of phosphorylated AMPK.[19] In the present study, sitagliptin increased the expression of p-AMPK in skeletal muscle of diabetic rats, partially by up-regulating PGC-1α and irisin expression. This suggests the existence of a PGC-1α–irisin–p-AMPK signaling pathway, in which PGC-1α increases irisin expression, thereby up-regulating p-AMPK expression. In this study, sitagliptin improved insulin resistance and glucose metabolism by activating this signaling pathway. The higher dose of sitagliptin (ST2 group) had a more significant effect on PGC-1α, irisin, and p-AMPK, suggesting that sitagliptin affected PGC-1α, irisin, and p-AMPK in a dose-dependent manner.

PGC-1α expression in skeletal muscle not only determines the metabolic state of the skeletal muscle, but is also closely associated with the creation of an anti-inflammatory environment. Local and systemic inflammatory responses were enhanced in PGC-1α-knockout mice, and transcription levels of the inflammatory cytokines TNF-α and IL-6 in muscle tissues were significantly increased, even in heterozygous PGC-1α$^{+/-}$ mice.[20] In contrast, over-expression of PGC-1α in skeletal muscle down-regulated serum and muscle IL-6 and TNF-α expression levels in rats,[21] suggesting that PGC-1α exerts an inhibitory effect on inflammatory cytokines. In this investigation, down-regulation of PGC-1α in skeletal muscle was associated with up-regulation of TNF-α levels in T2DM

rats. Irisin is also closely related to inflammation and can down-regulate TNF-α expression.[21] Inhibition of inflammatory cytokines by irisin was recently proposed to be related to suppression of the NLRP3 inflammasome signaling pathway.[22] In the current study, the decrease in irisin in skeletal muscle of T2DM rats and the resulting decreased inhibitory effect on inflammatory cytokines may thus have contributed to the increase in TNF-α in T2DM rats. Sitagliptin has been confirmed to reduce insulin resistance by inhibiting inflammatory cytokines, such as IL-6 and TNF-α, in diabetic rats.[18] Interestingly, some studies found that sitagliptin also inhibited the NLRP3 inflammasome[23] via an identical mechanism to that used by irisin to inhibit inflammatory cytokines. In this study, PGC-1α and irisin levels were up-regulated and TNF-α was down-regulated by sitagliptin. We suggest that the inhibitory effect of sitagliptin on inflammatory cytokines depends partially on up-regulating the expression of PGC-1α and irisin. Serum TNF-α levels were more evidently decreased in the ST2 group, probably due to the greater effect of the higher dose of sitagliptin on PGC-1α and irisin, thereby exerting a greater inhibitory effect on the inflammatory cytokine TNF-α. Some studies have shown that up-regulation of PGC-1α can lower blood lipid levels,[24] whereas high levels of irisin were accompanied by decreased blood lipid levels.[25] In addition, lipid metabolism was improved by up-regulating the expression levels of PGC-1α and irisin.[18] In the current study, TC and TG levels were also significantly decreased in the ST2 group, probably because of the effect of sitagliptin on PGC-1α and irisin. However, low-dose sitagliptin had no significant effect on blood lipids, possibly because this dose had less effect on PGC-1α and irisin.

The DPP-4 inhibitor sitagliptin may play a role in suppressing hypoglycemia.

The current results provide novel evidence for its use in the prevention and treatment of diabetes mellitus in clinical practice. However, the mechanism underlying the anti-hypoglycemic effect of DPP-4 inhibitors remains to be clarified, and more studies are needed to validate the conclusions of this preliminary study.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

ORCID iD

Yuntao Liu   https://orcid.org/0000-0002-6411-5865

References

1. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012; 481: 463–468.
2. Perakakis N, Triantafyllou GA, Fernández-Real JM, et al. Physiology and role of irisin in glucose homeostasis. *Nat Rev Endocrinol* 2017; 13: 324–333.
3. Yang Z, Chen X, Chen Y, et al. Decreased irisin secretion contributes to muscle insulin resistance in high-fat diet mice. *Int J Clin Exp Pathol* 2015; 8: 6490–4697.
4. Aroor AR, Habibi J, Ford DA, et al. Dipeptidyl peptidase-4 inhibition ameliorates Western diet-induced hepatic steatosis and insulin resistance through hepatic lipid remodeling and modulation of hepatic mitochondrial function. *Diabetes* 2015; 64: 1988–2001.
5. Sun CF, Jia GL, Li CD, et al. Early changes of cognitive function in type 2 diabetes rat and expression of p-NR2B, Wnt3a and ADAM10 in hippocampus. *Chin J Diabetes* 2018; 26: 150–155.
6. Benton CR, Holloway GP, Han XX, et al. Increased levels of peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC-1alpha) improve lipid utilisation, insulin signalling and glucose transport in skeletal muscle of lean and insulin-resistant obese Zucker rats. *Diabetologia* 2010; 53: 2008–2019.
7. Wang X, Gao H, Wu W, et al. The zinc transporter Slc39a5 controls glucose sensing and insulin secretion in pancreatic β-cells via Sirt1- and Pgc-1α-mediated regulation of Glut2. *Protein Cell* 2019; 10: 436–449.
8. Summermatter S, Shui G, Maag D, et al. PGC-1α improves glucose homeostasis in skeletal muscle in an activity-dependent manner. *Diabetes* 2013; 62: 85–95.
9. Li S, Fei Z, Xu Z, et al. *Enterococcus faecalis* sir2-like gene enhances aerobic metabolism of themselves and mitochondrial respiration of mammal cells to bring about improving metabolic syndrome through the PGC-1 α pathway. *J Tissue Eng Regen Med* 2018; 13: 143–155.
10. Stahel P, Kim JJ, Cieslar SR, et al. Supranutritional selenium intake from enriched milk casein impairs hepatic insulin sensitivity via attenuated IRS/PI3K/AKT signaling and decreased PGC-1α expression in male Sprague-Dawley rats. *J Nutr Biochem* 2017; 41: 142–150.
11. Kleiner S, Mepani RJ, Laznik D, et al. Development of insulin resistance in mice lacking PGC-1α in adipose tissues. *Proc Natl Acad Sci USA* 2012; 109: 9635–9640.
12. Yang Z, Chen X, Chen Y, et al. PGC-1 mediates the regulation of metformin in muscle irisin expression and function. *Am J Transl Res* 2015; 7: 1850–1859.
13. Wang L, Fan H, Zhou L, et al. Altered expression of PGC-1α and PDX1 and their methylation status are associated with fetal glucose metabolism in gestational diabetes mellitus. *Biochem Biophys Res Commun* 2018; 501: 300–306.
14. Wu H, Deng X, Shi Y, et al. PGC-1α, glucose metabolism and type 2 diabetes mellitus. *J Endocrinol* 2016; 229: 99–115.

15. Nagatomo F, Fujino H, Kondo H, et al. PGC-1α mRNA level and oxidative capacity of the plantaris muscle in rats with metabolic syndrome, hypertension, and type 2 diabetes. *Acta Histochem Cytochem* 2011; 44: 73–80.

16. Duan H, Ma B, Ma X, et al. Anti-diabetic activity of recombinant irisin in STZ-induced insulin-deficient diabetic mice. *Int J Biol Macromol* 2016; 84: 457–463.

17. Lee HJ, Lee JO, Kim N, et al. Irisin, a novel myokine, regulates glucose uptake in skeletal muscle cells via AMPK. *Mol Endocrinol* 2015; 29: 873–881.

18. Yang XQ, Yuan H, Li J, et al. Swimming intervention mitigates HFD-induced obesity of rats through PGC-1α-irisin pathway. *Eur Rev Med Pharmacol Sci* 2016; 20: 2123–2230.

19. Zheng W, Zhou J, Song S, et al. Dipeptidyl-peptidase 4 inhibitor sitagliptin ameliorates hepatic insulin resistance by modulating inflammation and autophagy in ob/ob mice. *Int J Endocrinol* 2018; 2018: 8309723.

20. Handschin C and Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. *Nature* 2008; 454: 463–469.

21. Wenz T, Rossi SG, Rotundo RL, et al. Increased muscle PGC-1alpha expression protects from sarcopenia and metabolic disease during aging. *Proc Natl Acad Sci USA* 2009; 106: 20405–20410.

22. Deng X, Huang W, Peng J, et al. Irisin alleviates advanced glycation end products-induced inflammation and endothelial dysfunction via inhibiting ROS-NLRP3 inflammasome signaling. *Inflammation* 2018; 41: 260–275.

23. Jo CH, Kim S, Park JS, et al. Anti-inflammatory action of sitagliptin and linagliptin in doxorubicin nephropathy. *Kidney Blood Press Res* 2018; 43: 987–999.

24. Oropeza D, Jouvet N, Bouyakdan K, et al. PGC-1 coactivators in β cells regulate lipid metabolism and are essential for insulin secretion coupled to fatty acids. *Mol Metab* 2015; 4: 811–822.

25. Bonfante ILP, Chacon-Mikahil MPT, Brunelli DT, et al. Obese with higher FNDC5/Irisin levels have a better metabolic profile, lower lipopolysaccharide levels and type 2 diabetes risk. *Arch Endocrinol Metab* 2017; 61: 524–533.