p38 Mitogen-activated Protein Kinase Plays an Inhibitory Role in Hepatic Lipogenesis*‡

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Hepatic lipogenesis is the principal route to convert excess carbohydrates into fatty acids and is mainly regulated by two opposing hormones, insulin and glucagon. Although insulin stimulates hepatic lipogenesis, glucagon inhibits it. However, the mechanism by which glucagon suppresses lipogenesis remains poorly understood. In this study, we have observed that p38 mitogen-activated protein kinase plays an inhibitory role in hepatic lipogenesis. Levels of plasma triglyceride and triglyceride accumulation in the liver were both elevated when p38 activation was blocked. Expression levels of central lipogenic genes, including sterol regulatory element-binding protein-1 (SREBP-1), fatty acid synthase, hydroxy-3-methylglutaryl coenzyme A reductase, farnesyl pyrophosphate synthase, and cytochrome P-450-51, were decreased in liver by fasting and in primary hepatocytes by glucagon but increased by the inhibition of p38. In addition, we have shown that p38 can inhibit insulin-induced expression of key lipogenic genes in isolated hepatocytes. Our results in hepatoma cells demonstrate that p38 plays an inhibitory role in the activation of the SREBP-1c promoter. Finally, we have shown that transcription of the PGC-1β gene, a key coactivator of SREBP-1c, was reduced in liver by fasting and in isolated hepatocytes by glucagon. This reduction was significantly reversed by the blockade of p38. Insulin-induced expression of the PGC-1β gene was enhanced by the inhibition of p38 but suppressed by the activation of p38. Together, we have identified an inhibitory role for p38 in the transcription of central lipogenic genes, SREBPs, and PGC-1β and hepatic lipogenesis.

Hepatic lipogenesis is essential for maintaining energy balance (1). Disorders of hepatic lipogenesis may lead to fatty liver, dyslipidemia, type II diabetes mellitus, and complications such as atherosclerosis (2). Lipogenesis in liver includes de novo synthesis of fatty acids and cholesterol. As a major site for synthesis of fatty acids, the liver converts excess carbohydrates into fat storage in the fed state. Fatty acids synthesized in the liver are converted into triglycerides and secreted as very low density lipoproteins, which transport fatty acids to the storage sites in adipocytes. Cholesterol synthesized in the liver are also transported to other tissues via very low density lipoproteins as essential building materials for steroid hormones and cellular membranes. However, excess production of fatty acids and cholesterol from the liver may contribute to a variety of lipid disorders. The lipogenic process in the liver is primarily regulated by central lipogenic transcription factors, sterol regulatory element-binding proteins (SREBPs) (reviewed in Refs. 3 and 4).

The SREBPs are basic helix-loop-helix-leucine zipper-containing transcription factors (5). Among three known SREBPs, SREBP-1a and -1c are encoded by the same gene; SREBP-1c lacks the N-terminal exon compared with SREBP-1a (6). SREBP-2 is encoded by a separate gene (7). Although SREBPs share similar lipogenic function, SREBP-1c is primarily involved in fatty acid synthesis, whereas SREBP-2 is mainly involved in cholesterol synthesis (8–10). In contrast, SREBP-1a is a potent activator of both fatty acid and cholesterol syntheses (9, 11, 12). SREBP-1c and -2 are predominant isoforms in the liver and major regulators of hepatic lipogenesis (13). SREBPs regulate lipogenesis by stimulating expression of their target genes, such as liver pyruvate kinase, acetyl CoA carboxylase, fatty acid synthase (FAS), Spot14, diacylglycerol acyltransferase, and glycerol-3-phosphate acyltransferase (reviewed in Ref. 4). The function of SREBPs is primarily regulated through protein cleavage and gene expression.

The “inactive” precursor form of SREBPs are integral membrane proteins of endoplasmic reticulum. Upon sterol deprivation, they are cleaved through two sequential steps to release the N terminus, which is translocated into the nucleus to activate the transcription of target genes (6, 14, 15). Transcription of SREBP genes in the liver is principally regulated by insulin and glucagon (16–18). Although the mechanism of SREBP gene transcription by these hormones has been intensively...
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studied, there are still significant gaps in our understanding. Recently, peroxisome proliferator-activated receptor γ co-activator-1β (PGC-1β) has been shown to interact with SREBP-1c as a co-activator in regulating the transcription of lipogenic genes (19). However, the signaling pathway from hormones to the SREBP promoters, such as the identity of specific kinases, remains largely unknown.

p38 mitogen-activated protein kinase (p38) is one member of the mitogen-activated protein kinase superfamily. It is a cellular sensor of many stresses caused by various stimuli (reviewed in Refs. 20–22). Essentially, any significant change in extracellular environment can activate p38 and set in motion certain protective mechanisms, such as activation and production of heat shock proteins, immune responses, and apoptosis. We and others have recently shown that p38 plays an important role in the control of energy balance in brown adipocytes, muscle cells, and hepatocytes (23–28). In this study, we investigated the role of p38 in the control of hepatic lipogenesis. Our results show that p38 is activated in liver by fasting and in isolated hepatocytes by glucagon. Suppression of p38 in liver or isolated hepatocytes led to elevated expression of lipogenic genes and increased triglyceride levels in both plasma and liver. Together our results support a critical role for p38 in the regulation of hepatic lipogenesis.

MATERIALS AND METHODS

Chemicals, Antibodies, and Plasmids—SB203580 (SB) was from Calbiochem. Glucagon and Percoll were from Sigma. Antibodies against p38 and phosphorylated p38 were from Cell Signaling Technology. Antibodies against SREBP-1 were from Santa Cruz Biotechnology. The SREBP-1c promoter construct (pBP1c, 1.3 kb) was a kind gift from Drs. Michael S. Brown and Joseph L. Goldstein (29). The constructs for dominant-negative p38α (p38(AF)) and MKK6E were kindly provided by Dr. Jiahua Han.

Animal Experiments—To examine the role of p38 in lipid metabolism, C57BL/6 mice (10 mice/group) were fed with normal (standard) chow diet or high fat diet (Research Diets catalog number D12330: 58.0 kcal% fat, 16.0 kcal% protein, and 26 kcal% carbohydrate) as noted. Six weeks later, some mice were treated with SB (30 mg/kg body weight/day through gastric gavages) or the vehicle solution for another 2 weeks as noted. SB and vehicle were administered one dose/day. At completion of these treatments, blood samples were collected for measurements of lipids, and livers were harvested for quantification of triglyceride (TG) and analyses of target proteins and mRNAs.

To further evaluate the role of p38 in expressions of lipogenic genes, C57BL/6 mice (6–8 weeks old) were fasted for 24 h in the presence or absence of SB (12.4 mg/kg body weight via immunoprecipitation) as noted. SB was administered as previously described (27). The fed mice were used as a control. Livers were collected for the measurements of lipogenic genes.

Preparation, Transfection, and Viral Infection of Primary Hepatocytes—Primary hepatocytes from C57BL/6 mice fed with normal chow diet at the regular schedule were prepared as previously described (30). Briefly, under anesthesia with pentobarbital (immunoprecipitation, 30 mg/kg body weight), livers were perfused with Hanks’ balanced salt solution (Invitrogen) at 5 ml/min for 8 min followed by continuous perfusion with serum-free Williams’ medium containing collagenase (Worthington, type II, 130 units/ml) (Invitrogen), HEPES (10 mM), and NaOH (0.004 N) at 5 ml/min for 12 min. Hepatocytes were harvested and purified with Percoll as described previously (31). The viability of hepatocytes was examined with trypan blue exclusion. Cells with viability >95% were used. Hepatocytes were inoculated into collagen-coated 6-well plates (5 × 10^5/well) in Williams’ medium. Cells were incubated overnight before any experimentation. MKK6E and p38-AF-FLAG (dominant negative p38α) were introduced into primary hepatocytes with Lipofectamine 2000 according to the manufacturer’s manuals (Invitrogen). For adenoviral infection, 50 active viral particles/cell in 1 ml of Williams’ medium with 2% fetal bovine serum were used to incubate with cells for 6 h followed by incubation with fresh medium containing 10% fetal bovine serum (32). At 36 h post-infection, levels of p38 and expression of genes in hepatocytes were detected by immunoblottings with appropriate antibodies and TaqMan real-time reverse transcription (RT)-PCR, respectively.

Culture and Transfection of Hepatoma Cell Line—The Hepa1c1c7 mouse hepatoma cell line was purchased from the American Type Culture Collection (Manassas, VA) and cultured with minimal essential α medium in the presence of 10% fetal bovine serum and antibiotics. Transient transfection of these cells was performed using Lipofectamine 2000 (Invitrogen) according to instructions from the manufacturer.

Immunoblotting—Tissue or whole-cell lysates were prepared by homogenization and sonication followed by the addition of 2× Laemmli sample buffer. Aliquots (5–10 μg protein/well) were resolved with mini-Tris-glycine gels (4–20%) (Invitrogen) and transferred to nitrocellulose membranes. Levels of p38 and SREBP-1 were detected with a 1:1000 dilution of each specific antibody (catalog numbers 9211S and 9212 from Cell Signaling Technology and catalog number sc-8984 from Santa Cruz Biotechnology) followed by a 1:10,000 dilution of goat anti-rabbit immunoglobulin G conjugated with alkaline phosphatase (RPN5783, Amersham Biosciences). Fluorescent bands were visualized with a Typhoon phosphorimaging device (Molecular Dynamics).

RNA Isolation and TaqMan Real-time RT-PCR—Total RNAs from liver were prepared by using RNA purification kits from Qiagen. Real-time RT-PCR TaqMan probes and reaction agents were purchased from Applied Biosystems. Reactions were performed according to manuals from the manufacturer. All results were normalized to levels of the GADPH gene. Catalog numbers for the probes are: SREBP-1 (Mm00550338_m1), SREBP-2 (Mm01306293_m1), FAS (Mm00662319_m1), PGC-1β (Mm00504720_m1), HMG CoA reductase (Mm01282491-g1), farnesyl pyrophosphate synthase (FPS) (Mm00830315_g1), and CYP51 (Mm0049968_m1).
Measurements of mRNA Degradation—Transcription of lipogenic genes in hepatocytes were activated by insulin and dexamethasone for 20 h and subsequently blocked by treatment with amanitin as described previously (33). Cells were then treated with either SB or vehicle solution as noted. Levels of representatives of lipogenic genes (SREBP-1c and PGC-1) were quantified with TaqMan real-time RT-PCR.

Measurements of Liver Triglyceride Content—Livers were homogenized in a buffer containing 18 mM Tris (pH 7.4), 300 mM D-mannitol, 50 mM EGTA, and 1 mM phenylmethylsulfonyl fluoride. Triglycerides in the lysates were extracted using a chloroform/methanol protocol as previously described (34). Levels of triglycerides were quantified by using triglyceride reagents from Sigma (catalog number T2449-10ML) and normalized to protein concentration. Lipid droplets in liver slides were visualized with Oil Red O staining.

RESULTS

Inhibition of p38 Leads to Elevation of Plasma Lipids and Fat Accumulation in Liver—During our study on the stimulatory role of p38 in hepatic gluconeogenesis (27), we unexpectedly observed that p38 might inhibit hepatic lipogenesis. To fully characterize this observation, we examined the effect of p38 inhibition on levels of plasma lipids and liver TG content in mice. As shown in Fig. 1, although plasma levels of total cholesterol (T-Chol), high density lipoprotein cholesterol (HDL-Chol), and triglycerides (TG) were measured. Results shown represent means ± S.D. of two independent experiments, each with 5 mice/group. *, p < 0.05 compared with –SB; **, p < 0.01 versus –SB. Plasma levels of non-esterified fatty acids (NEFA) (B) and insulin (C) from these animals were measured. Body weight (D) and food intake (E) were quantified.

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was noted that treatment of animals with SB did not significantly influence either levels of plasma non-esterified fatty acids and insulin or body weight and food consumption (Fig. 1, B–E). Together, these results show that the blockade of p38 can elevate TG levels in both plasma and liver, suggesting an inhibitory role for p38 in hepatic lipogenesis.

The Blockade of p38 Can Increase Transcript Levels of Lipogenic Genes in Fasted Liver—To investigate the possible role of p38 in suppression of hepatic lipogenesis, we chose to use fasting mice as models, because it is well known that hepatic lipogenesis is normally inhibited by fasting and p38 is activated in the liver during fasting (27). As expected (Fig. 3A), levels of lipogenic gene transcripts, including SREBP-1c, FAS, hydroxy-3-methylglutaryl coenzyme A reductase, FPS, and CYP51 genes in liver were quantified with TaqMan real-time RT-PCR. Results shown represent means ± S.D. of two independent experiments, each with 4 mice/group. *, p < 0.05 compared with +SB. B, levels of p38 phosphorylation in liver were detected by immunoblotting with antibodies against either total or phospho-p38. *, p < 0.05 comparing fasting without SB to fasting with SB.

FIGURE 3. p38 plays an inhibitory role in expression of key lipogenic genes in liver. Mice were fasted for 24 h in the presence or absence of p38 inhibitor SB. Fed mice were also treated with SB as noted. A, transcripts of SREBP-1c, SREBP-2, FAS, HMG CoA-R, FPS, and CYP51 genes in liver were quantified with TaqMan real-time RT-PCR. Results shown represent means ± S.D. of two independent experiments, each with 4 mice/group. *, p < 0.05 compared with +SB. B, levels of p38 phosphorylation in liver were detected by immunoblotting with antibodies against either total or phospho-p38. *, p < 0.05 comparing fasting without SB to fasting with SB.

p38 Is an Inhibitor of the SREBP-1c Promoter—To further define the role of p38 in hepatic lipogenesis, we examined the role of p38 in activation of the SREBP-1c promoter, which was introduced into Hepa1c1c7 hepatoma cells via transient transfection. Because insulin is known to stimulate transcription of the SREBP-1c gene (17, 37–39), activity of the SREBP-1c promoter was stimulated with insulin in the presence or absence of a p38 inhibitor. As shown in Fig. 5A, the SREBP-1c promoter was stimulated by insulin as expected, and this stimulation was further enhanced by the inhibition of p38. Similarly, the SREBP-1c promoter was suppressed by glucagon as expected, and the suppression was significantly reversed by the inhibition of p38 with either SB or siRNA-p38α (Fig. 5D). Together, these results further support the notion that p38 is an inhibitor of lipogenic gene expression in isolated hepatocytes.

p38 Can Inhibit Transcription of the PGC-1β Gene in Both Liver and Isolated Hepatocytes—PGC-1β was recently shown to be a critical coactivator of lipogenic gene expression through its interaction with SREBP-1c (19). To examine whether transcription of the PGC-1β gene is a target for p38 in the suppression of hepatic lipogenesis, we examined levels of PGC-1β transcripts in livers from fed or fasted mice with or without treatment with SB. As shown in Fig. 6A, levels of PGC-1β transcripts in liver were decreased by fasting; this decline was significantly, although not completely, reversed by the blockade of p38. To more directly study the effect of p38 on levels of glucagon, which is also the major promoter of hepatic glucose production and is always significantly elevated in the blood during fasting (35). Glucagon is a cAMP-producing hormone that can activate p38 in primary hepatocytes (27, 36). To determine whether p38 mediates glucagon suppression of hepatic lipogenesis, levels of key lipogenic gene transcripts and phosphorylation of p38 in primary hepatocytes were examined in the presence or absence of p38 blockade. As predicted, levels of SREBP-1c, SREBP-2, FAS, HMG CoA-R, and FPS transcripts were inhibited by glucagon (Fig. 4A). This inhibition was significantly reversed by the blockade of p38 with either SB or over-expression of dominant negative p38α (dn-p38α). To determine the role of p38 in insulin-induced transcription of key lipogenic genes, primary hepatocytes were stimulated by insulin in the presence of a p38 inhibitor or an activator. As shown in Fig. 4B, levels of key lipogenic genes SREBP-1c and FAS were elevated by insulin as expected, and this elevation was further enhanced by the inhibition of p38 with SB but prevented by the activation of p38 with MKK6E. Furthermore, levels of the SREBP-1 protein (membrane-bound) were significantly increased by all p38 inhibitors, including SB, dn-p38α, and small interfering RNA against p38α (siRNA-p38α) but decreased by glucagon (Fig. 4C). The nuclear form of SREBP-1 was also slightly elevated by the inhibition of p38. The scrambled siRNA had no effect. (Note: cells were not deprived of cholesterol in these experiments.) Phosphorylation of p38 in isolated hepatocytes was also stimulated by glucagon and blocked by either SB or siRNA-p38α (Fig. 4D). Our results indicated that the inhibition of p38 did not affect the stability of SREBP-1c mRNA (supplemental Fig. 1). Together, these results support the notion that p38 is an inhibitor of lipogenic gene expression in isolated hepatocytes.
PGC-1α transcripts, primary hepatocytes were treated with glucagon in the presence or absence of p38 inhibition. As shown in Fig. 6B, levels of PGC-1α transcripts were reduced by glucagon, but the reduction was completely prevented by the blockade of p38 with either SB or dn-p38. Similarly, insulin-induced expression of the PGC-1α gene was also enhanced by the inhibition of p38 but suppressed by the activation of p38 (Fig. 6C). To determine the possible role of p38 in the degradation of PGC-1α mRNA, the transcription of the PGC-1α gene was first stimulated by insulin and dexamethasone and then blocked by amanitin followed by treatment with SB. As shown in Fig. 6D, treatment with SB did not significantly influence levels of PGC-1α transcripts during a 24-h degradation course.

FIGURE 4. p38 plays an inhibitory role in transcription of lipogenic genes in primary hepatocytes. Primary hepatocytes were isolated and cultured as detailed under “Materials and Methods.” A, primary hepatocytes were stimulated with glucagon (50 nM, 16 h) in the presence or absence of p38 inhibitor SB (5 μM) or dominant negative p38α (dn-p38α). Transcripts of SREBP-1c, SREBP-2, FAS, HMGCoA-R, and FPS genes were quantified with TaqMan real-time RT-PCR. Results shown represent means ± S.D. of three experiments. *, p < 0.05 compared with all other treatments. B, primary hepatocytes were treated with insulin (100 nM) in the presence or absence of SB or MKK6E as noted followed by measurements of SREBP-1c and FAS transcripts by TaqMan real-time RT-PCR. *, p < 0.05 versus all other treatments. **, p < 0.05 versus basal. C, primary hepatocytes were stimulated by glucagon (50 nM, 16 h) in the presence or absence of SB, dn-p38α, or siRNA against p38α (siRNA-p38α). The scrambled siRNA was used as a control. Protein levels of membrane-bound and nuclear SREBP-1 were assessed by immunoblotting with antibodies against SREBP-1. *, p < 0.05 comparing lanes 3, 4, or 5 to lanes 1, 2, or 6. D, primary hepatocytes were treated with glucagon (50 nM, 30 min) in the presence or absence of SB or siRNA-p38α encoded by adenoviruses as detailed under “Materials and Methods.” Levels of total and phospho-p38α were also detected by immunoblotting. Results shown represent means ± S.D. of three experiments. *, p < 0.05 comparing phospho-p38α in either lanes 2 or 3 to lanes 1, 3, or 4.

FIGURE 5. p38 inhibits activation of the SREBP-1c promoter. The SREBP-1c promoter was introduced into Hepa1c1c7 cells via transient transfection. Cells were then treated for 16 h with either insulin (50 nM) (A) or glucagon (50 nM) (B) in the presence of p38 inhibitors (5 μM SB, dominant negative p38α, or siRNA against p38α) as noted. Promoter activities were subsequently quantified with luciferase assays and normalized to β-galactosidase activity (internal control). Results shown represent means ± S.D. of two independent experiments, each in triplicate. *, p < 0.05 compared with the basal level or to inhibition of p38; #, p < 0.05 versus all other treatments.

PGC-1β transcripts, primary hepatocytes were treated with glucagon in the presence or absence of p38 inhibition. As shown in Fig. 6B, levels of PGC-1β transcripts were reduced by glucagon, but the reduction was completely prevented by the blockade of p38 with either SB or dn-p38α. Similarly, insulin-induced expression of the PGC-1β gene was also enhanced by the inhibition of p38 but suppressed by the activation of p38 (Fig. 6C). To determine the possible role of p38 in the degradation of PGC-1β mRNA, the transcription of the PGC-1β gene was first stimulated by insulin and dexamethasone and then blocked by amanitin followed by treatment with SB. As shown in Fig. 6D, treatment with SB did not significantly influence levels of PGC-1β transcripts during a 24-h degradation course.

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DISCUSSION

Much is known about how hepatic lipogenesis is stimulated by metabolically important hormones such as insulin, whereas little is known about the mechanism by which hepatic lipogenesis is suppressed. It is generally accepted that glucagon is the major inhibitor of lipogenesis during fasting due to its activation of the cAMP/protein kinase A pathway (see Ref. 40 for review). Nevertheless, the mechanism(s) beyond protein kinase A have not been well defined. In this study, we have identified a critical role for p38 in the regulation of hepatic lipogenesis.

Specifically, the blockade of p38 leads to hypertriglyceridemia and fatty liver.

Many factors may contribute to the development of the hypertriglyceridemia and fatty liver observed in this study. Because p38 has been shown to play a stimulatory role in glucose uptake in skeletal muscles and adipocytes through expression of Glut4 (41–49), the blockade of p38 may reduce glucose uptake in these tissues, resulting in excess glucose supply. The excess glucose is then converted into fatty acids and contributes to the development of hypertriglyceridemia and fatty liver. The blockade of p38 may also cause fat accumulation by reducing oxidation of fatty acids, as p38 has been shown to promote activation and expression of PGC-1α (24, 27, 50), which is a critical player in skeletal muscles and hepatocytes in promoting fatty acid oxidation (51). We have previously reported that the blockade of p38 can prevent activation of CAMP response element-binding protein in both liver and isolated hepatocytes (27, 28). CAMP response element-binding protein has been previously shown to inhibit hepatic lipogenesis through stimulating expression of the Hairy Enhancer of Split-1 (HES-1) gene and consequently suppressing expression of the perilipin-1 gene (52).

Therefore, the inhibition of p38 seems to contribute to fat accumulation in the liver by suppressing activation of CAMP response element-binding protein. However, our results show that expression of the HES-1 gene was not significantly affected by the blockade of p38, whereas expression of the PPARγ gene was decreased instead of increased (supplemental Fig. 2). Thus, it is unlikely that blockade of CAMP response element-binding protein-mediated suppression of hepatic lipogenesis contributes to the fatty liver seen in this study. Additionally, the blockade of triglyceride export from hepatocytes may also cause fatty liver. Our results show that the blockade of p38 indeed decreases mRNAs of the microsomal triglyceride transport protein gene in liver (supplemental Fig. 2). Finally, our results clearly show that p38 plays an inhibitory role in the transcription of key lipogenic genes in both liver and isolated hepatocytes. Therefore, it is obvious that multiple factors contributed to the hypertriglyceridemia and fatty liver caused by the blockade of p38.

Although p38, along with c-Jun NH2-terminal kinase (the so-called stress-activated kinases), was originally linked to stress and cell death (20–22), it has since been recognized to be involved in a variety of other cellular functions such as development and differentiation (see Ref. 22 for review). Recently, we and others have observed that p38 plays an important role in energy balance through its involvement in the transcription of several genes in brown adipocytes, muscle cells, and hepatocytes, which regulate oxidative metabolism, thermogenesis, and glucose production (23–25, 27, 28, 50, 53). It has been previously shown (27, 36) in hepatocytes that p38 could be activated by CAMP-generating hormones, including glucagon. Because glucagon is the major hormone elevated in blood during fasting and has previously been shown in hepatocytes to be able to suppress expression of the central lipogenic gene SREBP-1c (17), we postulated that p38 might mediate glucagon suppression of hepatic lipogenesis. Our results in this study strongly support this hypothesis, as levels of plasma TG and hepatic TG content, along with expression of key lipogenic genes including SREBP-1c, were significantly enhanced in liver when p38 was inhibited in animals. In addition, our results from isolated hepatocytes and promoter analysis also show that p38 inhibits the transcription of the central lipogenic gene SREBP-1c. The exact mechanism by which p38 regulates lipogenesis in the liver is still not established yet.

PGC-1p appears to be an important mediator of p38 in the regulation of hepatic lipogenesis, as our results show that p38 can inhibit expression of the PGC-1β gene, which was recently shown to be a necessary coactivator of SREBP-1c in the transactivation of lipogenic genes, including the SREBP-1c gene.
itself (19). The promoter of the SREBP-1c gene contains both
the SREBP response element and the liver X receptor response
element (37, 54). Transcription of the SREBP-1c gene can be
auto-stimulated by SREBP proteins through the SREBP
response element (55–57) or stimulated by the LXR
agonists through the liver X receptor response element (37, 54). Because
PGC-1β possesses the domains for mediating its interactions
with both SREBP and LXR (19), it is possible that PGC-1β
regulates the transcription of SREBP-1c and other SRE- and liver X
receptor response element-containing genes through assem-
bling the SREBP and LXR complexes, and p38 regulates tran-
scription of key lipogenic genes (SREBP-1c) through expression of
the PGC-1β gene. It is noteworthy that Lin et al. (58) show an
increased expression of the PGC-1β gene in liver by fasting, and
we here show an opposite result, i.e. expression of the PGC-1β
gene is decreased by fasting. It is currently unclear what caused
this discrepancy. However, our computational analysis shows
that, unlike the PGC-1α promoter, which possesses a consen-
sus cAMP response element and is expected to be activated
by fasting or glucagon (59, 60), the PGC-1β promoter does not
contain a cAMP response element. Therefore, the PGC-1β pro-
moter is not necessarily activated by fasting or glucagon.

In summary, we have identified p38 as an important modu-
lator of hepatic lipogenesis. Because inhibition of lipogenesis is
necessary to protect the substrate supply for hepatic gluconeo-
genesis during fasting, this role of p38 may be pivotal for main-
taining plasma glucose levels. In addition, the inhibitory role of
p38 may also be important to limiting lipid synthesis in liver
when excess calories, particularly fats, are ingested. The exact
mechanism by which p38 inhibits transcription of the central
lipogenic genes, such as SREBP-1c and PGC-1β, requires fur-
ther investigation, which may yield new targets for manipulat-
ing hepatic lipogenesis for the treatment of lipid disorders.

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