Regulatory Role of Glycogen Synthase Kinase 3 for Transcriptional Activity of ADD1/SREBP1c

Kang Ho Kim‡§, Min Jeong Song‡§, Eung Jae Yoo‡§, Sung Sik Choe‡§, Sang Dai Park¶, and Jae Bum Kim‡§

From the §School of Biological Sciences, Seoul National University and the ¶International Vaccine Institute, Seoul 151-742, Korea

Adipocyte determination- and differentiation-dependent factor 1 (ADD1) plays important roles in lipid metabolism and insulin-dependent gene expression. Because insulin stimulates carbohydrate and lipid synthesis, it would be important to decipher how the transcriptional activity of ADD1/SREBP1c is regulated in the insulin signaling pathway. In this study, we demonstrated that glycogen synthase kinase (GSK)-3 negatively regulates the transcriptional activity of ADD1/SREBP1c. GSK3 inhibitors enhanced a transcriptional activity of ADD1/SREBP1c and expression of ADD1/SREBP1c target genes including fatty acid synthase (FAS), acetyl-CoA carboxylase 1 (ACC1), and steroyl-CoA desaturase 1 (SCD1) in adipocytes and hepatocytes. In contrast, overexpression of GSK3β down-regulated the transcriptional activity of ADD1/SREBP1c. GSK3 inhibitor-mediated ADD1/SREBP1c target gene activation did not require de novo protein synthesis, implying that GSK3 might affect transcriptional activity of ADD1/SREBP1c at the level of post-translational modification. Additionally, we demonstrated that GSK3 efficiently phosphorylated ADD1/SREBP1c in vitro and in vivo. Therefore, these data suggest that GSK3 inactivation is crucial to confer stimulated transcriptional activity of ADD1/SREBP1c for insulin-dependent gene expression, which would coordinate lipid and glucose metabolism.

Glycogen synthase kinase 3 (GSK3)1 is a serine/threonine kinase that has been implicated in multiple cellular processes, including the Wnt and insulin signaling pathways. Unlike other kinases, GSK3 is constitutively active in resting cells and is inhibited by several growth factors or hormones, such as Wnt ligands, insulin, epidermal growth factor, and platelet-derived growth factor (1–5). In the canonical Wnt pathway, interaction between Wnt and Frizzled receptor inhibits GSK3, which results in dephosphorylation of β-catenin leading to the nuclear accumulation of β-catenin and activation of β-catenin/T cell factor target genes (4, 6–9). Also, GSK3 plays an important role in the insulin signaling pathway and it phosphorylates and inhibits glycogen synthase in the absence of insulin (10). In insulin-sensitive tissues, insulin-derived GSK3 inactivation is mediated by phosphatidylinositol 3-kinase and protein kinase B/Akt (PKB/Akt), which phosphorylate at the N-terminal serine residue of GSK3 (serine 21 and serine 9 in GSK3α and -β, respectively) (5, 11, 12). Thus, recent reports suggest a potential role for GSK3 as a negative regulator of insulin signaling (13). Consistent with this notion, one of the GSK3 inhibitors, lithium chloride (LiCl), shows insulin-like effects including increase of glucose uptake, activation of glycogen synthase, and stimulation of glycogen synthesis in various tissues (13–15). Additionally, inhibition of GSK3 alters gene expression profiles in insulin-responsive cell lines. For example, LiCl selectively reduces expressions of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase genes, whose expression is also inhibited by insulin (16). Furthermore, it has been demonstrated that GSK3 can phosphorylate several transcription factors, including p53, HSF-1, and C/EBPα and regulate their transcriptional activities (17–19).

Adipocyte determination- and differentiation-dependent factor 1 (ADD1/SREBP1c) is a HHLH-ZIP transcription factor that is involved in the stimulation of many lipogenic genes (20–22), such as fatty acid synthase (FAS) (23), acetyl-CoA carboxylase (ACC) (24), and steroyl-CoA desaturase (SCD) (25). In insulin-sensitive tissues including fat, liver, and muscle, insulin stimulates the expression of ADD1/SREBP1c mRNA and its target genes via phosphatidylinositol 3-kinase and PKB/Akt (26–29). Therefore, it has been suggested that ADD1/SREBP1c plays a key role in orchestrating insulin-dependent lipid and glucose metabolism (22, 30). Furthermore, several groups have investigated the post-translational modifications of ADD1/SREBP1c that affect its transcriptional activity. Brown and Goldstein (31–34) have elegantly revealed that cholesterol-dependent proteolytic cleavage of SREBP family proteins is tightly controlled by SREBP cleavage-activating protein and Insigs. In addition, Kotzka et al. (35) reported that ADD1/SREBP1c is phosphorylated at the N-terminal end of the protein through the MAP kinase pathway, and such phosphorylation of ADD1/SREBP1c stimulates its transcriptional activity (35). However, PD98059, an inhibitor of MAP kinase pathway, did not antagonize the effect of insulin on the expression of ADD1/SREBP1c target genes in cultured hepatocytes (28, 36, 37), implying that the MAP kinase pathway might not be a major player for ADD1/SREBP1c target gene expression by insulin treatment.

Given the importance of GSK3 as a negative regulator of
insulin signaling and ADD1/SREBP1c as a mediator of insulin-responsive gene expression, it would be important to understand the molecular mechanism between inhibition of GSK3 and increase of ADD1/SREBP1c transcriptional activity by insulin. To address this question, we examined the roles of GSK3 on the regulation of transcriptional activity of ADD1/SREBP1c.

Here, we demonstrate that GSK3 inhibitors enhance the transcriptional activity of ADD1/SREBP1c and promote the expression of ADD1/SREBP1c target genes without de novo protein synthesis. Additionally, we reveal a phosphorylation event of ADD1/SREBP1c by GSK3. Taken together, these results propose a novel regulatory role of GSK3 in the insulin-dependent activation of ADD1/SREBP1c in adipocytes and hepatocytes.

**EXPERIMENTAL PROCEDURES**

**Reagents and Antibodies**—LcI and cycloheximide were obtained from Sigma and SB-216763 was purchased from Torcix. GSK3α antibody was purchased from BD Sciences. Polyclonal antibody against ADD1/SREBP1c was previously described (21). Mammalian expression vector for GSK3β was kindly provided from Dr. Junichi Sadoshina (New Jersey Medical School) (38).

**Cell Culture**—Murine 3T3-L1 preadipocytes were grown to confluence in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% bovine calf serum (JBI, Daegu, Korea). At confluence, differentiation of 3T3-L1 cells was induced with DMEM containing 10% fetal bovine serum, and HepG2 cells were maintained in DMEM supplemented 10% fetal bovine serum, and 5% phosphoric acid down, 5% phosphoric acid up, 5% phosphoric acid.

**Immunoprecipitation and Assay of Protein Kinases (IP Kinase Assay)**—Equal amounts of total cell extract were incubated with GSK3β antibody (Transduction Laboratories). The immunoprecipitates collected with protein A-Sepharose (Sigma) were pelleted and washed twice with 1 ml of NETN buffer (20 mM Tris-HCl (pH 8.0), 1 mM EDTA, 0.5% Nonidet P-40, and 100 mM NaCl). Activity of immunoprecipitated GSK3 complexes were determined by counting counts/min or autoradiography as mentioned previously.

**Orthophosphate Labeling—**HEK293 cells transfected with ADD1/SREBP1c expression vector were starved in low glucose DMEM with 0.1% bovine serum albumin for 24 h. After changing the culture medium to phosphate-free DMEM (Invitrogen) (PerkinElmer Life Sciences, Inc.) was added and cells were incubated for 2 h. After incubation, LiCl (10 mM, 1 h), SB-216763 (10 μM, 1 h), or insulin (100 nM, 30 min) were treated and total cell lysates were extracted with NETN buffer. Radiolabeled ADD1/SREBP1c proteins were obtained by immunoprecipitation with anti-ADD1/SREBP1c antibody. The precipitates were separated by SDS-PAGE (10% polyacrylamide gel) and subjected to autoradiography.

**RESULTS**

**Lithium Chloride Stimulates the Transcriptional Activity of ADD1/SREBP1c and Its Target Gene Expression**—To investigate whether the transcriptional activity of ADD1/SREBP1c is regulated by GSK3, LiCl, an inhibitor of GSK3, was used in luciferase reporter assays. Previous studies revealed that LiCl inhibits GSK3 activity with an IC50 of 2.5 mM and a 90% loss of basal promoter activity in the absence of ADD1/SREBP1c (22, 42, 43). As shown in Fig. 1A, LiCl stimulated the transcriptional activity of ADD1/SREBP1c in a dose-dependent manner. However, it had no influence on the basal promoter activity in the absence of ADD1/SREBP1c and its promoter region contains the binding sites for ADD1/SREBP1c (22, 42, 43). As shown in Fig. 1A, LiCl stimulated the FAS promoter activity in the presence of ADD1/SREBP1c in a dose-dependent manner. However, it had no influence on the basal promoter activity in the absence of ADD1/SREBP1c.

**Nuclear Translocation**—Total RNA was isolated with TRIzol reagent according to the manufacturer’s protocol. Twenty-five μg of each RNA were denatured in formamide and agarose gel electrophoresis and visualized by UVP BioImaging Systems.

**Inhibition of GSK3 by SB-216763 Stimulates ADD1/SREBP1c Target Gene Expression**—Because LiCl has several targets other than GSK3, such as the phosphatidylinositol signaling pathway via inhibition of inositol monophosphatase (44), we performed similar experiments using a selective GSK3 inhibitor, SB-216763 (45, 46). As shown in Fig. 3, A and B,
SB-216763 evidently enhanced FAS mRNA expression in 3T3-L1 adipocytes and HepG2 cells in a dose-dependent manner, similar to LiCl. The nuclear form of the SREBP1 protein was not significantly changed by SB-216763 treatment (Fig. 3C).

To clarify whether SB-216763 efficiently inhibits GSK3 kinase activity, IP kinase assays were conducted. After HepG2 cells were treated with or without GSK3 inhibitors, total cell lysates were immunoprecipitated with GSK3 antibody. Then, immune complexes were incubated with phospho-eIF2B peptide, one of the well-known substrates of GSK3 (40, 47), and GSK3 kinase activities were measured. The kinase activity of GSK3 was decreased (about 50% reduction) by LiCl or SB-216763 treatment at concentrations of 10 mM or 10 μM, respectively (Fig. 3D, lanes 3 and 4). These observations implicate that LiCl- or SB-216763-stimulated target gene expression of ADD1/SREBP1c is closely associated with the inhibition of GSK3 kinase activity.

Overexpression of GSK3β Inhibits Transcriptional Activity of ADD1/SREBP1c—To confirm the effect of GSK3 on the transcriptional activity of ADD1/SREBP1c, we investigated the effects of GSK3β overexpression. Luciferase reporter assays revealed that overexpression of GSK3β decreased the transcriptional activity of ADD1/SREBP1c in a dose-dependent fashion (Fig. 4A). Furthermore, we examined the effect of ADD1/SREBP1c target gene expression in the absence or presence of GSK3β overexpression. As shown in Fig. 4B, ectopic expression of GSK3β in HepG2 cells concomitantly inhibited FAS mRNA levels, whereas SB-216763 treatment reversed GSK3β-mediated down-regulation of FAS mRNA expression. These results suggest that GSK3β plays a negative regulator for ADD1/SREBP1c.

LiCl- and SB-216763-induced Target Gene Expression of ADD1/SREBP1c Does Not Require de Novo Protein Synthesis—Although it has been demonstrated that an increase of ADD1/SREBP1c mRNA expression is important for insulin-stimulated gene expression (30, 48), GSK3 inhibitors showed little effect on the mRNA level of ADD1/SREBP1c and protein level of nuclear SREBP1 (Figs. 2 and 3). Thus we hypothesized that the changes of the ADD1/SREBP1c target gene expression with GSK3 inhibitors can occur at the level of post-translational modification such as phosphorylation. To test the above idea, cycloheximide, an inhibitor of de novo protein synthesis (49), was treated in the absence or presence of LiCl or SB-216763. As shown in Fig. 5, A and B, cycloheximide did not alter the induction of FAS mRNA expression by LiCl or SB-216763 treatment. These results suggest that GSK3-mediated regulation of the ADD1/SREBP1c transcriptional activity does not require...
FIG. 3. Inhibition of GSK3 by SB-216763 promotes ADD1/SREBP1c target gene expression. A, Northern blot analysis of differentiated 3T3-L1 adipocytes treated with SB-216763, a specific GSK3 inhibitor, for 18 h. B, the same experiments were performed in HepG2 cells. C, Western blot analysis for nuclear SREBP1 and GSK3 in 3T3-L1 adipocytes and HepG2 hepatocytes. D, GSK3 kinase activity was determined in the absence or presence of GSK3 inhibitors. LiCl (10 mM) or SB-216763 (10 μM) were treated into starved HepG2 hepatocytes for 2 h. Whole cell lysates were immunoprecipitated with a GSK3 antibody and in vitro kinase assays were carried out with 100 μM phospho-eIF2B peptide substrates at 30 °C for 1 h. GSK3 kinase activity was determined by measuring count/min.

FIG. 4. Overexpression of GSK3β inhibits transcriptional activity of ADD1/SREBP1c. A, HEK293 cells were cotransfected with mammalian expression vectors for ADD1/SREBP1c and GSK3β. Luciferase activity was measured and normalized to protein concentration of each sample. B, GSK3β was overexpressed in HepG2 cells by transient transfection. After serum starvation for 12 h, SB-216763 (10 μM) was treated for 24 h and Northern blot analysis was carried out with total RNA. DMSO, dimethyl sulfoxide.

FIG. 5. Cycloheximide (CHX) treatment does not affect LiCl- and SB-216763-induced gene expression. A, Northern blot analysis in HepG2 cells. After being starved for 24 h, cells were pretreated with cyclohexamide (50 μM) for 2 h. The cells were then incubated with LiCl (10 mM) or SB-216763 (10 μM) for 12 h. Total RNA was isolated and Northern blot analysis was performed as described under “Experimental Procedures.” B, the same experiments were performed in 3T3-L1 adipocytes.
Rat1-IR cells were transfected and starved as described above. Cells were treated with LiCl (10 mM, lane 4), insulin (100 mM, lane 6), or both (lane 8) for 24 h. FAS luciferase reporter (100 ng) and ADD1/SREBP1c expression DNA (50 ng) were cotransfected. All transfection experiments were performed in duplicate and repeated at least three times. B. Northern blot analysis. After serum starvation, 3T3-L1 adipocytes were treated with LiCl or insulin as in panel A for 12 h. Total RNA was isolated and analyzed using Northern blot. C, a semiquantitative reverse transcriptase-PCR experiment was carried out with ADD1/SREBP1c-specific primers (see details under “Experimental Procedures”). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used to normalize each sample.

additional protein synthesis, and that modulation of ADD1/SREBP1c transcriptional activity by GSK3 is presumably accomplished by post-translational modification of ADD1/SREBP1c.

Lithium Chloride Does Not Completely Mimic Insulin-stimulated Gene Expression—It has been reported that LiCl mimics insulin-stimulated glucose metabolism including an increase of glycogen synthesis and glucose uptake and regulates several hepatic gluconeogenic gene expressions, including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (16). However, it has not been clearly understood whether LiCl sufficiently mediates insulin-dependent gene expression. To clarify the idea whether LiCl is able to substitute for insulin action in regulation of several gene expression, we performed a luciferase reporter assay in Rat1-IR cells in the presence or absence of LiCl and/or insulin. Treatment of insulin or LiCl stimulated the transactivation of FAS promoter by ADD1/SREBP1c (Fig. 6A, lanes 4 and 6), and simultaneous treatment of LiCl and insulin showed additive effects (Fig. 6A, lane 8). Likewise, cotreatment of LiCl and insulin increased FAS mRNA expression on 3T3-L1 adipocytes (Fig. 6B). But LiCl had minor effects on the expression level of ADD1/SREBP1c, whereas insulin dramatically stimulated ADD1/SREBP1c expression (Fig. 6C). Together, these results implicate that LiCl does not completely mimic insulin effects, at least, for the activation of ADD1/SREBP1c, suggesting that LiCl and insulin might have cooperative effects to stimulate ADD1/SREBP1c activity.

GSK3β Phosphorylates ADD1/SREBP1c in Vitro and in Vivo—Because inhibition of GSK3 by LiCl or SB-216763 increased the transcriptional activity of ADD1/SREBP1c without de novo protein synthesis, we decided to examine whether GSK3 is directly able to phosphorylate ADD1/SREBP1c protein. GSK3 has two isoforms, GSK3α and -β share 98% homology in their catalytic domain and have similar substrate specificity (50, 51). Because GSK3β is highly expressed in adipocytes and hepatocytes, we used GSK3β in the following experiments. To test the possibility that ADD1/SREBP1c is a novel substrate of GSK3β, we purified recombinant GSK3β proteins from E. coli or insect cells. When in vitro kinase assays were conducted with recombinant GSK3β proteins from E. coli, ADD1/SREBP1c was strongly phosphorylated as well as GSK3β itself, implying that ADD1/SREBP1c is a putative substrate of GSK3β, at least, in vitro (Fig. 7A). We obtained the same results using GSK3β proteins purified from insect cells (Fig. 7B). Furthermore, to validate the effect of purified recombinant GSK3β protein, we examined whether the kinase activity of recombinant GSK3β is directly inhibited by LiCl or SB-216763. Treatment of LiCl caused a significant reduction of kinase activity of GSK3β, whereas treatment of SB-216763 completely abolished the kinase activity of GSK3β (Fig. 7C). Next, to test whether GSK3β phosphorylates ADD1/SREBP1c in vivo, endogeneous GSK3β was obtained by IP, and IP kinase assays were carried out with ADD1/SREBP1c as substrate. As shown in Fig. 7D, ADD1/SREBP1c was clearly phosphorylated by endogenous GSK3β in both HepG2 hepatocytes and 3T3-L1 adipocytes, implying that ADD1/SREBP1c is a novel substrate for GSK3.

In addition, we performed in vivo orthophosphate labeling in the absence or presence of LiCl or insulin. Consistent with the in vitro kinase assay (Fig. 7), the basal phosphorylation level of ADD1/SREBP1c protein was decreased by LiCl and SB-216763 treatment (Fig. 8A). Previously, it has been reported that insulin might induce serine phosphorylation of ADD1/SREBP1c (22). We also observed that total phosphorylation of ADD1/SREBP1c was moderately increased by insulin (Fig. 8B, lane 3), and insulin treatment partially rescued LiCl-mediated reduction (Fig. 8B, lane 5), implying that GSK3 might phosphorylate ADD1/SREBP1c in resting status. Thus, it appears that GSK3 and other kinase(s) would be involved in the regulatory phosphorylation of ADD1/SREBP1c to mediate insulin-dependent gene expression.

**DISCUSSION**

ADD1/SREBP1c is a member of key transcription factors that regulate genes involved in cholesterol and fatty acid metabolism. Three isoforms of the SREBP family have been identified in several mammalian species. SREBP-1a and ADD1/SREBP1c are generated by using alternative promoters from a single gene. SREBP-2 is derived from a different gene with 47% similarity to SREBP-1 (52). Among the three SREBP isoforms, the transcript level of ADD1/SREBP1c is sensitively controlled by insulin and nutritional status, which are associated with lipid and glucose metabolism (30, 48). As a major anabolic hormone, insulin enhances the transcriptional activity of ADD1/SREBP1c at the level of its own transcription and post-translational modifications (22, 26, 28, 35, 48, 53). With this regulatory mechanism, ADD1/SREBP1c induces expression of several lipogenic genes, which leads to fatty acid and triglyceride synthesis and regulates expression of several genes involved in glucose metabolism (28, 30, 54, 55), suggesting that...
ADD1/SREBP1c plays a critical role in insulin-stimulated gene expression for whole body energy homeostasis. Indeed, ADD1/SREBP1c-specific knockout mice reveal not only a severe decrease of hepatic and plasma triglyceride with reduced fat mass but also elevation of plasma glucose levels (56).

Several lines of recent evidence indicate that GSK3 is involved in insulin resistance, which is defined as the status where peripheral tissues cannot respond to insulin and is closely associated with obesity and type II diabetes. Inhibition of GSK3 improves insulin resistance not only by an increase of glucose disposal rate in Zucker diabetic rats but also by inhibition of gluconeogenic genes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in hepatocytes (16, 57, 58). Furthermore, selective GSK3 inhibitors potentiate insulin-dependent activation of glucose transport and utilization in muscle in vitro and in vivo (58). GSK3 also directly phosphorylates serine/threonine residues of insulin receptor substrate-1, which leads to impairment of insulin signaling (59, 60).

In this study, we identified a novel role of GSK3 in the regulation of ADD1/SREBP1c transcriptional activity. Treatment of GSK3 inhibitors remarkably enhanced the transcriptional activity of ADD1/SREBP1c and stimulated the expression of its target genes such as FAS, SCD1, and ACC1, which are known to be key players for fatty acid metabolism as well as insulin-sensitive genes, in adipocytes and hepatocytes (Figs. 1–3). Accordingly, we observed that the levels of ADD1/SREBP1c target gene expression by GSK3 inhibitors were similar to those by insulin (Fig. 6), implicating that stimulation of ADD1/SREBP1c by insulin appears to be mediated, at least partly, by GSK3 inhibition. We also observed that insulin augmented the effects of the GSK3 inhibitor on the transcriptional activity of ADD1/SREBP1c.

In addition to the role of GSK3 in insulin signaling, these results might provide a clue to explain why expression of sev-
eral lipogenic genes is reduced in fat tissues of insulin-resistant animals (61). Compared with lean mice, the levels of GS3K and its enzyme activity are elevated in fat tissues or skeletal muscles of obese and diabetic mice models (62, 63), proposing that an increase of GS3K might be associated with abnormal energy metabolism by disrupting insulin action. Under these circumstances, it appears that transcriptional activity of ADD1/SREBP1c might be repressed by increased GS3K activity, leading to the reduced expression of lipogenic genes in fat tissues of obese and diabetic mice.

Previously, Roth et al. (64) demonstrated that MAP kinase phosphorylates SREBP-1a at serine 117 in vitro and mutation of this serine residue to alanine abolishes responsiveness of SREBP-1a to insulin and platelet-derived growth factor. However, the same for ADD1/SREBP1c was not confirmed and inhibitors of the MAP kinase pathway did not inhibit insulin-stimulated ADD1/SREBP1c target gene expression (28, 36, 37). We are currently investigating the phosphorylation site(s) of ADD1/SREBP1c by GSK3 and the functional roles of those sites in regulating the transcriptional activity of ADD1/SREBP1c.

To identify the phosphorylation residue(s) of ADD1/SREBP1c by GS3Kβ, we performed phosphoamino acid analysis. As a result, we observed that ADD1/SREBP1c was predominantly phosphorylated at serine residues (Supplemental Materials Fig. 1). Furthermore, by using different truncated ADD1/SREBP1c recombinant proteins, we observed that the N-terminal end of ADD1/SREBP1c was phosphorylated by GS3Kβ (Supplemental Materials Fig. 2). Although we identified at least six putative target sites of GS3Kβ in the N-terminal portion of the ADD1/SREBP1c protein, the exact site(s) of phosphorylation has not been identified currently. We are currently investigating the phosphorylation site(s) of ADD1/SREBP1c by GS3Kβ and the functional roles of those sites in regulating the transcriptional activity of ADD1/SREBP1c.

Taken together, these data suggest that GS3K plays a role in regulating the activity of ADD1/SREBP1c and that insulin-mediated induction of ADD1/SREBP1c target gene expression might be associated with the regulation of GS3K. Consistent with this view, inhibitors of GS3K, both LiCl and SB-216763, stimulate ADD1/SREBP1c target gene expression by altering its transcriptional activity. Therefore, GS3K appears to negatively regulate the transcriptional activity of ADD1/SREBP1c by phosphorylating ADD1/SREBP1c and this repression process is probably revealed when GS3K is suppressed in the presence of the insulin signaling pathway.

Acknowledgments—We thank Yun Sok Lee and Jun-Jae Chung for critically reading the manuscript.
Regulation of ADD1/SREBP1c Activity by GSK3

Berthelier-Lubrano, C., Spiegelman, B., Kim, J. B., Ferre, P., and Foufelle, F. (1999) Mol. Cell. Biol. 19, 3760–3768

56. Liang, G., Yang, J., Horton, J. D., Hammer, R. E., Goldstein, J. L., and Brown, M. S. (2002) J. Biol. Chem. 277, 9520–9528

57. Cline, G. W., Johnson, K., Regittiag, W., Perret, P., Tozzo, E., Xiao, L., Damico, C., and Shulman, G. I. (2002) Diabetes 51, 2903–2910

58. Ring, D. B., Johnson, K. W., Henriksen, E. J., Nuss, J. M., Goff, D., Kinnick, T. R., Ma, S. T., Reeder, J. W., Samuels, I., Slabiak, T., Wagman, A. S., Hammond, M. R., and Harrison, S. D. (2003) Diabetes 52, 588–595

59. Greene, M. W., and Garofalo, R. S. (2002) Biochemistry 41, 7082–7091

60. Eldar-Finkelman, H., and Krebs, E. G. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 9660–9664

61. Lan, H., Rabaglia, M. E., Stoehr, J. P., Nadler, S. T., Schueler, K. L., Zou, F., Yandell, B. S., and Attie, A. D. (2003) Diabetes 52, 688–700

62. Eldar-Finkelman, H., Schreyer, S. A., Shinohara, M. M., LeBoeuf, R. C., and Krebs, E. G. (1999) Diabetes 48, 1662–1666

63. Nikoulina, S. E., Ciaraldi, T. P., Mudaliar, S., Mohideen, P., Carter, L., and Henry, R. R. (2000) Diabetes 49, 263–271

64. Roth, G., Kotaka, J., Kremer, L., Lehr, S., Lohaus, C., Meyer, H. E., Krone, W., and Muller-Wieland, D. (2000) J. Biol. Chem. 275, 33302–33307
Regulatory Role of Glycogen Synthase Kinase 3 for Transcriptional Activity of ADD1/SREBP1c
Kang Ho Kim, Min Jeong Song, Eung Jae Yoo, Sung Sik Choe, Sang Dai Park and Jae Bum Kim

J. Biol. Chem. 2004, 279:51999-52006.
doi: 10.1074/jbc.M405522200 originally published online October 4, 2004

Access the most updated version of this article at doi: 10.1074/jbc.M405522200

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

Supplemental material:
http://www.jbc.org/content/suppl/2004/10/26/M405522200.DC1

This article cites 64 references, 39 of which can be accessed free at
http://www.jbc.org/content/279/50/51999.full.html#ref-list-1