Reduced Adiposity and Liver Steatosis by Stearoyl-CoA Desaturase Deficiency Are Independent of Peroxisome Proliferator-activated Receptor-α*

Makoto Miyazaki‡, Agnieszka Dobrzyn‡, Harini Sampaithi, Seong-Ho Lee‡, Weng Chi Man‡, Kiki Chu‡, Jeffrey M. Peters†, Frank J. Gonzalez‡, and James M. Ntambi***

From the Departments of ‡Biochemistry and §Nutritional Sciences, University of Wisconsin, Madison, Wisconsin 53706, the *Department of Veterinary Science and Center for Molecular Toxicology and Carcinogenesis, The Pennsylvania State University, University Park, Pennsylvania 16802, and †Laboratory of Metabolism, NCI, National Institutes of Health, Bethesda, Maryland 20892

Stearoyl-CoA desaturase catalyzes the rate-limiting step in the biosynthesis of monounsaturated fatty acids, which are required for normal rates of synthesis of triglycerides, cholesterol esters, and phospholipids. Mice with a targeted disruption of the stearoyl-CoA desaturase 1 (SCD1) isoform are protected against diet and leptin deficiency-induced adiposity, have increased energy expenditure, and have up-regulated expression of hepatic genes encoding enzymes of fatty acid β-oxidation. Because peroxisome proliferator-activated receptor-α (PPARα) is a key transcription factor that induces the transcription of fatty acid β-oxidation and thermogenic genes, we hypothesized that the increased fatty acid oxidation observed in SCD1 deficiency is dependent on activation of the PPARα pathway. Here we show that mice nullizygous for SCD1 and PPARα are still protected against adiposity, have increased energy expenditure, and maintain high expression of PPARα target genes in the liver and brown adipose tissue. The SCD1 deficiency rescued hepatic steatosis of the PPARα−/− mice. The SCD1 mutation increased the phosphorylation of both AMP-activated protein kinase and acetyl-CoA carboxylase, thereby increasing CPT activity and stimulating the oxidation of liver palmitoyl-CoA in the PPARα null mice. The findings indicate that the reduced adiposity, reduced liver steatosis, increased energy expenditure, and increased expression of PPARα target genes associated with SCD1 deficiency are independent of activation of the PPARα pathway.

Stearoyl-CoA desaturase (SCD)† catalyzes the rate-limiting step in the biosynthesis of monounsaturated fatty acid from saturated fatty acids. SCD, in conjunction with the cofactors NADH, cytochrome b₅ reductase, and cytochrome b₅₆, introduces a single double bond into its substrates, palmitic acid (16:0) and stearic acid (18:0), to generate the products, palmitoleic (16:1) and oleic acid (18:1). These products are the most abundant fatty acids found in triglycerides, cholesterol esters, and phospholipids. Four mouse isoforms of SCD (SCD1, SCD2, SCD3, and SCD4) (1–4) and two human isoforms have been characterized (5, 6). The mouse SCD1 isoform is the best studied and is highly regulated by several dietary and hormonal factors including insulin, leptin, glucose, fructose, cholesterol, and polyunsaturated fatty acids (7, 8). We recently found that mice with a disruption in the SCD1 gene have increased energy expenditure, reduced body adiposity, increased insulin sensitivity, and are resistant to diet-induced obesity (9, 10). The SCD1−/− mice also have reduced hepatic triglycerides and cholesterol esters and are resistant to the generation of liver steatosis (11–14). Associated with the reduced body fat in SCD1-deficient mice, the expression of several genes encoding enzymes of lipid synthesis including fatty-acid synthase and glycerol 3-phosphate acyltransferase are down-regulated (9).

Peroxisome proliferator-activated receptors (PPARs) are members of the superfamily of nuclear receptors (15) that consist of three distinct isoforms, α, β/δ, and γ, with different ligand specificities and tissue distribution. PPARs are primarily expressed in brown adipose tissue and the liver and, to a lesser extent, in kidneys, skeletal muscle, and heart (16), whereas PPARγ is abundant in adipose tissue functioning as the key transcription factor of adipocyte differentiation (17, 18). PPARα null (19), PPARβ/δ null (20, 21), and conditional PPARγ null mice (22–27) have been generated, and studies with these mice have demonstrated that PPARα controls the expression of genes involved in mitochondrial and peroxisomal β-oxidation, fatty acid uptake, or binding and lipoprotein assembly and transport while PPARβ/δ controls genes of fatty acid oxidation in muscle and brown adipose tissue (28, 29). Using adipose tissue-specific PPARδ−/− transgenic mice, it was demonstrated that PPARδ activation in adipose tissue leads to enhanced fatty acid oxidation, improved lipid profiles, reduced adiposity, and resistance to both diet-induced obesity and genetically predisposed obesity (28, 29). Additionally, the disruption of PPARγ in the liver has been shown to improve the fatty liver phenotype of leptin-null mice, suggesting that PPARγ can also regulate lipid metabolism in the liver in addition to its known role in adipogenesis (26). One of the physiological stimuli of PPARα is the fasting state, and it is hypothesized that the free fatty acids

Received for publication, May 12, 2004
Published, JBC Papers in Press, June 4, 2004, DOI 10.1074/jbc.M405327200
that are delivered from adipose tissue to the liver act as ligands and activate the receptor (30). The fatty acids are also oxidized in conjunction with increased synthesis of ketone bodies. Several in vivo studies have also shown that synthetic PPARα ligands such as fibrates markedly induce the transcription of hepatic β-oxidation genes and BAT-thermogenic genes including UCP1, UCP2, and UCP3, (31–36). The increased expression of thermogenic genes is negatively correlated with obesity in rodents (37–39).

Despite the great expansion of our understanding of the function of PPARα, it remains unclear when and how the PPAR signaling pathways are triggered in an intact organism and how they specifically affect lipid and carbohydrate metabolism. Recently, we presented evidence that SCD1 deficiency protects mice against diet and leptin deficiency-induced adiposity, reduces hepatic triglyceride concentration, and induces the expression of PPARα target genes in the liver. We hypothesized that the elimination of the SCD1 gene in mice generates a signal (e.g. a fatty acid or fatty acid derivative) that activates the PPARα pathway, because fatty acids are known to activate PPARs (40–42). To test this possibility, we generated mice that are deficient in both SCD1 and PPARα (SCD1+/−/PPARα+/−). These mice would be expected to show reduced expression of PPARα target genes and reduced energy expenditure as well as accumulation of hepatic triglyceride. We report here that the expression of PPARα target genes in the liver and brown adipose tissue remain elevated in the SCD1+/−/PPARα−/− mice. The reduced adiposity and increased energy expenditure due to SCD1 deficiency were not ameliorated. The SCD deficiency rescued hepatic steatosis of the PPARα−/− mice. The rate of fatty acid oxidation and activity of CPT-1 as well as the phosphorylation of AMPK and ACC were higher in the SCD1+/−/PPARα−/− mice relative to PPARα null controls. The levels of malonyl-CoA were lower in the SCD1+/−/PPARα−/− mice. Taken together, these data demonstrate that the increased fatty acid β-oxidation and reduced adiposity due to SCD1 deficiency are independent of the PPARα pathway.

EXPERIMENTAL PROCEDURES

The generation of the SCD1+/− mice in 129S6/SvEv background and PPARα−/− mice in 129/SvJae was described previously (19, 43, 44). To obtain PPARα−/− on a background of SCD1 deficiency, SCD1+/− mice were crossed with PPARα−/− and the F1 progeny of these matings (SCD1+/−/PPARα−/−) were then crossed to obtain mice that had both mutations of PPARα and SCD alleles (SCD1−/−/PPARα−/−). Animals were housed individually in a pathogen-free facility operating at room temperature in 12-h light/dark cycles. All of the animals were allowed free access to water and were fed ad libitum except during food restriction procedures. Animals were fed a high fat diet (21 w/w % fat, Harlan Teklad Madison, WI) at 8 weeks of age. Food consumption was monitored daily, and body weight was recorded every week. Animals were sacrificed when 16-weeks old. All of the studies were approved by the animal care research committee of the University of Wisconsin-Madison.

Materials—Radioactive [32P]dCTP (3000 Ci/mmol) was obtained from DuPont (Wilmington, DE). Thin-layer chromatography plates (TLC Silica Gel G60) were from Merck (Darmstadt, Germany). 1-[3H]Carnitine and [14C]palmitoyl-CoA were purchased from American Radiolabeled Chemicals (St. Louis, MO). Anti-phospho-ACC antibody was obtained from Upstate Biotechnology (Waltham, MA). Anti-ACC1, ACC2, and CPT-1 antibodies were from Alpha Diagnostic International (San Antonio, TX). Other chemicals were purchased from Sigma or Fisher Scientific.

Isolation and Analysis of RNA—Total RNA was extracted from the livers of SCD1−/−, PPARα−/−, and SCD1−/−/PPARα−/− mice as well as the appropriate wild-type controls using TRIzol reagent (Invitrogen). For Northern blot analysis, fifteen micrograms of total RNA were separated by 1.0% agarose/2.2M formaldehyde gel electrophoresis and transferred onto a nylon membrane. The membranes were hybridized with [32P]-labeled cDNA probes for AOX, VLCAD, CPT-1, UCP-1, UCP-2, and UCP-3 as previously described (9, 45). The UCP-1 probe was kindly provided by Dr. Ezaki (National Institute of Health and Nutrition, Tokyo, Japan).

Preparation of Mitochondria and Measurement of Mitochondrial Fatty Acid Oxidation—Mitochondria were isolated essentially as described by Vance (46). The mixture used to measure mitochondrial fatty acid oxidation contained in a final volume of 2.5 ml: 2 ml of modified Krebs-Henseleit buffer, pH 7.4, 0.2 mM [14C]palmitoyl-CoA bound to 7.2 mg/ml bovine serum albumin, 4 mM ATP, 0.5 mM t-carnitine, 0.05 mM coenzyme A, 2 mM dithiothreitol, and 0.5 mM of suspended mitochondria (5 mg of protein/ml). Palmitoyl-CoA oxidation was determined in the presence and absence of 2 mM KCN, and the cyanide-sensitive part of the oxidation was taken as mitochondrial oxidation (47). Labeled CO2 was trapped in 10 mM KOH. An aliquot of the neutralized extracts was analyzed for the [14C] content of the ketone bodies (48), and another aliquot was adjusted to pH 4 with 3 M acetate buffer and extracted twice with petroleum ether to remove traces of [14C]palmitoyl-CoA and the aqueous phase was then counted (acid-soluble labeled oxidation products) (48).

Measurement of CPT-1 Activity—The livers from wild-type, SCD1−/−, PPARα−/−, SCD1−/−/PPARα−/− mice were snap-frozen. CPT-1 activity was assayed in isolated mitochondria as described by Bremer (49).

Immunoblot Analysis—Immunoblot analyses of phosphorylated AMPK and ACC as well as protein levels of α1 and α2 AMPK and ACC1 and ACC2 were carried out as described previously (50).

Blood and Tissue Sampling—Mice were fasted for 16 h and sacrificed by CO2 asphyxiation and/or cervical dislocation. Blood was collected aseptically by direct cardiac puncture and centrifuged (15,000 × g, 5 min, 4 °C) to collect plasma. Plasma cholesterol and triglyceride levels were measured by using commercial kits (Roche Applied Science). Plasma fatty acids and liver triglycerides were measured by gas-liquid chromatography as previously described (51). Plasma glucose concentrations were measured by using commercial kits (Sigma). Liver malonyl-CoA levels were measured as described previously (52). Retroperitoneal, reproductive, mesenteric, and subcutaneous fat pads were used to determine total fat pad content. Histology was performed on livers, and white adipose tissue was fixed in 10% formalin and stained with hematoxylin and eosin.

RESULTS

SCD1 Mutation Protected PPARα−/− Mice against Adiposity—Although the growth curves of PPARα−/− and SCD1−/−/PPARα−/− mice were similar to those of WT and SCD1−/− mice (Fig. 1A), the SCD1 mutation significantly decreased white adipose tissue mass of male (Fig. 1B) and female (Fig. 1C) PPARα−/− and wild-type mice. On average, food intake was significantly greater in male SCD1−/−/PPARα−/− mice than in PPARα−/− mice (0.17 ± 0.01 versus 0.11 ± 0.01 g/g body weight/day; n = 7 p < 0.001) (Fig. 1D). To determine whether the SCD1 mutation increases energy expenditure in the PPARα−/− mice, we compared the weight loss of wild-type, SCD1−/−, PPARα−/−, and SCD1−/−/PPARα−/− mice after a 16-h fast. Because energy intake is eliminated, the weight loss under fasting conditions provides a simple observation of energy expenditure (53). Fig. 1E shows that fasting-induced weight loss was higher in SCD1−/− and SCD1−/−/PPARα−/− mice than in the wild-type and PPARα−/− mice. These results suggest that decreased adiposity and increased energy expenditure in the SCD1−/− mice are independent of PPARα activation.

SCD1 Mutation Reduced Hepatic and Plasma Triglyceride in PPARα−/− Mice—Fig. 2A shows that under fed and fasting conditions, the contents of liver triglycerides in SCD1−/−/PPARα−/− were 30 and 46% less, respectively, relative to those of the PPARα−/− mice. The fasting plasma triglyceride (Fig. 2B) and cholesterol (Fig. 2C) concentrations were significantly lower in SCD1−/− and SCD1−/−/PPARα−/− mice than in wild-type and PPARα−/− mice. Plasma free fatty acid levels were lower in SCD1−/− and SCD1−/−/PPARα−/− relative to wild-type and PPARα−/− mice (Fig. 2D). Plasma cholesterol and free fatty acid concentrations were higher in PPARα−/− mice than in wild-type mice, consistent with previous reports (30, 43).

SCD1 Mutation Protected PPARα−/− Mice against Diet-induced Obesity and Adiposity—A high fat diet caused weight gain in wild-type and PPARα−/− mice, whereas the body
weights of SCD1−/− and SCD1−/−/PPARα−/− mice were not significantly altered (Fig. 3A). Food intake was significantly greater in male SCD1−/−/PPARα−/− mice than in PPARα−/− mice (0.20 ± 0.01 g versus 0.11 ± 0.01 g/g body weight/day; n = 6 p < 0.001). The weights of reproductive fat pads of the female and male PPARα−/− mice were 60 and 20% higher, respectively, relative to the wild-type mice, but the fat pad weights of the SCD1−/− and SCD1−/−/PPARα−/− mice were 68 and 66% less, respectively, than those of PPARα−/− mice (Fig. 3C). Histological examination of the epidydimal fat pads revealed smaller adipocytes in both SCD1−/− and SCD1−/−/PPARα−/− than in those of wild-type and PPARα−/− mice (Fig. 3D). These observations suggest that the protection against adiposity and diet-induced obesity by SCD1 deficiency is not controlled by PPARα.

SCD1 Mutation Rescues Liver Steatosis of PPARα−/− Mice—Histological liver sections of male PPARα−/− mice fed a high fat diet showed large lipid-filled vacuoles, whereas those of SCD1−/−/PPARα−/− mice showed little or no vacuoles and were similar to those of SCD1−/− mice (Fig. 4A). The liver steatosis of the female PPARα−/− mice was reduced in the SCD1−/−/PPARα−/− (Fig. 4B). Fig. 4C shows that the liver triglyceride content was 50% higher in the male PPARα−/− mice relative to the wild-type mice upon feeding a high fat diet but reduced by greater than 80% in the SCD1−/−/PPARα−/− mice. The triglyceride content was reduced by 65% in the female SCD1−/−/
PPARα−/− relative to the PPARα+/− mice. BAT sections of male PPARα−/− mice fed the high fat diet showed large lipid-filled vacuoles, whereas those of SCID1−/−/PPARα−/− mice showed small vacuoles and were similar to those of SCID1−/− mice (Fig. 4D). SCID1−/−/PPARα−/− female mice (n = 8). C, fasting plasma cholesterol concentration of wild-type (WT) SCID1−/−, PPARα−/−, and SCID1−/−/PPARα−/− female mice (n = 6). *, p < 0.05 versus wild-type mice; #, p < 0.05 versus PPARα−/− mice. FFA, free fatty acids.

**SCD1 Mutation Increases Expression of PPARα Target Genes in Liver and BAT of PPARα−/− Mice**—To investigate whether the SCID1 mutation increased the expression of PPARα target genes in PPARα−/− mice, we measured the mRNA levels of AOX, VLCAD, and liver CPT in the livers and BAT and also BAT-thermogenic genes (UCP-1, UCP2, and UCP3) of wild-type, SCID1−/−, PPARα−/−, and SCID1−/−/PPARα−/− mice. Fig. 5A shows that the mRNA levels for AOX, liver CPT, and VLCAD were still elevated in the livers of SCID1−/−/PPARα−/− mice. The expression of the PPARα mRNA in liver was not altered between the wild-type and SCID1−/− mice. These results suggest that the increased expression of PPARα target genes due to SCID1 deficiency occurs through a PPARα-independent process.

**SCD1 Mutation Increases Fatty Acid Oxidation in PPARα−/− Mice**—To determine whether the SCD1 mutation increases the rate of fatty acid β-oxidation in PPARα−/− mice, we assayed the oxidation of [14C]palmitoyl-CoA in liver mitochondria isolated from PPARα−/− and SCID1−/−/PPARα−/− mice. The oxidation of [14C]palmitoyl-CoA was 54% higher (n = 5 mice/group, p < 0.05) in the liver (Fig. 6A) of SCID1−/−/PPARα−/− mice compared with PPARα−/− mice. Oxidation of [14C]palmitoyl-CoA was also increased in the BAT of SCID1−/−/PPARα−/− mice relative to PPARα−/− mice (data not shown). CPT-1 is the enzyme that is responsible for the transport of activated fatty acid into mitochondria for β-oxidation, and its activity would be expected to increase during increased fatty acid oxidation. Fig. 6B shows that the CPT-1 protein level and enzyme activity are 35 and 60% higher, respectively, in the liver of SCID1−/−/PPARα−/− mice than in the liver of PPARα−/− mice (n = 6 mice/group, p < 0.001). The increase in CPT-1 protein level is consistent with the increase in CPT-1 mRNA shown in Fig. 5A.

The increase in CPT-1 activity could be attributed to a decrease in malonyl-CoA, the substrate for lipogenesis, and inhibitor of fatty acid oxidation. The content of malonyl-CoA is 35% less (n = 6 mice/group, p < 0.001) in the SCID1−/−/PPARα−/− than in the PPARα−/− mice (Fig. 6C). Malonyl-CoA levels were also reduced in the BAT of SCID1−/−/PPARα−/− mice (data not shown). Because malonyl-CoA production can be blocked by serine 79 phosphorylation of ACC (50, 54–57), we measured phospho-ACC (α plus β) in the livers of PPARα−/− and SCID1−/−/PPARα−/− mice. The level of Ser-79 phosphorylation of ACC was 75% higher in the SCID1−/−/PPARα−/− mice relative to the PPARα−/− mice (Fig. 6D), whereas the total amount of ACC1 and ACC2 protein was decreased by 60 and 50%, respectively, in SCID1−/−/PPARα−/− mice. Because ACC Ser-79 phosphorylation is catalyzed by AMPK, which is activated by phosphorylation (56–59), we also measured phospho-AMPK. The amount of phosphorylated AMPK was 50% higher in the liver of SCID1−/−/PPARα−/− mice relative to the PPARα−/− mice, whereas the total amounts of α1-AMPK and α2-AMPK were not significantly changed. These results confirm that the increased fatty acid oxidation observed in the liver of SCID1−/−-deficient mice is independent of PPARα pathway and involves other mechanisms including the activation of AMPK (50).

**DISCUSSION**

We showed previously that mice with a deficiency of SCID1 are protected against increased adiposity, have increased energy expenditure, and show up-regulation of PPARα target genes in the liver. Liver and plasma triglycerides were decreased, and the genes of lipogenesis were down-regulated. These observations led to the hypothesis that one of the consequences of SCID1 deficiency is to partition fat toward increased oxidation while decreasing lipogenesis. PPARα is the predominant PPAR subtype expressed in mouse liver and BAT, and it plays a central role in the transcriptional activation of peroxi-
somal, mitochondrial, and microsomal fatty acid oxidation genes in these tissues (15, 16). To test the hypothesis that SCD1 deficiency activates the PPAR pathway, we generated SCD1/PPAR mice and studied them with respect to adiposity, energy expenditure, and expression of PPAR target genes in the liver and BAT tissue. The study shows that SCD1/PPAR mice are still protected against adiposity, show increased energy expenditure, have reduced liver steatosis, and show increased fatty acid oxidation. The expression of PPAR target genes in the liver and BAT remains elevated. Taken together, these results suggest that the phenotypes generated by SCD1 deficiency are independent of the PPAR pathway.

The mechanism of increased expression of PPAR target genes in the liver and BAT of SCD1/− mice is still unknown. However, as recently reported by Kertsen et al. (30), the results in BAT are consistent with the PPAR-independent mechanism of the induction of the UCP-1 gene expression upon fasting. In BAT and under fasting conditions, other transcription factors such as PPAR, PPARγ, and thyroid hormone receptor have been shown to control the expression of UCP1 (60). These transcription factors are co-activated by binding with a cold-inducible co-activator PPARγ coactivator 1α, which is induced through the β3-adrenergic receptor signaling (60). We previously found that SCD1−/− mice exhibited increased expression of the β3-adrenergic receptor isoform without alteration in the expression of the β1 and β2 isoforms. The expression of PPARγ coactivator 1α levels is increased in BAT (61) and in the liver.2 Therefore, the increased expression of UCPs and fatty acid oxidation genes in BAT of SCD1−/− may be due to activation of either PPARγ or thyroid hormone receptor with the binding of PPARγ coactivator 1α.

The muscle CPT-1 and UCP-3 mRNA levels are higher in the muscle of SCD1/− and SCD1/−/PPAR−/− mice (data not shown). The major PPAR isoform in muscle is δ/β. Thus the increased fatty acid oxidation caused by SCD1 deficiency may not be confined to the liver and BAT but may be global and regulated by different PPAR isoforms expressed in different tissues. The SCD1 deficiency could be generating ligands for other PPAR isoforms and not PPARα as previously proposed. PPARδ-transgenic mice and mice treated with PPARδ-specific agonists like SCD1−/− mice are protected from high fat diet-induced adiposity and insulin resistance because of the induc-

---

2 M. Miyazaki and J. M. Ntambi, unpublished data.
Stearoyl-CoA Desaturase and PPARα

We hypothesized previously that the reduction in hepatic triglycerides in SCD1−/− mice was due to increased PPARα-mediated oxidation of the fatty acids. We found in this study that the hepatic triglyceride levels were lower and that fatty acid oxidation was higher in SCD1−/−/PPARα−/− relative to the PPARα−/− mice. Moreover, male PPARα−/− mice exhibited a severe liver steatosis after high fat feeding, whereas little fat deposition was observed in the liver of SCD1−/−/PPARα−/− mice. These observations suggested that the reduction of hepatic triglycerides and increased fatty acid oxidation by SCD1 deficiency were independent of PPARα activation. Therefore, several alternative mechanisms for increased fatty acid oxidation by SCD1 deficiency are considered. First, although the PPARα target genes were still elevated in the SCD1−/−/PPARα−/− mice, lipogenesis was still down-regulated. The protein levels of ACC1 and ACC2 in the liver of SCD1−/−/PPARα−/− mice were lower than those in PPARα−/− mice (Fig. 6D), consistent with a decrease in ACC gene expression. The reduction in fatty acid synthesis and AMPK-mediated inactivation of acetyl-CoA carboxylase (Fig. 6D) can concomitantly enhance fatty acid oxidation by reducing malonyl-CoA levels and thereby removing the inhibition on CPT-1. However, the mechanisms of inhibition of lipogenesis and activation of AMPK by SCD1 deficiency are presently unknown.

Fig. 4. A, liver sections from male mice fed a high fat diet. Magnification, ×200. B, liver sections from female mice fed a high fat diet. Magnification, ×200. C, liver triglyceride (TG) content in mice fed a high fat diet (n = 3–6). D, BAT sections from mice fed a high fat diet. Magnification, ×200. E, BAT TG content in male mice fed a high fat diet (n = 3). *, p < 0.05 versus wild-type (WT) mice; #, p < 0.05 versus PPARα−/− mice.
In summary, it has long been known that PPARα controls the expression of a number of genes involved in mitochondrial and peroxisomal β-oxidation and plays an important role in maintaining energy homeostasis. The results presented here support the hypothesis that there are other mechanisms induced by SCD1 deficiency that lead to activation of genes of fatty acid oxidation independent of PPARα activation. Also, as we showed earlier (50) and in the results shown here, post-transcriptional mechanisms such as the activation of AMPK induced by SCD1 deficiency can be partly responsible for the increased fatty acid oxidation in the SCD1⁻⁻/PPARα⁻⁻ double knock-out mice. Overall, the studies show that the SCD1 deficiency overrides the PPARα deficiency and continues to protect mice against adiposity through increased thermogenesis and increased fatty acid oxidation. A further understanding of the regulation of SCD and the development of inhibitors for its activity will be important steps in the treatment of obesity and its associated risk factors.

Acknowledgment—We thank Dr. Grahame Hardie for AMPK antibodies.

REFERENCES

1. Ntambi, J. M., Buhrow, S. A., Kaestner, K. H., Christy, R. J., Sibley, E., Kelly, T. J., Jr., and Lane, M. D. (1988) J. Biol. Chem. 263, 17291–17300
Reduced Adiposity and Liver Steatosis by Stearoyl-CoA Desaturase Deficiency Are Independent of Peroxisome Proliferator-activated Receptor-α
Makoto Miyazaki, Agnieszka Dobrzyn, Harini Sampath, Seong-Ho Lee, Weng Chi Man, Kiki Chu, Jeffrey M. Peters, Frank J. Gonzalez and James M. Ntambi

J. Biol. Chem. 2004, 279:35017-35024.
doi: 10.1074/jbc.M405327200 originally published online June 4, 2004

Access the most updated version of this article at doi: 10.1074/jbc.M405327200

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 59 references, 27 of which can be accessed free at http://www.jbc.org/content/279/33/35017.full.html#ref-list-1