Different Sterol Regulatory Element-binding Protein-1 Isoforms Utilize Distinct Co-regulatory Factors to Activate the Promoter for Fatty Acid Synthase*

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Sterol regulatory element-binding proteins (SREBPs) activate genes of cholesterol and fatty acid metabolism. In each case, a ubiquitous co-regulatory factor that binds to a neighboring recognition site is also required for efficient promoter activation. It is likely that gene- and pathway-specific regulation by the separate SREBP isoforms is dependent on subtle differences in how the individual proteins function with specific co-regulators to activate gene expression. In the studies reported here we extend these observations significantly by demonstrating that SREBPs are involved in both sterol regulation and carbohydrate activation of the FAS promoter. We also demonstrate that the previously implicated Sp1 site is largely dispensable for sterol regulation in established cultured cells, whereas a CCAAT-binding factor/nuclear factor Y is critically important. In contrast, carbohydrate activation of the FAS promoter in primary hepatocytes is dependent upon SREBP and both the Sp1 and CCAAT-binding factor/nuclear factor Y sites. Because 1c is the predominant SREBP isoform expressed in hepatocytes and 1a is more abundant in sterol-depleted established cell lines, this suggests that the different SREBP isoforms utilize distinct co-regulatory factors to activate target gene expression.

When cells are cultured in medium containing sufficient cholesterol the sterol regulatory element-binding proteins (SREBPs) are sequestered in the ER by two membrane spanning domains. When cellular sterol levels drop, the amino-terminal portions of the SREBPs are released from the ER by two ordered proteolytic events (1). The liberated mature SREBPs then enter the nucleus where they activate transcription of various genes in the fatty acid and cholesterol metabolic pathways (2–8). Additionally, fatty acids have also been shown to affect the regulated processing of the SREBPs from their membrane bound precursor state (9, 10); thus, the SREBPs are important regulators of both cholesterol and fatty acid metabolism.

SREBPs are weak activators of transcription by themselves, and for efficient promoter activation they require co-regulatory transcription factors that bind nearby DNA sequences. In the promoter for the low density lipoprotein (LDL) receptor this co-regulator is Sp1 (11). In contrast, recent studies have demonstrated that CCAAT-binding factor/nuclear factor Y (CBF/NF-Y) interacts with SREBP and is a key co-regulatory factor for 3-hydroxy-3-methylglutaryl-coenzyme A synthase, farnesyl-diphosphate synthase, and squaleone synthase promoters (12–14).

In our previous report, we determined that two closely spaced SREBP-binding sites are important for SREBP-mediated sterol regulation of the rat fatty acid synthase promoter (15). We also noted the presence of an Sp1-binding site in the sterol regulatory region of the FAS promoter, and we showed that Sp1 functioned together with SREBP to synergistically activate the FAS promoter. These earlier studies were performed using a Drosophila SL2 transfection assay system where both SREBP and Sp1 were expressed from exogenously supplied plasmid templates (3). However, the synergistic effect of SREBP and Sp1 on the FAS promoter was about an order of magnitude lower than observed for either the LDL receptor or acetyl coenzyme A carboxylase promoters. Thus, we reasoned there may be another transcription factor that could work together with SREBPs to activate the FAS promoter to high levels.

In the region of the rat FAS promoter that is required for sterol regulation (3) there is an inverted CCAAT sequence (16) that has been shown to bind several proteins including the CBF/NF-Y factor (17, 18). As mentioned above, this heterotrimeric factor has been shown to function together with SREBP to activate some of the genes of cholesterol metabolism. Thus, it was important to further evaluate the roles of Sp1 and CBF/NF-Y as potential co-regulators for SREBP-mediated activation of the FAS promoter. In the present report we show that the CBF/NF-Y site is critical for sterol regulation and for activation by ectopically expressed SREBP-1a and -2 in mammalian cells, whereas the Sp1 site is dispensable.

The promoter for FAS, like those of other key lipogenic genes, is also activated by a nutritional and hormonal process that is dependent on both insulin action and carbohydrate metabolism (19). In previous studies, mutations that disrupt the E-Box element that lies within and overlaps the tandem SREBP sites mentioned above were shown to be defective for insulin-dependent activation of FAS (20, 21). In the present report we show that mutations that disrupt the tandem SREBP sites but leave the E-box intact are defective for stimulation by glucose and insulin treatment in primary hepatocytes where SREBP-1c is the major isoform. Additionally, both NF-Y and Sp1 sites are absolutely required as well. Thus, the two
SREBP-1 isoforms appear to have distinct co-regulator requirements to efficiently stimulate the FAS promoter in response to different nutritional challenges.

MATERIALS AND METHODS

Cells and Media—The CV-1, HepG2, and SL2 cell lines were used in transient transfections conditions as described before (11, 15). Lipoprotein-deficient serum was prepared by ultracentrifugation of newborn bovine serum as described previously (22). Cholesterol and 25-hydroxycholesterol were obtained from Steraloids Inc., and stock solutions were dissolved in ethanol.

Cell Culture and Transient Transfection Assay—CV-1 cells were grown in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum and were plated at 125,000 cells/60-mm dish on day 0. On day 1 cells were transfected by the calcium phosphate co-precipitation method as described previously (11). Each dish received 5 μg of each test reporter construct plasmid and the non-sterol-regulated CMV2 β-galactosidase plasmid, which contains the cytomegalovirus (CMV) promoter fused to the Escherichia coli β-galactosidase gene as an internal control for transfection efficiency. In addition, dishes received 2.5 μg of salmon sperm DNA. Where indicated, cells were also transfected with the indicated amount of plasmid DNA corresponding to pNF-YA29, which we received from Dr. Mantovani (23). Dishes were incubated at 37 °C in 5% CO2.

On day 2, 12–16 h after transfection dishes were washed three times with 1× phosphate-buffered saline and refed either induced (Dulbecco's modified Eagle's medium and 10% lipid-deficient serum) or suppressed medium (same as induced medium but also containing 12 μg/ml cholesterol and 1 μg/ml 25-hydroxycholesterol), and dishes were incubated for another 24 h. On day 3 cells were harvested by scraping, and duplicate dishes were pooled prior to extraction of soluble protein extracts by three freeze thaw cycles. Luciferase and β-galactosidase activity were measured as described under “Enzyme Assays” below.

HepG2 cells were cultured in modified essential medium containing 10% fetal bovine serum and seeded for experiments at 175,000 cells/60-mm dish on day 0. On day 1 cells were transfected by the calcium phosphate co-precipitation method with the same amount of test plasmid, CMV2 β-galactosidase control plasmid, and salmon sperm DNA as described above for CV-1 cells. In addition, half of the dishes received a CMV expression clone encoding either amino acids 1–490 of the human SREBP-1a or 1–481 of human SREBP-2 proteins at the levels indicated in the figures, whereas the other half of the dishes only received salmon sperm DNA as a control (11). 5 h after transfection cells were treated with 1% trophenyl-D-galactopyranoside as substrate (26). The normalized luciferase values were determined by dividing the luciferase activity in relative light units by the β-galactosidase activity (A420/h). The data presented here are from several experiments performed in duplicate for each plasmid (see figure legends for exact number of individual experiments).

Enzyme Assays—The luciferase activities were measured in a lumimeter with a luciferin reagent from Promega Biotec. β-Galactosidase assays were performed by a standard colorimetric procedure with 2-nitrophenyl-β-D-galactopyranoside as substrate (26). The normalized β-galactosidase values were determined by dividing the β-galactosidase activity in relative light units by the β-galactosidase activity (A420/h).

RESULTS

The cis-acting elements necessary for sterol regulation of the rat FAS promoter were previously shown to reside between −150 to −43 relative to the transcription initiation site (+1) (3). In a follow up study we showed that two adjacent binding sites for SREBPs located between −72 and −53 are crucial for this effect (15). We also demonstrated that a GC-rich sequence at −80 bound the ubiquitous Sp1 factor and that ectopic expression of both SREBP and Sp1 would synergistically activate the FAS promoter in Drosophila SL2 cells.

However, the degree of synergistic activation of the FAS promoter by SREBP and Sp1 was an order of magnitude lower than for SREBP-Sp1 synergistic activation of the LDL receptor and acetyl coenzyme A carboxylase promoters (3, 5, 27). In addition to the Sp1-binding site at −80 there is a recognition site for CBF/NF-Y within the region of the FAS promoter that is required for sterol regulation (Fig. 1, bottom panel, and Refs. 15 and 16).

To determine whether Sp1, CBF/NF-Y, or both were important co-regulators for SREBP-dependent and sterol-regulated activation of the FAS promoter, we first evaluated the effects of mutations in the DNA-binding sites for Sp1 or NF-Y on sterol regulation (Fig. 1). Multi-base substitution mutations were inserted into the Sp1 or CBF/NF-Y sites, and the resultant mutant promoters were analyzed in transient transfection assays for sterol regulation in CV-1 cells as described under “Materials and Methods.” The Sp1 mutant was regulated by sterols in a similar fashion as the wild type promoter, whereas the CBF/NF-Y mutant was totally defective for sterol regulation. These data demonstrate that the CCAAT element is required for sterol regulation of the FAS promoter, whereas the Sp1 site is not.

We also compared these mutants with the wild type pro-
The inverted CCAAT motif is required for sterol regulation of the rat FAS promoter in CV-1 cells. The DNA sequence corresponding to the top strand of the rat FAS promoter from -103 to -53 is shown at the bottom. The $n$ in parentheses corresponds to 8 bases that are not shown. The underlined letters denote the E-box motif, and the two overlined regions designated I and II represent each of two separate SREBP recognition sites (15). The inverted CCAAT motif and the Sp1-binding sites are overlined and labeled. The enlarged bold letters correspond to the bases that were mutated in either the inverted CCAAT motif or the Sp1 consensus site. Mutant plasmids were analyzed for sterol regulation and luciferase values were normalized as described under “Materials and Methods.” The normalized luciferase values for cells transfected with the wild type FAS promoter were evaluated more precisely by performing a concentration curve with the CBF/NF-Y expression plasmids in CV-1 cells. Therefore, it is a useful cell based assay system for the analysis of transcription factor requirements for promoter activation because it provides a negative background for such studies (29). For example, this assay system was used to directly show that SREBP and Sp1 function as co-activators of the LDL receptor promoter (11). 

To directly test this hypothesis we developed a co-stimulation assay for SREBP and CBF/NF-Y in Drosophila SL2 cells. We prepared Drosophila -based expression constructs for all three CBF/NF-Y subunits and first added them individually or in different combinations to determine which if any were functionally missing (Fig. 5). The results demonstrated that significant activation of the FAS promoter was achieved only when all three CBF/NF-Y expression constructs were added along with SREBP whereas the combination of SREBP and Sp1 was much less active (Fig. 5, compare lanes 4 and 12). The inclusion of Sp1, SREBP, and all three NF-Y subunits resulted in an even higher level of activation (lane 11). 

The requirement for CBF/NF-Y in activation of the FAS promoter was evaluated more precisely by performing a concentration curve with the CBF/NF-Y expression plasmids in the presence or absence of a fixed amount of the SREBP-1a and Sp1 expressing constructs (Fig. 6). From this series of experiments it is clear that CBF/NF-Y alone (triangles) or in combination with Sp1 (diamonds) is not very effective, whereas SREBP-1a addition on top of NF-Y resulted in a significant stimulation of FAS promoter activity at all concentrations of CBF/NF-Y plasmids (squares). When Sp1 was included in addition to SREBP-1a, there was a higher level of activation observed at every concentration of CBF/NF-Y (circles). 

FAS expression is activated by insulin signaling and carbohydrate metabolism, and the FAS promoter has been studied as a model for lipogenic gene activation (19). A region encompassing the E-box and tandem SREBP sites discussed here is required for activation of the FAS promoter by insulin and carbohydrate signaling (20). To explore the potential roles of the SREBP, NF-Y, and Sp1 sites in activation of the FAS promoter by insulin and glucose, we evaluated the effects of the Sp1 and NF-Y site mutations described in Fig. 1 and the SREBP-binding site mutants we analyzed previously (15) on activation of the FAS promoter in primary rat hepatocytes in response to insulin and glucose (Fig. 7). The wild type promoter was activated over 6-fold by the addition of insulin and a high concentration of glucose, whereas the mutations in either the NF-Y or Sp1 sites resulted in a loss in activation. Additionally, we analyzed three other mutations that we made for our previous study that helped us determine that the tandem SREBP
sites (and not the E-box element) are the critical cis-acting sites for sterol regulation. One of the mutations alters the E-box sequence and downstream SREBP site simultaneously (mutant B); another mutation alters the upstream SREBP site without affecting the E-box sequence (mutant D), and one mutant alters both SREBP sites simultaneously (mutant A/B/C). All three of these additional mutations disrupted SREBP binding to one (mutants B and D) or both (mutants A/B/C) SREBP sites and were defective for sterol regulation (15). The data in Fig. 7 demonstrate that all three mutants are also defective for activation by insulin/glucose. Taken together these experiments document that the two tandem SREBP sites as well as both the Sp1 and NF-Y site are important for insulin/glucose activation of the FAS promoter.

Because the major isoforms of SREBPs in sterol-depleted cultured cells are SREBP-1a and SREBP-2 and the major nuclear SREBP isoform in normal hepatocytes is SREBP-1c (30), the experiments presented so far suggest that SREBP-1c may require both Sp1 and NF-Y for efficient activation of the FAS promoter, whereas activation by SREBP-1a would be largely dependent only on NF-Y. To test this possibility we analyzed the co-regulatory factor requirements for each of SREBP-1a and -1c in Drosophila SL2 cells where we can specifically manipulate the functional levels of SREBPs, NF-Y, and Sp1 directly by co-transfection (Fig. 8). We evaluated the activation of the FAS promoter by increasing concentrations of NF-Y in the presence of SREBP-1a or SREBP-1c expressing constructs in the presence or absence of co-transfected Sp1 plasmid. Consistent with the mammalian cell studies and our other SL2 studies, efficient activation by SREBP-1a occurred when SREBP-1a and NF-Y were co-transfected (Fig. 8, open squares); however, high level of activation by SREBP-1c required that both NF-Y- and Sp1-expressing plasmids were included (Fig. 8, compare open and closed circles).

**DISCUSSION**

Cholesterol and fatty acid metabolism are coordinately regulated through the action of the SREBPs. However, when separate control of each pathway is required there has to be a mechanism to modulate one process independently from the other. Because the SREBPs require generic factors as transcriptional co-regulators, it is likely that part of the independent regulation results from the recruitment of distinct transcriptional co-regulators by SREBPs to activate key genes of one process or the other. Thus, the first step in understanding how the SREBPs differentially regulate gene expression is to identify the important SREBP co-regulatory proteins in the promoters for critical genes of each pathway such as FAS.

In our previous work we showed there are two critical SREBP sites and a putative co-regulatory Sp1 site in the region of the FAS promoter that is essential for SREBP activation and sterol regulation in cultured cells. We also demonstrated that SREBPs and Sp1 could synergistically activate the FAS promoter in Drosophila SL2 cells (13). However, we noted that the
degree of activation by SREBP and Sp1 was modest compared with the robust activation that resulted from the interaction of these same two factors on the LDL receptor and acetyl coenzyme A carboxylase promoters (3, 5, 11). Also, there is a CBF/NF-Y site close to the putative key Sp1 site (16). Based on these observations we designed a series of experiments to specifically evaluate the roles of CBF/NF-Y and Sp1 as co-regulators in SREBP activation of the FAS promoter.

We introduced multi-base substitutions within the predicted recognition sites for both Sp1 and NF-Y and evaluated the effects on sterol regulation (Fig. 1) and activation by ectopically introduced and constitutively active forms of either SREBP-1a or -2 in cultured cells (Fig. 2). The results demonstrate that the CBF/NF-Y site is essential for sterol regulation and activation by both individual SREBPs, whereas the Sp1 site does not play an important role. We confirmed that the mutations we introduced did destroy Sp1 binding (Fig. 3) and that CBF/NF-Y activity is required for sterol regulation of FAS (Fig. 4). Thus, CBF/NF-Y is the critical co-regulator for SREBP activation of the FAS promoter in response to sterol deprivation.

We also evaluated the SREBP co-regulator specificity in a Drosophila SL2 transfection assay. For these studies we first
had to determine whether the SL2 cells could be used to evaluate activation by exogenously supplied CBF/NF-Y and which if any of the three individual subunits were functionally missing in these cells. The experiments in Fig. 5 demonstrate that SL2 cells are indeed an efficient host-cell system to evaluate activation by mammalian CBF/NF-Y and that efficient activation required that expression vectors for all three CBF/NF-Y subunits were together with the SREBP-1a expressing plasmid. A further stimulation of FAS promoter activity was observed when the Sp1 plasmid was additionally added. To more carefully evaluate the roles of CBF/NF-Y and Sp1, we performed a series of experiments where the CBF/NF-Y expressing plasmids were added at increasing concentrations in the presence and absence of a fixed amount of the SREBP or Sp1 expressing constructs (Fig. 6). The results clearly document that CBF/NF-Y and SREBP synergistically activate the FAS promoter; however, a further stimulation was observed when Sp1 was added. Thus, Sp1 augments the stimulatory activity of SREBP and CBF/NF-Y.

We have used a similar co-transfection assay to evaluate the co-regulator requirements for SREBP activation and sterol regulation in the promoter for 3-hydroxy-3-methylglutaryl-coenzyme A synthase (31). In this promoter, three separate proteins: SREBP, CBF/NF-Y, and cAMP element-binding protein/activating transcription factor are all simultaneously required for sterol regulation and appreciable activation in SL2 cells. This is similar to but distinct from the FAS promoter where the third unique third factor (in this case Sp1) is not essential for sterol regulation but does provide a further stimulation of promoter activity in the co-transfection assay.

The FAS proximal promoter harbors a compact arrangement of transcription factor-binding sites. The two key SREBP sites that we have identified overlap the two halves of a classic E-box at −65. This is the consensus site for classic bHLH DNA-binding factors such as upstream stimulatory factor (20). There are also the Sp1 and CBF/NF-Y sites that are analyzed here and another classic SREBP site at −150. The current results taken together with previous studies strongly suggest that the two tandem SREBP sites that flank the E-box and the CBF/NF-Y site are the key elements for sterol regulation by the SREBPs.

USF binding to the E-box at −65 has been implicated in the activation of FAS by insulin signaling (20), but other studies suggest an involvement for SREBPs in this process (21, 32). Because a mutation that alters SREBP binding and activation by sterol deprivation (mutant D) but leaves the E-box element unaltered is also defective for insulin/glucose activation (Fig. 7), our results are consistent with an involvement of SREBPs in this process. Additionally, the analysis of the NF-Y and Sp1 site mutants extend these observations and suggest that both of these co-regulatory factors are required for insulin/glucose activation. This is different for sterol regulation where the NF-Y site is crucial, whereas the Sp1 site was largely dispensable (Fig. 1).
Sterol and Carbohydrate Regulation of FAS Promoter by SREBPs

The sterol regulation experiments were performed in cultured cells where the 1a isofrom is more prevalent, and the insulin/glucose activation studies were performed in hepatocytes where 1c is the most abundant SREBP isofrom expressed. This suggested that activation of the FAS promoter by SREBP-1a may require NF-Y predominantly and not Sp1, whereas activation by SREBP-1c may require both NF-Y and Sp1. The two SREBP-1 isofroms differ as a result of alternative promoter usage and unique mRNA splicing (30). The effect is that the amino-terminal region of 1c lacks 29 amino acids that are present in 1a and has 5 additional unique residues. This region of SREBP-1a contains its transcription activation domain, which has been shown to interact with the CBP/p300 co-activator family (33) as well as with the more recently identified ARC/DRIP multi-subunit complex (34). Native SREBP-1c is a much weaker transcriptional activator than 1a (30). It does not efficiently interact with CBP/p300, and it interacts with only a subset of the ARC/DRIP components. Thus, efficient activation by SREBP-1c would be predicted to require additional factors relative to SREBP-1a, and our data are consistent with this view. To directly investigate this possibility we performed activation experiments in Drosophila SL2 cells where we can directly manipulate the identity and functional levels of the individual transcription factors (Fig. 8). The results of these experiments are consistent with the results from the mammalian cell transfection experiments and indicate that efficient activation of the FAS promoter by SREBP-1a is largely dependent on NF-Y and not Sp1, whereas SREBP-1c requires both co-regulatory factors to efficiently activate the FAS promoter.

Our data are also consistent with a model where the amino termini of the different SREBP-1 isofroms differentially affect protein-protein interactions between SREBP-1 and NF-Y or Sp1 that may alter DNA binding. However, we have previously shown that SREBP-1 and NF-Y interact directly in solution. This effect required prior assembly of the NF-Y factor into its heterotrimeric complex and only required a small region of the SREBP-1 protein including its DNA-binding domain (12). The amino-terminal region where SREBP-1a and -1c differ was totally dispensable for the interaction. In the LDL receptor promoter we have also demonstrated that SREBP stimulates Sp1 to bind the LDL receptor promoter DNA, but this effect only requires the SREBP DNA-binding domain as well (11). It also required only a small portion of the Sp1 protein surrounding its DNA-binding domain. However, for transcriptional synergy in cells additional domains of both SREBP and Sp1 were required (35). Thus, synergy occurs at two steps: one is at the level of DNA binding, and the other is after DNA binding where the transcriptional activation domains of each protein are essential. Based on the fact that the in vitro protein-protein interaction between NF-Y and SREBP and the in vitro interaction between Sp1 and SREBP only require the DNA-binding domain of SREBP, we think it is likely that a similar two-step model for transcriptional synergy is also likely in the FAS promoter.

The differential recruitment of co-regulators by the SREBPs and mechanisms that specifically target their interactions with SREBPs could provide at least a partial basis for selective activation of FAS and fatty acid metabolism independently from cholesterol synthesis. In this regard, we have recently demonstrated that the yin yang 1 protein (YY1) can selectively down-regulate the LDL receptor promoter through targeting the gene-specific interaction between Sp1 and SREBP that is required to activate the LDL receptor promoter (36).

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