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Transcriptional activation of SHP by PPAR-γ in liver

Ha-il Kim [a,b,1], Yoo-Kyung Koh [a,b,1], Tae-Hyun Kim [a,b], Sool-Ki Kwon [a,b], Seung-Soon Im [a,b], Hueng-Sik Choi [d], Kyung-Sup Kim [a,b,c], Yong-Ho Ahn [a,b,*]

[a] *Department of Biochemistry and Molecular Biology, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemoon-gu, Seoul 120-752, Republic of Korea*

[b] *Center for Chronic Metabolic Disease Research, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemoon-gu, Seoul 120-752, Republic of Korea*

[c] *Institute of Genetic Science, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemoon-gu, Seoul 120-752, Republic of Korea*

[d] *Hormone Research Center, Chonnam National University, Kwangju 500-757, Republic of Korea*

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Abstract

The mechanism of how PPARγ decrease gluconeogenic gene expressions in liver is still unclear. Since PPARγ is a transcriptional activator, it requires a mediator to decrease the transcription of gluconeogenic genes. Recently, SHP has been shown to mediate the bile acid-dependent down regulation of gluconeogenic gene expression in liver. This led us to explore the possibility that SHP may mediate the antigluconeogenic effect of PPARγ. In the present study, we have identified and characterized the presence of functional PPRE in human SHP promoter. We show the binding of PPARγ/RXRα heterodimer to the PPRE and increased SHP expression by rosiglitazone in primary rat hepatocytes. Taken together with the previous reports about the function of SHP on gluconeogenesis, our results indicate that SHP can mediate the acute antigluconeogenic effect of PPARγ.
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Keywords: PPARγ; Gluconeogenesis; SHP

Liver plays a major role in regulating blood glucose level by maintaining the balance between the storage and release of glucose. Especially liver is the only organ that produce glucose *de novo* via gluconeogenesis. It is regulated by the activities of glucose-6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK) and fructose-1,6-bisphosphatase (FBP1). Among these genes, G6Pase and PEPCK are regulated by the hormonal balance between insulin and glucagon. Several transcription factors, including forkhead transcription factor (FOXO1), glucocorticoid receptor (GR), hepatocyte nuclear factor (HNF4), and peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1) are known to contribute to this transcriptional regulation [1–7].

Peroxisome proliferator-activated receptor γ (PPARγ) is a nuclear hormone receptor comprised of an agonist-dependent activation domain and a DNA binding domain [8]. PPARγ heterodimerizes with retinoid X receptor α (RXRα) and activates the transcription of target genes through the binding of the PPAR response element (PPRE). Upon binding of the agonist, the transcriptional activity of PPARγ is increased. Synthetic agonists of PPARγ, thiazolidinediones (TZDs), are known to improve glucose tolerance by enhancing insulin sensitivity [8,9]. PPARγ agonists increase the expression of genes involved in glycolysis, glycogen synthesis and lipogenesis, and decrease the genes involved in gluconeogenesis and fatty acid oxidation [10,11]. Several genes involved in glycolysis and lipogenesis have been identified as direct targets of

* Corresponding author. Address: Department of Biochemistry and Molecular Biology, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemoon-gu, Seoul 120-752, Republic of Korea. Fax: +82 2 312 5041.
E-mail address: yha111@yumc.yonsei.ac.kr (Y.-H. Ahn).

[1] These authors contributed equally to this work.

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PPARγ. However, it is not clear the mechanism of how PPARγ agonists affect gluconeogenic genes.

Small heterodimer partner (SHP) is an atypical nuclear receptor that lacks a conventional DNA binding domain [12]. The gene expression of SHP is regulated by several transcription factors including farnesoid X receptor (FXR), liver X receptor (LXR), HNF4, liver receptor homolog-1 (LRH-1), steroidogenic factor-1, and estrogen-related receptor-γ [13–18]. It has been reported to interact with several transcriptional factors and repress their transcriptional activity either by competing with coactivators for binding to the transcriptional factors or by recruiting corepressors directly to its transcriptional repression domain [19]. SHP is also known to play an important role in the regulation of cholesterol homeostasis [20,21].

In this study, we identified a functional PPRE in the human SHP promoter. We also show that rosiglitazone directly activates SHP gene expression in hepatocytes. These data suggest that SHP mediates the antigluconeogenic effects of PPARγ agonists in the liver.

Experimental procedures

Plasmids. The SHP promoter-luciferase reporter construct, pSHP-2190 contained the −2190/+29 region of the human SHP gene [20]. Serial deletion constructs pSHP-1263, pSHP-605, pSHP-478, pSHP-244, pSHP-185, and pSHP-1 were subcloned into pGL3 basic vectors. pSHP-1263m1, pSHP-1263m2, pSHP-1263m3, pSHP-1263m4, and pSHP-1263m5 were produced by introducing substitution mutations into pSHP-1263. The truncated mutants, pSHP-1263T1, pSHP-1263T2, pSHP-1263T3, pSHP-1263T12, pSHP-1263T23, pSHP-1263T13, and pSHP-1263T123 were constructed by inserting restriction enzyme sites in the appropriate positions and excising the −289/−245, −244/−186, −185/−44, −289/−186, −185/−44, −289/−245, and −185/−44, −289/−44 regions from pSHP-1263. Characteristics of the expression plasmid of PPARγ and RXRα were described previously [22]. V5-tagged PPARγ expression plasmid (pcPPARγ) was constructed by subcloning mouse PPARγ cDNA from pCMX-PPARγ into pcDNA3.1/V5 (Invitrogen, Carlsbad, CA). The sequences of all constructs were confirmed by DNA sequencing.

Cell culture and transient transfection assay. Primary hepatocytes were isolated from Sprague–Dawley rats and cultured as described previously [23]. Alexander cells and HepG2 cells were also cultured as described previously [23]. Transient transfection and luciferase assays were performed as described previously [10]. Luciferase activities were normalized by β-galactosidase activities and were expressed as fold increase relative to the basal activity of the reporters in the absence of overexpression vectors. Rosiglitazone was a gift from GlaxoSmithKline Korea (Seoul, Korea) and *9-cis* retinoic acid was purchased from Sigma–Aldrich (St. Louis, MO).

Isolation of total RNA, reverse transcription, and real time polymerase chain reaction. Total RNA was extracted and reverse transcription were performed as previously described [22]. Quantitative real time PCR was performed using ABI PRISM 7000 Sequence Detection System instrument and software (Applied Biosystems, Foster City, CA) according to the manufacturer's protocol with minor modification. Briefly, an appropriate amount of the reverse transcription reaction mixture was amplified with specific primers using SYBR green PCR master mix (Applied Biosystems, Foster City, CA) in a total volume of 20 μL. Data were processed by comparative C_T method and expressed as fold increase relative to the basal transcription level. The amount of target mRNA was normalized by determining β-actin mRNA level by real time PCR. Oligonucleotides used in PCR are shown in Table 1.

In vitro translation and electrophoretic mobility shift assay (EMSA). *In vitro*-translated PPARγ/V5 and RXRα were prepared as described previously [24]. An oligonucleotide covering the −103/−57 region of human SHP gene was used as wild-type probe and m2, m3 were used as mutant probes. βGK-PPRE was used as a positive control to confirm the binding of PPARγ/RXRα heterodimer [24]. For competition assays, 10-M excessive unlabeled oligonucleotides were added to the reaction mixture. Two

Table 1
Oligonucleotides used in PCR and EMSA

Name	Sequence
hSHP-103/-70s	TTTCAATGAACATGACTTCTGGAGTCAAGGTTGT
hSHP-103/-70as	ACAACCTTGACTCCAGAAGTCATGTTCATTGAAA
hSHP-103/-70m1s	TTTCAACCCGGGTGACTTCTGGAGTCAAGGTTGT
hSHP-103/-70m1as	ACAACCTTGACTCCAGAAGTCACCCGGGTTGAAA
hSHP-103/-70m2s	TTTCAATGAACACCCGGGCTGGAGTCAAGGTTGT
hSHP-103/-70m2as	ACAACCTTGACTCCAGCCCGGGTGTTCATTGAAA
hSHP-103/-70m3s	TTTCAATGAACATGACTTCCCCGGGCAAGGTTGT
hSHP-103/-70m3as	ACAACCTTGCCCGGGGAAGTCATGTTCATTGAAA
hSHP-87/-58m4s	TTCTGGAGTCACCCGGGTTGGGCCATTCCC
hSHP-87/-58m4as	GGGAATGGCCCAACCCGGGTGACTCCAGAA
hSHP-87/-58m5s	TTCTGGAGTCAAGGTTGTTCCCGGGTTCCC
hSHP-87/-58m5as	GGGAACCCGGGAACAACCTTGACTCCAGAA
human SHPs	CCTCTTCAACCCCGATGTGCC
human SHPas	GCCAGCGATGTCAACATCTCC
rat SHPs	CCTCTTCAACCCAGATGTGCC
rat SHPas	GTTCAGTGATGTCAACATCTCC
human PEPCKs	GATGAGCCGCTAGCTTCA
human PEPCKas	TTGCCGAAGTTGTAGCCA
rat PEPCKs	CTTTGGCTACAACTTCGGCAAG
rat PEPCKas	CCCAGAATTCCTTAGAGATTCCG
human G6Ps	GGTGGGTTTTGGATACTGACT
human G6Pas	CAATGCCTGACAGGACTCCA
rat G6Ps	GTGGGTCCTGGACACTGACT
rat G6Pas	CAATGCCTGACAAGACTCCA

Underlined sequences indicate the mutated site.

microliters of anti-V5 antibody (Temecula, CA, USA) was added to the reaction mixture for the supershift assay.

Results

To test the effect of PPARγ on SHP expression in hepatocytes, HepG2 cells and primary hepatocytes isolated from rat liver were treated with the ligands of PPARγ and RXRα. Rosiglitazone increased SHP mRNA level by 1.7-fold whereas *9-cis* retinoic acid increased SHP mRNA level by 6.6-fold in HepG2 cell lines. Combined treatment of rosiglitazone and *9-cis* retinoic acid increased SHP expression 16.4-fold, indicating the synergistic induction of SHP expression by the ligands of PPARγ and RXRα (Fig. 1). SHP expression was also increased by rosiglitazone and *9-cis* retinoic acid by 2.7-fold and 56.2-fold, respectively in primary hepatocytes. Rosiglitazone and *9-cis* retinoic acid increased SHP expression synergistically (92.8-fold). The synergism in the induction of SHP gene expression by rosiglitazone and *9-cis* retinoic acid suggests the regulation of SHP expression by PPARγ and the possible presence of a PPARγ response element in the SHP promoter.

In order to test whether PPARγ regulates the SHP promoter, we transfected the luciferase reporter construct which is linked to −2.2 kb region of the human SHP promoter into Alexander cells with or without overexpression of PPARγ and/or RXRα in the presence of their appropriate ligands [20]. As shown in Fig. 2, the SHP promoter was activated by ectopic expression of RXRα in the presence of *9-cis* retinoic acid and the promoter was activated synergistically by the coexpression of RXRα and PPARγ in the presence of their respective ligands. The activation of promoter was well closely correlated with that of SHP mRNA level in hepatocytes. In order to localize *cis*-element(s) which is responsible for PPARγ/RXRα, we performed 5′ serial deletion of SHP promoter. The SHP promoter was activated by either RXRα or PPARγ/RXRα until the 5′ end of the promoter was deleted down to position −478. Further deletion down to −244 resulted in the loss of RXRα-responsiveness although the response to PPARγ/RXRα still remained. The loss of RXRα-responsiveness could be explained by the presence of LXRE and FXRE in this region [13,14,25]. When we deleted to +1 of the SHP gene, the response to PPARγ/RXRα disappeared completely. This result indicates that the PPRE may be present in the −185/+1 region of the SHP gene promoter.

The consensus sequence of PPRE was known to be DR+1, a hexameric consensus sequence (AGGTCA) in a direct repeat spaced by one nucleotide. However, we could not find a typical consensus sequence of PPRE in the −185/−44 region. Therefore, we prepared scanning mutants by introducing point mutations in the −100/−60 region of

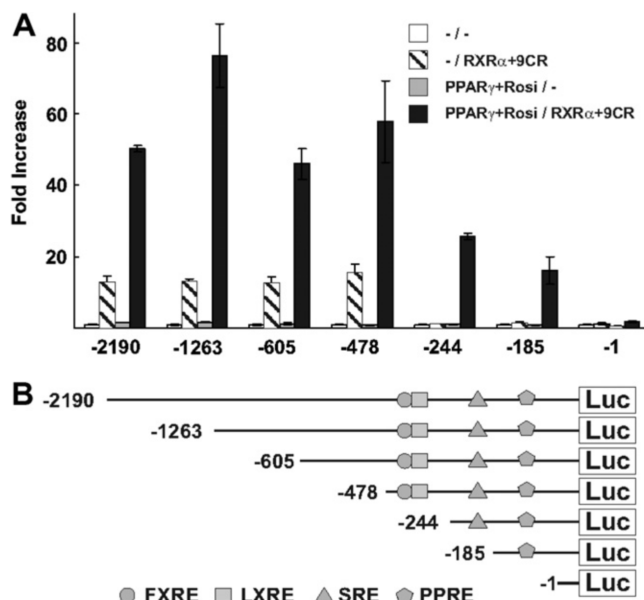

Fig. 2. PPARγ activated the human SHP promoter. (A) Luciferase reporter under the control of human SHP promoter pSHP-2190 and its 5′ serial deletion constructs were cotransfected into Alexander cells with or without expression vectors of PPARγ and/or RXRα. Appropriate ligands for receptors were treated after transfection: 1 μM of rosiglitazone (Rosi) for PPARγ and 1 μM of *9-cis* retinoic acid (9CR) for RXRα were used. White bar, without overexpression of PPARγ and RXRα and without treatment of *9-cis* retinoic acid and rosiglitazone; back slash bar, with expression of RXRα and with treatment of *9-cis* retinoic acid; gray bar, with expression of PPARγ and with treatment of rosiglitazone; black bar, with expression of PPARγ and RXRα and with treatment of *9-cis* retinoic acid and rosiglitazone. (B) Structures of truncated mutants of human SHP promoter luciferase reporter constructs were shown below. Luciferase reporter were cotransfected into Alexander cells with or without PPARγ and RXRα expression vectors and incubated in the presence or absence of rosiglitazone (1 μM, Rosi) as indicated. White bar, without overexpression of PPARγ and RXRα without treatment of rosiglitazone; gray bar, with expression of PPARγ and RXRα without treatment of rosiglitazone; black bar, with expression of PPARγ and RXRα and with treatment of rosiglitazone. (A,B) Normalized luciferase activities are shown as means ± SD of three independent experiments in a triplicate and are expressed as fold increase relative to the basal activity.

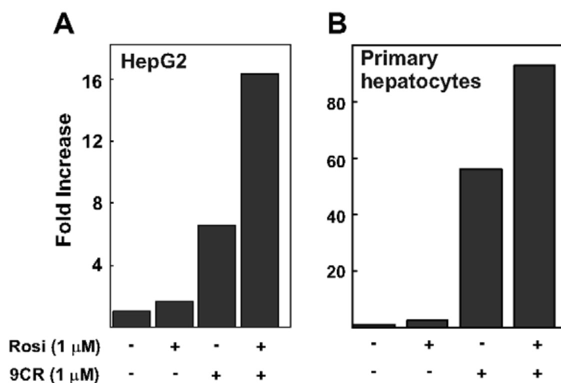

Fig. 1. Rosiglitazone increased SHP expression in HepG2 cells and primary hepatocytes. HepG2 cells (A) and primary hepatocytes (B) were treated with rosiglitazone (1 μM) and/or *9-cis* retinoic acid (1 μM) for 24 h. Total RNA was prepared and subjected to reverse transcription. The transcription levels of SHP and β-actin were quantitated by real time PCR. Quantity of the mRNA was normalized with respect to β-actin mRNA. Data were as fold increase relative to the basal transcription level in the absence of ligands.

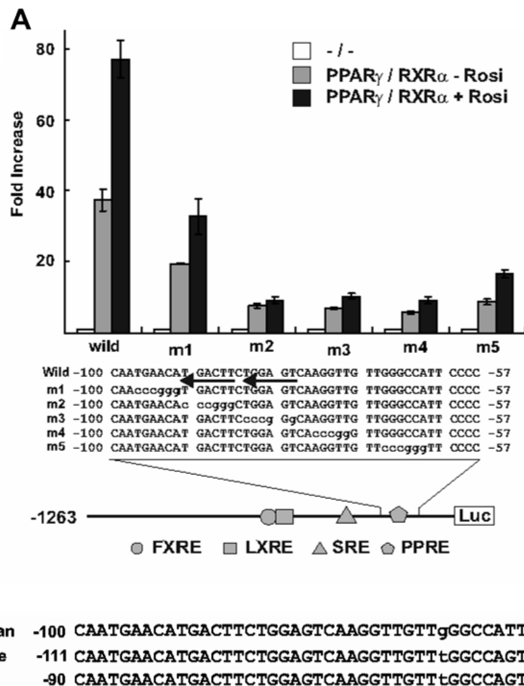

Fig. 3. Identification of the PPRE in the SHP promoter. (A) Point mutations were introduced into the SHP promoter as indicated. Luciferase reporters were cotransfected into Alexander cells with or without PPARγ and RXRα expression vectors and incubated in the presence or absence of rosiglitazone (1 μM, Rosi) as indicated. White bar, without overexpression of PPARγ and RXRα without treatment of rosiglitazone; gray bar, with expression of PPARγ and RXRα without treatment of rosiglitazone; black bar, with expression of PPARγ and RXRα and with treatment of rosiglitazone. Normalized luciferase activities are shown as means ± SD of three independent experiments in a triplicate and are expressed as fold increase relative to the basal activity. (B) DNA sequence of the human SHP −100/−57 region compared with the mouse SHP −111/−68 and the rat SHP −90/−47 region.

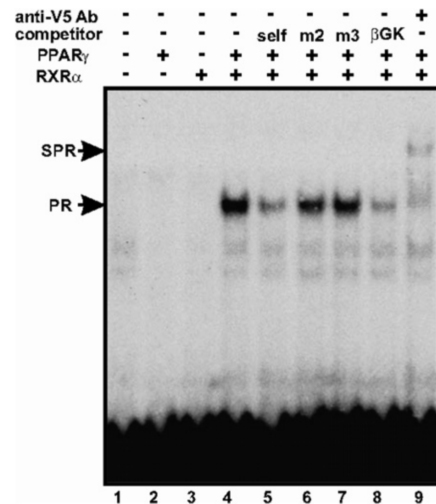

Fig. 4. PPARγ/RXRα heterodimer binds to the functional PPRE in the SHP promoter. EMSA using *in vitro*-translated PPARγ and RXRα was performed. The oligonucleotide covering the −100/−57 region was used as a probe. Wild-type oligonucleotide (self), mutant oligonucleotides (m2, m3) and βGK-PPRE (βGK)-containing oligonucleotides were used as competitors. ^{32}P-labeled probe was incubated with *in vitro*-translated PPARγ (2 μL) and/or RXRα (2 μL) as indicated. Two μL of anti-V5 antibody was added into the reaction mixture (lane 4). PR indicates band shifted by the PPARγ/RXRα heterodimer and SPR indicates supershifted band by anti-V5 antibody.

the SHP promoter and checked the PPARγ responsiveness in order to localize the PPRE (Fig. 3). Wild-type and m1 promoters were activated by PPARγ/RXRα and further activated by rosiglitazone, although the level of activation of the m1 promoter was less than that of the wild-type promoter. The m2, m3, m4, m5 promoters showed a small increase in the promoter activity by PPARγ/RXRα and the m2, m3, m4 mutants were not further activated by rosiglitazone. These results indicate the presence of the PPRE in the −91/−71 region of the human SHP gene promoter, which was further supported by the presence of highly conserved sequences between species in the −100/−57 region. The DNA sequence of the −100/−57 region of the human SHP gene was perfectly matched with that of the −111/−68 region of the mouse SHP gene and that of the −90/−47 region of the rat (Fig. 3). The high conservation of PPREs between species suggests that the PPRE plays an important role in the regulation of SHP gene expression. In order to know whether the PPARγ/RXRα heterodimer binds to this functional PPRE, we performed an electrophoretic mobility shift assay, using the −103/−70 region of the SHP gene as a probe (Fig. 4). We prepared recombinant PPARγ and RXRα by *in vitro* transcription and translation. V5 tag was fused to the C-terminal end of PPARγ. Neither PPARγ (lane 2) nor RXRα (lane 3) binds to the probe, but a heterodimer of PPARγ and RXRα (lane 4) binds to the probe. When 10-M excess competitors were added to the reaction mixture, self-competitor (lane 5) and βGK-PPRE (lane 6) competed with the binding of the PPARγ/RXRα heterodimer. However, mutant competitors, m2 and m3, did not compete with the binding of the PPARγ/RXRα heterodimer (lanes 7 and 8). Anti-V5 antibody could supershift the binding of PPARγ/RXRα heterodimer (lane 9). These data indicate that the heterodimer of PPARγ and RXRα was bound to the −91/−71 region of the SHP gene and the region could function as a PPRE of the human SHP promoter.

Discussion

PPARγ agonists are now firmly believed to improve insulin sensitivity and glucose homeostasis in type 2 diabetic subjects. However, there has been a debate on the mechanism of PPARγ agonists on hepatic glucose metabolism. Major metabolic changes in the liver by PPARγ agonists have been rather considered to be secondary effect although PPARγ is known to be able to regulate hepatic gene expression directly [10]. Synthetic PPARγ ligands, such as thiazolidinedione (TZD), are known to decrease hepatic glucose production *in vivo* [26,27]. Tyrosine-based non-TZD PPARγ agonist GW1929 decreases the expression of PEPCK and G6Pase in the liver of Zucker Diabetic

Fatty (ZDF) rats [11]. PEPCK transcription is decreased by 30% within 24 h after treatment with GW1929 when the reduction of blood glucose level does not occur. This early reduction of PEPCK expression in spite of high blood glucose level suggests that GW1929 can directly affect the expression of hepatic gluconeogenic genes. Treatment with GW1929 for 7 days decreased the transcription of PEPCK by more than 70% and also lower blood glucose level in the ZDF rats. This late profound reduction of PEPCK expression after decrease of blood glucose level is likely to be secondary to the systemic improvement of glucose homeostasis. Although PPARγ agonists are known to increase PEPCK expression in adipocytes, they are not able to increase PEPCK gene expression in hepatocytes. Actually, in some cases PPARγ agonists are shown to decrease PEPCK expression in hepatocytes. GW1929 increased PEPCK expression in white adipose tissues and decreased expression in the liver when ZDF rats were administrated with GW1929 for 7 days [28–30]. Given that PPARγ is not a transcriptional repressor but an activator and the early reduction of hepatic PEPCK expression is small, PPARγ seems to have a mediator to inhibit the transcription of PEPCK in hepatocytes.

SHP, an atypical nuclear hormone receptor devoid of a DNA binding domain, is known to antagonize the function of glucocorticoid receptor (GR) and HNF4 [31,32], thereby inhibiting the gluconeogenic gene expression. SHP is also known to decrease the expression of PGC-1 which works as a positive regulator of hepatic gluconeogenesis [4,6,33]. Recently Yamagata et. al. proposed a model that SHP mediates the bile acid-dependent down regulation of gluconeogenic gene expression in the liver [34]. According to that model, increased levels of SHP could displace cAMP response element binding protein (CREB) binding protein (CBP) by competing for interaction with FOXO1 on the G6Pase promoter and HNF4 on the PEPCK promoter. In addition, many nuclear receptors are known to be involved in the transcriptional regulation of SHP [13,17,25,32]. This led us to consider SHP as a mediator of PPARγ dependent suppression of gluconeogenesis and attempt to explore the regulation of SHP expression by PPARγ.

In the present study, we have identified the PPRE in the human SHP promoter. We demonstrated that PPARγ-activated SHP gene expression in cultured hepatocytes. Our results, together with the previous reports that PPARγ agonists can decrease glucose production in the liver of type 2 diabetic subjects and that SHP inhibits the gluconeogenic gene expressions, indicate that SHP can mediate the acute antigluconeogenic effect of PPARγ.

Acknowledgments

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