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Overexpression of Jazf1 reduces body weight gain and regulates lipid metabolism in high fat diet

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ABSTRACT

Jazf1 is a 27 kDa nuclear protein containing three putative zinc finger motifs that is associated with diabetes mellitus and prostate cancer; however, little is known about the role that this gene plays in regulation of metabolism. Recent evidence indicates that Jazf1 transcription factors bind to the nuclear orphan receptor TR4. This receptor regulates PEPCK, the key enzyme involved in gluconeogenesis. To elucidate Jazf1's role in metabolism, we fed a 60% fat diet for up to 15 weeks. In Jazf1 overexpression mice, weight gain was found to be significantly decreased. The expression of Jazf1 in the liver also suppressed lipid accumulation and decreased droplet size. These results suggest that Jazf1 plays a critical role in the regulation of lipid homeostasis. Finally, Jazf1 may provide a new therapeutic target in the management of obesity and diabetes.

1. Introduction

Lipid metabolism is separated into lipogenesis and lipolysis. Lipogenesis is the process by which acetyl-CoA is converted to fats. Lipogenesis related genes typically include SREBP1-c, FAS and ACC. SREBP1-c is a critical regulator of extension of lipid storage in liver [1], as well as an important factor in transcriptional regulation of the fatty acid synthetic genes, FAS and ACC [2]. FAS is an enzyme that catalyzes fatty acid synthesis via the production of palmitate from acetyl-CoA and malonyl-CoA [3]. Similarly, ACC, which synthesizes malonyl-CoA from acetyl-CoA, is an important enzyme in triglyceride biosynthesis. ACC is predominantly expressed in the lipogenesis related tissues, liver and adipose [4]. Lipolysis is the breakdown of lipids. HSL and ATGL are important lipolysis related genes. HSL is an intracellular lipase that is capable of hydrolyzing stored triglycerides to free fatty acids in adipose tissue [5]. ATGL initiates the breakdown of intracellular triglycerides into fatty acid monomers in adipose tissue [6]. An imbalance between lipogenesis and lipolysis is caused by abnormal lipid metabolism (dyslipidemia), and obesity is a major element leading to the development of dyslipidemia [7].

Obesity is caused by poor diet, especially excess energy intake. Obesity is also the major pathological factor that predisposes individuals to insulin resistance [8,9], which is the central feature of metabolic syndrome, whereby target tissues fail to respond efficiently to normal concentrations of insulin [10].

TR4 belongs to a subclass of orphan nuclear receptors. TR4 is highly expressed in several tissues, including the testis, brain, kidney, liver, and adipose tissue. Although the precise physiological functions of TR4 remain poorly understood [11], recent reports suggest that certain fatty acids and eicosanoids bind to and enhance the transcriptional activity of TR4, suggesting that TR4 might function as a lipid sensor [12]. Other studies have provided evidence of a role of TR4 in lipid metabolism and gluconeogenesis [13,14]. TR4 also regulates various genes in diverse pathways, including apoE, Gata1, PEPCK, and CD36 [15–17].

PEPCK is the key enzyme controlling the rate of gluconeogenesis based on its expression levels. PEPCK is mainly expressed in the liver and kidney, where it participates in gluconeogenesis and glyceroneogenesis [18]. PEPCK activity can be controlled at the transcriptional level in response to nutritional conditions. A recent study found that genes involved in the gluconeogenic pathway in response to energy expenditure and storage, including PEPCK,

Abbreviations: Jazf1, Juxtaposed with another zinc finger protein 1; TR4, testicular orphan nuclear receptor 4.

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exhibit a rhythmicity in their mRNA levels and their corresponding regulatory hormones and/or transcriptional regulators [19].

Jazf1, a protein with unknown function, is a basic protein with a molecular mass of 27.1 kDa that contains three putative zinc finger motifs [20]. Variants of Jazf1 are associated with an increased risk of prostate cancer, an increased risk of diabetes, and an increased height [21]. This gene encodes a nuclear protein with three C2H2-type zinc fingers and functions as a transcriptional repressor. Chromosomal aberrations involving this gene are associated with endometrial stromal tumors. Alternatively spliced variants that encode different protein isoforms have been described; however, not all variants have been fully characterized. A recent study indicated that Jazf1 acts as a strong repressor of DR1-dependent transcriptional activation by the TR4 [22]. Jazf1 interacts specifically with the ligand-binding domain of TR4 and functions as a TR4-selective cofactor that may play an important role in mediating transcriptional repression by TR4 [22].

In this study, we focused on the role of Jazf1 in lipid metabolism in a Jazf1 over-expression transgenic mouse model. Specifically, we generated TG mice to elucidate the function of the Jazf1 gene in lipid metabolism.

2. Materials and methods

2.1. Generation of transgenic mice and experimental protocol

The Jazf1 ORF, 13.5-day post-coitus embryo cDNA, was subcloned into the pEGFP-N1 vector (Clontech). The plasmid DNA for microinjection was purified using a Plasmid Midi Kit (Qiagen). The expression cassette was prepared by digesting the recombinant vector DNA with DraIII. Fertilized one-cell embryos were obtained from BDF1 females. A DNA cassette was purified by dialysis in Tris/EDTA (TE, pH 8.0) and microinjected into the pronuclei of fertilized embryos. Injected embryos were cultured for 20 h before transference into pseudopregnant female ICR mice. Animals were raised and kept under specific pathogen-free conditions. Genomic DNA was extracted from offspring tail biopsies, and the Jazf1 transgene was identified by PCR followed by 1% agarose gel electrophoresis. All animal experiments were carried out in accordance with the guidelines for animal experimentation and under permission from the Kyungpook National University, Animal Use and Care Committee. Jazf1-overexpression transgenic mice (TG) [23] and wild-type littermate mice (WT) were housed in laboratory cages at a temperature of 25 °C and a humidity of 50% under a 12 h dark/light cycle (lights on at 7 a.m.). For diet-induced obesity, male mice were fed normal diet (ND, 10% fat, Research Diets Inc.) and high fat diet (HFD, 60% fat, Research Diets Inc.) starting at 8 weeks.

The body weight and food intake were monitored weekly. In addition, fasting glucose was determined in blood collected from the tail vein of male mice once per week for 15 weeks after a 16 h fasting using a glucometer (ACCU-CHEK, Roche) [24].

2.2. Reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA was isolated from liver and epididymal WAT (eWAT) of WT and TG mice using Trizol reagent (MRC) according to the manufacturer's instructions. RT-PCR was performed in a total volume of 50 μl containing 2 μl of first-strand cDNA (Enzynomics).

2.3. Real-time PCR

Liver and eWAT were collected from WT and TG mice and analyzed for lipid metabolism-related gene expression by real-time PCR (Table 1). Real-time PCR was then performed using the SYBR premix Ex Taq (TliRnaseHPlus; TAKARA). To examine the relative mRNA expression of lipid metabolism and lipolysis and lipogenesis-related genes, real-time PCR was performed using the Step One Plus Real-Time PCR System (Applied Biosystems).

2.4. Western blot analysis

Protein expression levels were determined by Western blotting using specific antibodies, JAZF1 (ab80329), TR4 (ab10930) and PEPCK (ab40843), against the respective proteins. Protein quantification was performed using the DaVinci software.

2.5. Glucose tolerance test (GTT) and insulin tolerance test (ITT)

Mice were fasted overnight (16 h) before the test after fed for 15 weeks. Glucose was then injected intraperitoneally (1 g/kg; Sigma) and blood samples were collected before injection and at 0, 15, 30, 60, 75, 90, 105 and 120 min after the injection. Mice were then injected with insulin (0.75 U/kg) in ~0.1 ml 0.9% NaCl intraperitoneally, and a drop of blood (5 μl) was taken from the cut tail vein before the injection of insulin and at 0, 15, 30, 60, 75, 90, 105 and 120 min after injection. The blood glucose levels of all samples were measured using a glucometer.

2.6. Histological analysis

For histological examination of the liver and epididymal WAT (eWAT), mice were euthanized when they reached 4 months of age. The livers and eWAT from the WT and TG mice were then fixed overnight in 10% buffered formalin, embedded in paraffin wax, and sectioned at 5 um. Sagittal sections were subsequently stained with hematoxylin and eosin using standard histology techniques.

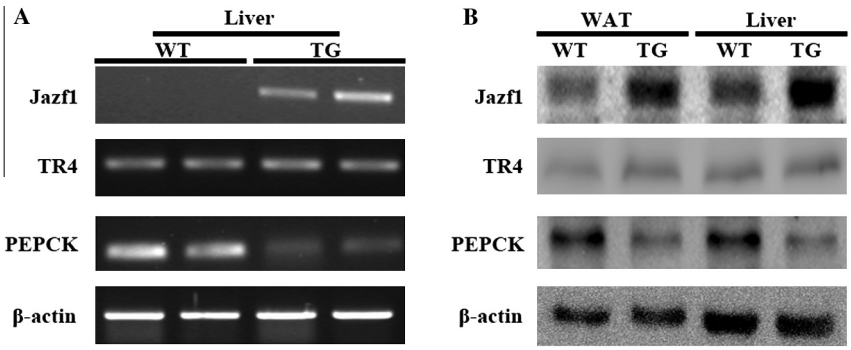

Fig. 1. Jazf1 inhibited PEPCK activity via TR4. (A) Expression levels of TR4 and PEPCK in liver from WT and TG mice were measured by PCR and normalized to β-actin expression. (B) Protein expression levels of Jazf1, TR4 and PEPCK in eWAT and liver from WT and TG mice were measured by Western blot.

The liver tissue sections were collected and covered with O.C.T (optimal cutting temperature) gel and kept at −80 °C. Frozen sections ofmouse liver tissue (⩽10 μm) were fixed in 3.7% formaldehyde for 10 min and then rinsed with PBS and 60% isopropanol, after which they were stained with 0.5% Oil Red O in 60% 2-propanol for 15 min. After washing with distilled water, the nuclei were stained with hematoxylin for 2 min and rinsed thoroughly with distilled water.

2.7. Plasma biochemical analysis

Blood samples were taken by periorbital vein for biochemical analysis. Triglyceride, total cholesterol, LDL, HDL levels in plasma were measured using a commercially kits (abcam).

2.8. Statistical analyses

All results are expressed as the means ± SEM from at least three independent experiments. Groups were compared by ANOVA, with a $p < 0.05$ being taken to indicate statistical significance.

3. Results

3.1. Jazf1 inhibited PEPCK activity via TR4

Jazf1, TR4 and PEPCK are mainly expressed in metabolic tissue, such as liver and adipose tissue. Therefore, the mRNA expression levels and protein expression levels of these genes were compared in liver and adipose tissue from TG and WT mice. PCR was conducted to examine mRNA expression levels of Jazf1, TR4 and PEPCK in liver from WT and TG mice. The results of PCR revealed no difference in TR4 mRNA expression in liver from WT and TG. This repression of TR4 was probably made by the binding of Jazf1 and TR4. The theory is confirmed by low levels of mRNA found in PEPCK, which is downstream gene of TR4 (Fig. 1A). TR4 was reported to regulate PEPCK in a previous study [13]; therefore, Western blotting was carried out to quantitatively examine protein expression levels of Jazf1, TR4 and PEPCK in liver and WAT from WT and TG mice. The results revealed no difference in TR4 protein expression in liver and WAT between WT and TG mice, but PEPCK protein

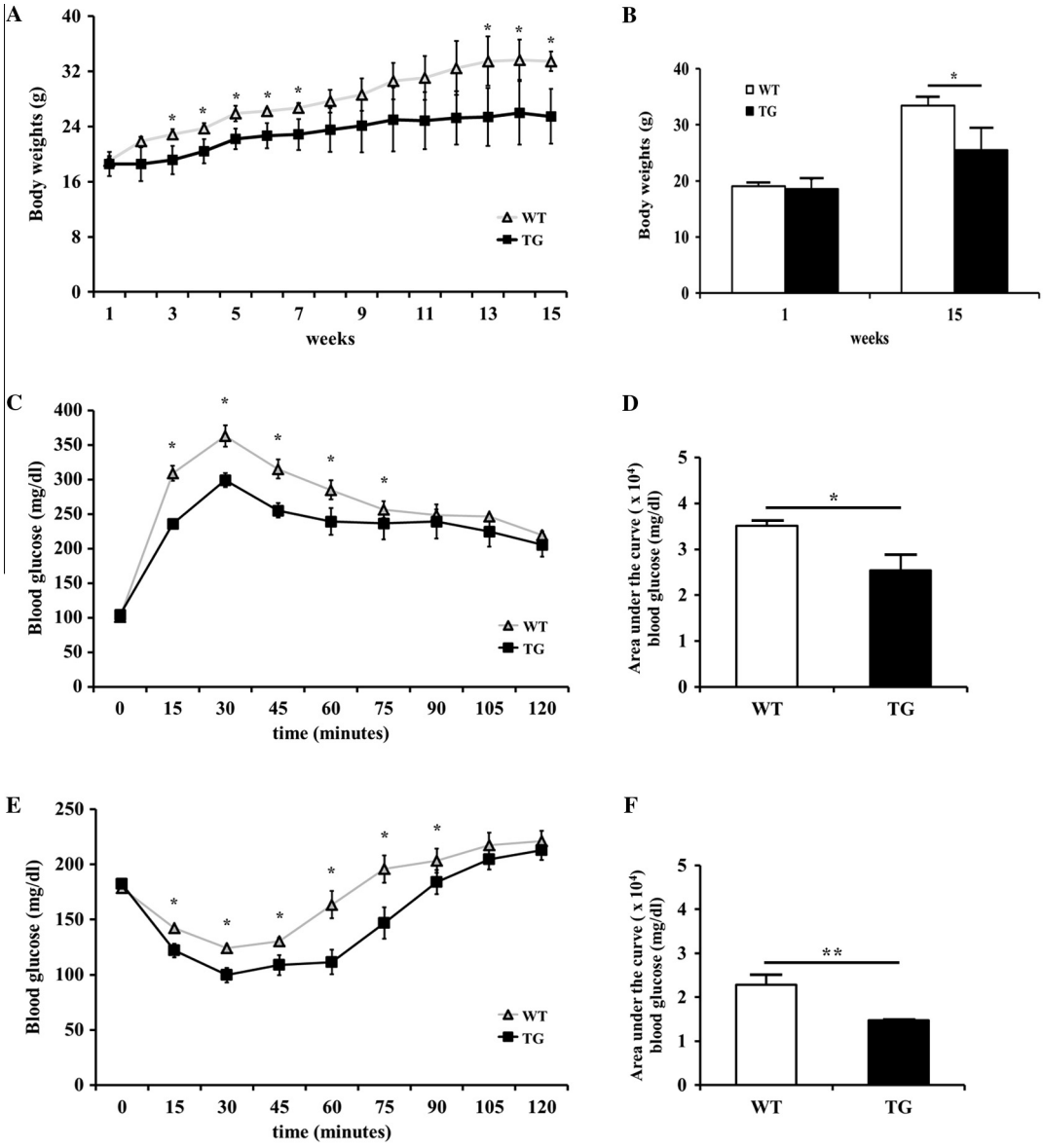

Fig. 2. Body weight, blood glucose and insulin sensitivity were measured in wild type and transgenic mice. (A and B) Eight week old male mice were fed ND and HFD for 15 weeks and the body weight and food intake were monitored weekly. Mice were fasted overnight before the test. (C and D) Blood samples were taken after the I.P. injection of glucose (1 g/kg) and (E and F) insulin after fed for 15 weeks (0.75 U/kg). $^{*}p < 0.05$.

expression was shown to be decreased in WT mice (Fig. 1B). Jazf1, known as a TR4 binding protein, did not regulate the mRNA and protein levels of TR4. Instead, the mRNA and protein levels of PEPCK, the downstream gene of TR4, were expressed on a low level. Therefore, Jazf1 does not inhibit mRNA and protein expression of TR4, but does inhibit mRNA and protein expression of PEPCK through inhibition of TR4 function.

3.2. Body weight, blood glucose and insulin sensitivity in WT and TG during 60% fat diet

Obesity is a risk factor for the development of insulin resistance, a physiological condition in which cells fail to respond to the normal actions of the hormone insulin, [7]; therefore, we investigated whether these effects were associated with Jazf1. The body weight of TG mice was significantly lower than that of WT mice for 15 weeks (Fig. 2A). In particular, body weight gain of TG mice was more decreased 7 g than WT in 15 weeks (Fig. 2B). Blood glucose level is an indicator of insulin resistance and obesity caused by diet; accordingly, we measured the blood glucose after providing mice with the HFD. The blood glucose levels of TG mice were generally lower than those of the WT mice (data not shown). The result revealed no significant difference in food intake between groups (data not shown), indicating that differences in body weight and blood glucose were not related to food intake.

The symptoms of insulin resistance include increased blood glucose levels and reduced glucose uptake in peripheral tissue. Blood glucose levels of TG mice were significantly lower than those of WT mice after intraperitoneal injection with glucose (Fig. 2C). Compared to the blood glucose levels indicated by the AUC, TG mice were significantly lower which is statistically meaningful (Fig. 2D). Moreover, the blood glucose levels of TG mice were significantly lower than those of WT mice (Fig. 2E). Significantly a lower glucose level indicated by the AUC of TG mice is also shown in ITT (Fig. 2F).

Overall, these findings indicated that Jazf1 reduced weight gain due to a high fat diet and insulin sensitivity of TG mice was improved relative to that of WT mice.

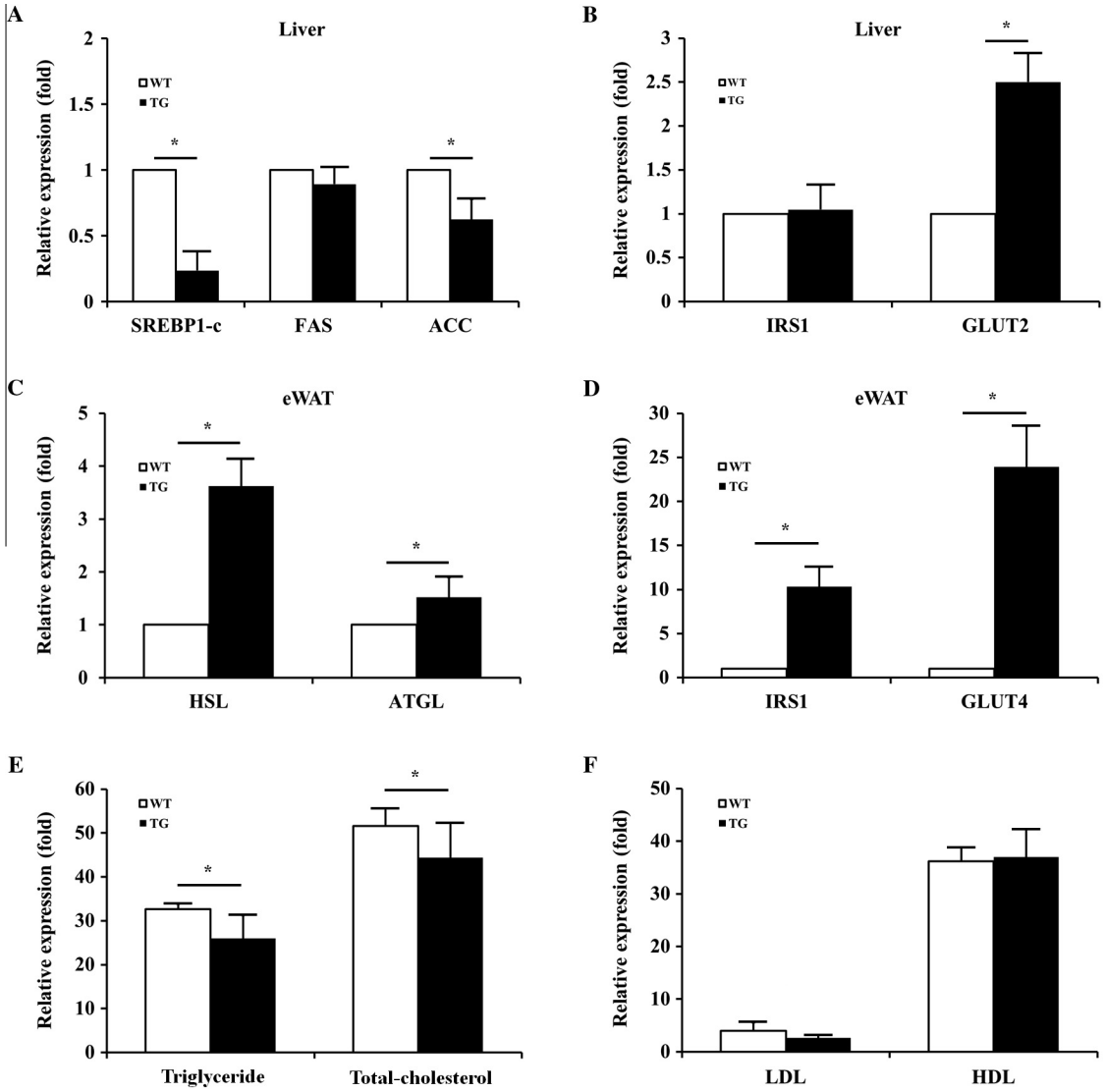

Fig. 3. Effect of JAZF1 on expression of metabolism indicator. Total RNA was isolated from livers and eWAT in each group and subjected to qRT-PCR to determine the effects of Jazf1 on the expression of several genes normalized to β-actin levels. (A) The mRNA expression of important genes involved in lipid and (B) glucose metabolism were measured in liver. (C) The mRNA expression of important genes involved in lipid and (D) glucose metabolism were measured in eWAT. (E and F) Expression of metabolism indicator in blood, $^{*}p < 0.05$, $^{**}p < 0.01$.

3.3. Expression of metabolism indicator in WT and TG

To investigate whether Jazf1 regulates lipid and glucose metabolism in the peripheral tissue, the mRNA expression of important genes involved in lipid and glucose metabolism were measured. To accomplish this, real-time PCR was used to examine the mRNA expression of various genes. As shown in Fig. 3A, mRNA levels for ACC and SREBP1-c were decreased in the liver. The FAS levels were not significantly different from the basal levels (Fig. 3A); however, GLUT2 transcription was significantly higher than that of control levels (Fig. 3B). Lipogenesis related genes were expressed at lower levels in TG than WT mice, while glucose metabolism related genes of TG mice were higher than those of WT mice in the liver. These data indicate that Jazf1 decreased lipogenesis and increased glucose metabolism in the liver.

To explore the molecular mechanisms involved in lipolysis and glucose metabolism in eWAT, real-time PCR was conducted to measure the mRNA expression of HSL, ATGL, IRS1 and GLUT4. As shown in Fig. 3C, the mRNA levels of HSL and ATGL, which are transcription factors involved in lipolysis, were increased in eWAT from TG mice (Fig. 3C). In addition, the expression of IRS1, GLUT1 and GLUT4 mRNA was significantly higher in TG than WT mice (Fig. 3D). Lipolysis related genes of TG mice were lower than those of WT mice, while glucose metabolism related genes of TG mice were higher than those of WT mice in eWAT. These data indicate that Jazf1 improved lipolysis and glucose metabolism in eWAT (Fig. 3C and D).

Blood analysis focused on major lipid metabolic predictive factors, sucg as triglyceride, cholesterol, LDL and HDL showed that the lipid level of Tg mice were confirmed in the overall metabolic process. Triglyceride and cholesterol in blood of TG mice were more decrease than those of WT mice (Fig. 3E). LDL and HDL levels were not significantly different between WT and TG mice (Fig. 3F).

3.4. Decreased of lipid accumulation in liver and WAT

We confirmed histological changes in the liver and eWAT, which are metabolic tissue. According to H&E staining, lipid droplets and adipocytes in the liver of TG mice were smaller than those of WT mice, demonstrating that lipid accumulation was decreased in the liver and eWAT of TG (Fig. 4A). The representative images of Oil Red O staining demonstrated that overexpression of Jazf1 resulted in decreased lipid accumulation in the liver. Staining showed that liver tissue over-expressing Jazf1 had a lower intracellular lipid content than that of WT mice (Fig. 4B). These results suggest lipid accumulation of Jazf1 in liver tissue.

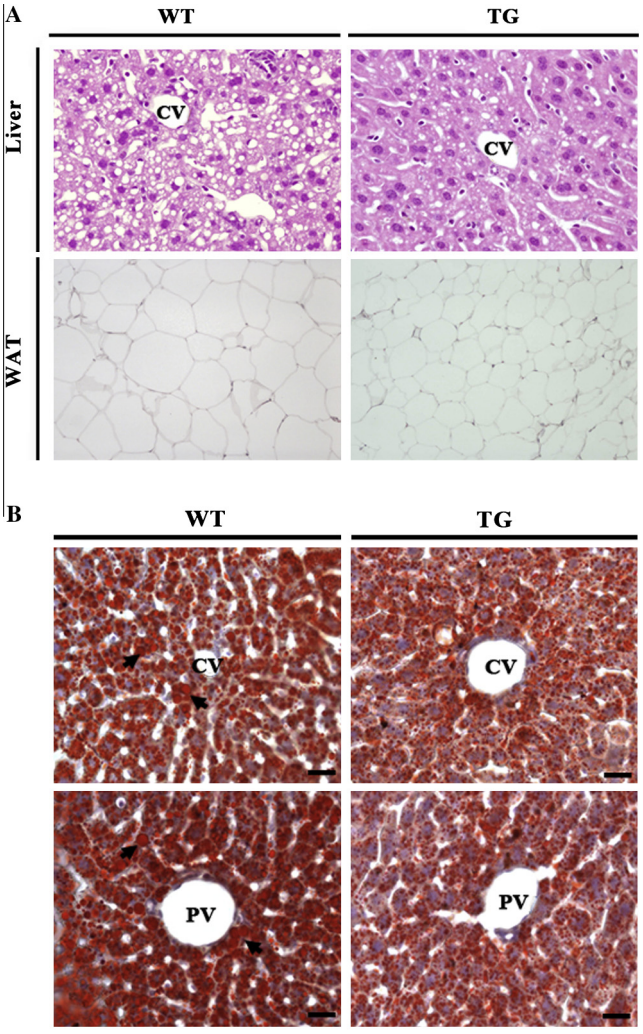

Fig. 4. Lipid accumulation and adipocyte overexpression of Jazf1 in mice. (A) H&E staining in liver and eWAT from WT and TG mice. (B) Liver was fixed and stained with Oil Red O, after which the stained lipids were extracted and measured.

4. Discussion

This study demonstrated that Jazf1 regulated activation of PEPCK and decreased lipid accumulation and lipid droplet size. In a previous study, Jazf1-overexpressing transgenic mice (TG) that express mouse Jazf1 cDNA under the control of the CMV promoter were generated [2]. Moreover, a recent study showed that overexpression of Jazf1 in adipocytes and hepatocytes led to reduced lipogenesis and increased lipolysis [25]. In addition, genome-wide association studies have verified associations between Jazf1 and diabetes mellitus and prostate cancer [26]. However, little is known about the function of this gene in regulating metabolism. Therefore, we investigated changes of lipid metabolism in mice based on these previous *in vitro* studies. A linkage and association analysis found Jazf1 region affecting human height [27]. In addition, genome wide association studies have identified that there is strong statistical evidence that Jazf1 is associated with diabetes [28].

Jazf1 was expressed in almost all the tissues of mice [23], with the highest levels detected in testes and adipose tissues, which are often connected to lipid metabolism.

Jazf1 interacts specifically with the ligand-binding domain of TR4, subclass of orphan nuclear receptors [15,29] and acts as a strong repressor of DR1-dependent transcriptional activation by TR4 [30]. The results of Western blot analysis showed that TR4 expression did not differ at the protein level, but that the decrease in protein expression of PEPCK in TG mice was less than in WT mice (Fig. 1). As a result, Jazf1 does not inhibit mRNA and protein expression of TR4, but Jazf1 inhibits the mRNA and protein expression of PEPCK through inhibition of TR4 function. The body weight of TG mice was significantly lower than that of WT mice. In addition, Jazf1 reduced weight gain and improved insulin sensitivity in mice provided with the high fat diet (Fig. 2).

To investigate whether Jazf1 regulates lipid and glucose metabolism in the peripheral tissue, Real-time PCR was conducted to examine mRNA expression of SREBP1-c, FAS, ACC, HSL, ATGL, IRS1, GLUT2 and GLUT4. SREBP1-c, FAS and ACC are transcription factor that plays important roles in the controls of fatty acid metabolism and adipogenesis [31] (see Table 1).

The mRNA levels of ACC and SREBP1-c of TG were decreased, while those of GLUT2 of TG were significantly increased in the liver (Fig. 3). To explore the molecular mechanisms involved in lipolysis

Table 1
Real-time PCR primers sequences.

Gene	Primer sequence
SREBP-1c	Forward GAT CAA AGA GGA GCC AGT GC
	Reverse TAG ATG GTG GCT GCT GAG TG
FAS	Forward TGG TGG GTT TGG TGA ATT GTC
	Reverse GCT TGT CCT GCT CTA ACT GGA AGT
ACC	Forward ATG TCC GCA CTG ACT GTA ACC A
	Reverse TGC TCC GCA CAG ATT CTT CA
HSL	Forward AAG ACC ACA TCG CCC ACA
	Reverse CTG AAG GCT CTG AGT TGC T
ATGL	Forward TGC TAC CCG TCT GCT CTT TC
	Reverse GAC CTG ATG ACC ACC CTT TC
IRS1	Forward CGC CTG GAG TAT TAT GAG AAC GA
	Reverse GTC AGC CCG CTT GTT GAT GT
GLUT2	Forward GGC TAA TTT CAG GAC TGG TT
	Reverse TTT CTT TGC CCT GAC TTC CT
GLUT4	Forward CCC ACA AGG CAC CCT CAC TA
	Reverse CCT TTT CCT TCC CAA CCA TTG

and glucose metabolism in eWAT, mRNA levels of HSL, ATGL IRS1 and GLUT4 of TG were increased in eWAT (Fig. 3). Additionally, triglyceride and cholesterol levels in blood were decreased in TG mice. These data indicate that Jazf1 increased lipogenesis in the liver, decreased lipolysis in eWAT and increased glucose metabolism in peripheral tissue.

Lipid accumulation occurs in the liver and WAT. Histological staining showed that Jazf1 had a lower intra-cellular lipid content than the WT mice (Fig. 4), which suggests that Jazf1 decreased lipid accumulation in peripheral tissue.

In conclusion, we confirmed that overexpression of Jazf1 *in vivo* led to reduced lipogenesis via reduced expression of SREBP1-c and ACC and increased lipolysis through upregulation of HSL and ATGL. Because it decreases the maturation of lipid droplets and fat storage, reduces lipid synthesis, and increases lipolysis, we speculate that Jazf1 is a potential target for regulating metabolism and obesity.

Acknowledgments

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References

[1] J.D. Horton, J.L. Goldstein, M.S. Brown, SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver, J. Clin. Invest. 109 (2002) 1125–1131.
[2] P. Ferre, F. Foufelle, Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c, Diabetes Obes. Metab. 12 (Suppl. 2) (2010) 83–92.
[3] S. Kersten, Mechanisms of nutritional and hormonal regulation of lipogenesis, EMBO Rep. 2 (2001) 282–286.
[4] D. Cheng, C.H. Chu, L. Chen, J.N. Feder, G.A. Mintier, et al., Expression, purification, and characterization of human and rat acetyl coenzyme A carboxylase (ACC) isozymes, Protein Expr. Purif. 51 (2007) 11–21.
[5] F.B. Kraemer, W.J. Shen, Hormone-sensitive lipase: control of intracellular tri-(di-)acylglycerol and cholesteryl ester hydrolysis, J. Lipid Res. 43 (2002) 1585–1594.
[6] G. Wolkart, A. Schrammel, K. Dorffel, G. Haemmerle, R. Zechner, et al., Cardiac dysfunction in adipose triglyceride lipase deficiency: treatment with a PPARalpha agonist, Br. J. Pharmacol. 165 (2012) 380–389.
[7] S. Guerra, F. Boscari, A. Avogaro, B. Di Camillo, G. Sparacino, et al., Hemodynamics assessed via approximate entropy analysis of impedance cardiography time series: effect of metabolic syndrome, Am. J. Physiol. Heart Circ. Physiol. 301 (2011) H592–H598.
[8] B.B. Kahn, J.S. Flier, Obesity and insulin resistance, J. Clin. Invest. 106 (2000) 473–481.
[9] M. Barton, O. Baretella, M.R. Meyer, Obesity and risk of vascular disease: importance of endothelium-dependent vasoconstriction, Br. J. Pharmacol. 165 (2012) 591–602.
[10] L.H. Opie, Metabolic syndrome, Circulation 115 (2007) e32–e35.
[11] Y. Zhang, Y.T. Chen, S. Xie, L. Wang, Y.F. Lee, et al., Loss of testicular orphan receptor 4 impairs normal myelination in mouse forebrain, Mol. Endocrinol. 21 (2007) 908–920.
[12] S. Xie, Y.F. Lee, E. Kim, L.M. Chen, J. Ni, et al., TR4 nuclear receptor functions as a fatty acid sensor to modulate CD36 expression and foam cell formation, Proc. Natl. Acad. Sci. USA 106 (2009) 13353–13358.
[13] N.C. Liu, W.J. Lin, E. Kim, L.L. Collins, H.Y. Lin, et al., Loss of TR4 orphan nuclear receptor reduces phosphoenolpyruvate carboxykinase-mediated gluconeogenesis, Diabetes 56 (2007) 2901–2909.
[14] N.C. Liu, W.J. Lin, I.C. Yu, H.Y. Lin, S. Liu, et al., Activation of TR4 orphan nuclear receptor gene promoter by cAMP/PKA and C/EBP signaling, Endocrine 36 (2009) 211–217.
[15] C. Chang, S.L. Da Silva, R. Ideta, Y. Lee, S. Yeh, et al., Human and rat TR4 orphan receptors specify a subclass of the steroid receptor superfamily, Proc. Natl. Acad. Sci. USA 91 (1994) 6040–6044.
[16] C. Chang, J. Kokontis, L. Acakpo-Satchivi, S. Liao, H. Takeda, et al., Molecular cloning of new human TR2 receptors: a class of steroid receptor with multiple ligand-binding domains, Biochem. Biophys. Res. Commun. 165 (1989) 735–741.
[17] T. Hirose, W. Fujimoto, T. Tamaai, K.H. Kim, H. Matsuura, et al., TAK1: molecular cloning and characterization of a new member of the nuclear receptor superfamily, Mol. Endocrinol. 8 (1994) 1667–1680.
[18] R.W. Hanson, L. Reshef, Regulation of phosphoenolpyruvate carboxykinase (GTP) gene expression, Annu. Rev. Biochem. 66 (1997) 581–611.
[19] R.D. Rudic, P. McNamara, D. Reilly, T. Grosser, A.M. Curtis, et al., Bioinformatic analysis of circadian gene oscillation in mouse aorta, Circulation 112 (2005) 2716–2724.
[20] M.D. Adams, M.B. Soares, A.R. Kerlavage, C. Fields, J.C. Venter, Rapid cDNA sequencing (expressed sequence tags) from a directionally cloned human infant brain cDNA library, Nat. Genet. 4 (1993) 373–380.
[21] T.A. Manolio, Genomewide association studies and assessment of the risk of disease, N. Engl. J. Med. 363 (2010) 166–176.
[22] T. Nakajima, S. Fujino, G. Nakanishi, Y.S. Kim, A.M. Jetten, TIP27: a novel repressor of the nuclear orphan receptor TAK1/TR4, Nucleic Acids Res. 32 (2004) 4194–4204.
[23] K.B. Bae, M.O. Kim, D.H. Yu, M.J. Shin, H.J. Kim, et al., Overexpression of Jazf1 induces cardiac malformation through the upregulation of pro-apoptotic genes in mice, Transgenic Res. 20 (2011) 1019–1031.
[24] L. Yang, P. Huang, F. Li, L. Zhao, Y. Zhang, et al., C-Jun amino-terminal kinase-1 mediates glucose-responsive upregulation of the RNA editing enzyme ADAR2 in pancreatic beta-cells, PLoS One 7 (2012) e48611.
[25] L. Li, Y. Yang, G. Yang, C. Lu, M. Yang, et al., The role of JAZF1 on lipid metabolism and related genes in vitro, Metabolism 60 (2011) 523–530.
[26] G. Thomas, K.B. Jacobs, M. Yeager, P. Kraft, S. Wacholder, et al., Multiple loci identified in a genome-wide association study of prostate cancer, Nat. Genet. 40 (2008) 310–315.
[27] A. Johansson, F. Marroni, C. Hayward, C.S. Franklin, A.V. Kirichenko, et al., Common variants in the JAZF1 gene associated with height identified by linkage and genome-wide association analysis, Hum. Mol. Genet. 18 (2009) 373–380.
[28] N. Grarup, G. Andersen, N.T. Krarup, A. Albrechtsen, O. Schmitz, et al., Association testing of novel type 2 diabetes risk alleles in the JAZF1, CDC123/CAMK1D, TSPAN8, THADA, ADAMTS9, and NOTCH2 loci with insulin release, insulin sensitivity, and obesity in a population-based sample of 4,516 glucose-tolerant middle-aged Danes, Diabetes 57 (2008) 2534–2540.
[29] T. Hirose, R. Apfel, M. Pfahl, A.M. Jetten, The orphan receptor TAK1 acts as a repressor of RAR-, RXR- and T3R-mediated signaling pathways, Biochem. Biophys. Res. Commun. 211 (1995) 83–91.
[30] G.S. Hotamisligil, N.S. Shargill, B.M. Spiegelman, Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance, Science 259 (1993) 87–91.
[31] A.K. Stoeckman, H.C. Towle, The role of SREBP-1c in nutritional regulation of lipogenic enzyme gene expression, J. Biol. Chem. 277 (2002) 27029–27035.