The Orphan Nuclear Receptor Rev-Erbα Is a Peroxisome Proliferator-activated Receptor (PPAR) γ Target Gene and Promotes PPARγ-induced Adipocyte Differentiation*

Rev-Erbα (NR1D1) is an orphan nuclear receptor encoded on the opposite strand of the thyroid receptor α gene. Rev-Erbα mRNA is induced during adipocyte differentiation of 3T3-L1 cells, and its expression is abundant in rat adipose tissue. Peroxisome proliferator-activated receptor γ (PPARγ) (NR1C3) is a nuclear receptor controlling adipocyte differentiation and insulin sensitivity. Here we show that Rev-Erbα expression is induced by PPARγ activation with rosiglitazone in rat epididymal and perirenal adipose tissues in vivo as well as in 3T3-L1 adipocytes in vitro. Furthermore, activated PPARγ induces Rev-Erbα promoter activity by binding to the direct repeat (DR)-2 response element Rev-DR2. Mutations of the 5' or 3' half-sites of the response element totally abrogated PPARγ binding and transcriptional activation, identifying this site as a novel type of functional PPARγ response element. Finally, ectopic expression of Rev-Erbα in 3T3-L1 preadipocytes potentiated adipocyte differentiation induced by the PPARγ ligand rosiglitazone. These results identify Rev-Erbα as a target gene of PPARγ in adipose tissue and demonstrate a role for this nuclear receptor as a promoter of adipocyte differentiation.

Adipocyte differentiation is a complex biological process, which is reflected at the molecular level by the transcriptional activation of a number of adipocyte-specific genes and by the acquisition of the ability to accumulate cytoplasmic lipid droplets (1–3). The nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ,1 NR1C3) (4, 5) and members of the CCAAT enhancer-binding protein (C/EBP) family (6–12) play key roles in this adipogenic process. In addition, the adipocyte differentiation and determination factor-1 (SREBP-1/ADD1) appears to promote adipocyte differentiation by activating the expression of PPARγ and increasing the synthesis of endogenous PPARγ ligands (13–15). Members of the PPAR family bind as heterodimers with the retinoid X receptors (RXR) to specific response elements termed peroxisome proliferator response elements (PPRE) (for review see Ref. 16). These PPREs usually consist of a direct repeat of the PuGGTCA motif spaced by one nucleotide (DR1). The transcriptional activity of the PPARs is activated by a number of different fatty acid metabolites, most notably products of the cyclooxygenase and lipoxygenase pathways. In addition, a large number of synthetic compounds are known to be potent and subtype specific PPAR ligands. For example, thiazolidinedione compounds used as insulin sensitizers in the treatment of type II diabetes are high affinity PPARγ ligands (17).

Rev-Erbα (NR1D1) is another nuclear receptor, the expression of which is induced during adipocyte differentiation (18). Rev-Erbα is highly expressed in adipose tissue but also in skeletal muscle, liver and brain (18–21). Since no ligand has been identified so far, Rev-Erbα is considered as an orphan member of the nuclear receptor superfamily. Rev-Erbα has been shown to act as a negative regulator of transcription (22) binding either as monomer on nuclear receptor half-site motifs flanked 5' by an AT-rich sequence (ATPuGGTCA), or as a homodimer to a direct repeat of the PuGGTCA motif spaced by two nucleotides (DR2).

We have previously shown that PPARα activates the expression of Rev-Erbα through an atypical PPRE, a DR-2 element, in the Rev-Erbα promoter (23). Transcriptional activation by PPARγ through a DR-2 element has so far not been reported. However, since Rev-Erbα is induced during the course of adipocyte differentiation, we decided to investigate whether PPARγ could be involved in transcriptional induction of Rev-Erbα expression in adipocytes. Furthermore, we wanted to investigate whether Rev-Erbα plays a modulatory role in the process of adipogenesis. Our results from both in vivo and in vitro studies demonstrate that treatment with the PPARγ agonist rosiglitazone increases Rev-Erbα gene expression and that PPARγ activates Rev-Erbα transcription via the Rev-DR2 response element present in the human Rev-Erbα promoter. Finally, we show that ectopic expression of Rev-Erbα in 3T3-L1 preadipocytes significantly augments the adipogenic activity of the PPARγ selective ligand rosiglitazone.

MATERIALS AND METHODS

Animals—Male Sprague-Dawley rats (10 weeks old) were treated for 14 days by gavage with rosiglitazone (10 mg/kg/d) suspended in 1% carboxymethylcellulose solution. Control animals received an equal...
protein and the neomycin resistance by the infected cells. GP + E86 cells (15,000/cm²) were transfected with the MFG plasmid constructs (2 µg) using LipofectAMINE (Invitrogen) and selected for resistance using the genetic analog G418 (0.8 mg/ml, Invitrogen). 3T3-L1 cells were infected with the GP + E86-produced MFG-Neo or MFG-Rev viruses essentially as previously described (35). Genetic-resistant infected cell pools were used for the studies within three passages after infection.

**Cell Culture and Differentiation—**3T3-L1 cells were cultured in growth medium containing DMEM and 10% calf serum. The cells were differentiated by the method of Bernlohr et al. (34). 2 days post-confluent cells (designated day 0) were switched to differentiation medium (DMEM, 10% fetal calf serum, 1 µM dexamethasone, 10 µg/ml insulin, and 0.5 mM 3-methyl-1-isobutylxanthine (IBMX) (Sigma)) for 2 days. Thereafter, the cells were cultured in post-differentiation medium (DMEM, 10% fetal calf serum, insulin) with or without rosiglitazone (1 µM). The medium was changed every day. Retroviral infected 3T3-L1 preadipocytes were cultured under the same conditions, but differentiated either with (standard differentiation conditions) or without (rosiglitazone-dependent differentiation conditions) dexamethasone. After treatment the cells were fixed with 10% formaldehyde in phosphate-buffered saline and stained with Oil Red O (Sigma) or total RNA was extracted as described above (35).

**RESULTS**

**Activation of PPARγ Increases Rev-Erbα mRNA Levels in Adipose Tissue—**In order to determine whether PPARγ activation affects Rev-Erbα expression in vivo, rats were treated for 14 days with rosiglitazone, a highly specific and potent PPARγ ligand (36). The expression of Rev-Erbα was analyzed in epididymal and perirenal adipose tissue by Northern blot analysis. Compared with control treated rats, rosiglitazone treatment strongly increased Rev-Erbα mRNA levels both in epididymal and perirenal adipose tissue (Fig. 1), whereas no change in control β-actin mRNA levels was observed. These experiments demonstrate that PPARγ activators increase Rev-Erbα mRNA levels in adipose tissue in vivo.

**PPARγ Activation Induces Rev-Erbα mRNA in 3T3-L1 Preadipocytes—**To study the molecular and cellular mechanisms of this induction, we next investigated the regulation of Rev-Erbα mRNA expression by rosiglitazone in the 3T3-L1 preadipocyte cell line. Cells were grown until confluency in medium containing calf serum. 2 days post-confluent cells (designated day 0), cells were transferred to medium containing fetal calf serum and differentiated with the classic differentiation mixture containing dexamethasone, IBMX, and insulin. From day 2, either 1 µM rosiglitazone or vehicle was added. RNA was harvested at day 0, 2, 4, 6, and 8 and used for Northern analysis. As previously reported (18), Rev-Erbα mRNA levels increased upon differentiation of preadipocytes into adipocytes (Fig. 2, A and B). However, compared with the standard differentiation treatment...
Rev-Erbα mRNA levels were induced earlier in the presence of rosiglitazone. Moreover, Rev-Erbα mRNA levels were higher after 8 days in fully differentiated 3T3-L1 adipocytes treated with rosiglitazone compared with controls (Fig. 2, A and B). Rosiglitazone is known to be a potent inducer of differentiation, thus in order to distinguish between direct effects of rosiglitazone on Rev-Erbα gene expression and indirect effects mediated via increased differentiation, we investigated whether rosiglitazone was able to induce Rev-Erbα in fully differentiated day 10 adipocytes. As shown in Fig. 2, C and D, rosiglitazone activated the expression of Rev-Erbα as well as the adipocyte lipid-binding protein (ALBP/aP2), a well-characterized PPARγ target gene (5), in mature adipocytes. Inhibition of protein synthesis by cycloheximide caused a superinduction of Rev-Erbα and could therefore not be used to investigate whether the induction of Rev-Erbα was mediated directly by PPARγ (data not shown). Nevertheless, these experiments demonstrate that activation of PPARγ increases Rev-Erbα mRNA during in vitro differentiation of 3T3-L1 preadipocytes as well as in mature adipocytes.

**PPARγ Induces Rev-Erbα Expression at the Transcriptional Level**—PPARα has previously been shown to activate the human Rev-Erbα promoter in hepatocytes via a DR-2 element (23), through which Rev-Erbα represses also its own transcription (29). To determine whether this site also mediates the activation of the Rev-Erbα promoter by PPARγ in adipocytes, transfection assays were carried out using luciferase reporter constructs driven by the Rev-Erbα promoter. 3T3-L1 cells were cotransfected with the PPARγ expression vector (pSG5-hPPARγ) or empty vector (pSG5) and treated with rosiglitazone or...
vehicle. Rev-Erbα promoter activity was induced by PPARγ cotransfection, an effect that was enhanced in the presence of rosiglitazone (Fig. 3). By contrast, Rev-Erbα promoter activity was unaffected by rosiglitazone in the absence of overexpressed PPARγ, probably due to the insufficient levels of endogenous PPARγ in non-confluent preadipocytes. These data indicate that Rev-Erbα gene transcription is induced by rosiglitazone via PPARγ.

To further investigate the importance of the DR-2 element in the induction by PPARγ, Rev-Erbα promoter constructs in which the Rev-DR2 site was mutated, were tested next. Mutations affecting the 5′-AGGTCA motif (pGL2hRev-Erbα as described (29) (Fig. 4A)) of the Rev-DR2 site resulted in the loss of Rev-Erbα promoter inducibility by rosiglitazone and PPARγ (Fig. 4B). These results indicate that the Rev-DR2 site mediates the transcriptional induction of Rev-Erbα by PPARγ.

To assess whether the Rev-DR2 site could also function as a PPARγ-responsive element in front of a heterologous promoter, transient transfection experiments were performed using constructs containing the wild-type or mutated versions of the Rev-DR2 site (Fig. 4B) cloned in front of the heterologous SV40 promoter (Rev-DR2, Rev-DR2M5′ and Rev-DR2M3′). In COS cells, cotransfection of pSG5-hPPARγ on the Rev-DR2 driven SV40 reporter vector led to a 2.5-fold induction of transcription activity compared with empty pSG5 vector cotransfection (Fig. 4C). This effect was enhanced in the presence of rosiglitazone. By contrast, PPARγ did not activate the Rev-DR2 site mutated in its 5′-AGGTCA half-site (Rev-DR2M5′). Furthermore, mutation of the 3′-half-site (Rev-DR2M3′) of the DR2 site also abolished transactivation by PPARγ. These results clearly demonstrate that the Rev-Erbα human promoter is regulated by PPARγ and that this induction is mediated via the Rev-DR2 site.

PPARγ Binds as a Heterodimer with RXRα to the Rev-DR2 Site—To investigate whether PPARγ binds directly to the Rev-DR2 site, electrophoretic mobility shift assays (EMSA) were performed using in vitro synthesized PPARγ and RXRα proteins. Since the Rev-DR2 site was previously described as a Rev-Erbα response element, binding of Rev-Erbα was assayed as a control (Fig. 5A). As expected (29), Rev-Erbα bound both as homo- and as monomer to the Rev-DR2 site. Furthermore, no binding was observed on the Rev-DR2 oligonucleotide carrying a mutation in the 5′-half-site (M5′), whereas Rev-Erbα bound only as a monomer to the Rev-DR2 carrying a mutation in the

![Diagram](image-url)
3′-half-site (M3′) in accordance with previous observations (29). RXRα or PPARγ alone did not bind to either wild-type or mutated Rev-DR2 sites confirming that PPARγ cannot bind as a monomer. By contrast, binding to the Rev-DR2 site was observed when PPARγ was incubated in the presence of RXRα. The binding was specific since it was competed out by excess of unlabeled oligonucleotide (Fig. 5A). The specificity of the binding complex was verified by the addition of a specific anti-PPARγ antibody (38), which inhibited formation of the PPARγ/RXRα complex. The binding was prevented by mutation of both the 5′- (M5′) or 3′- (M3′) half-sites of the Rev-DR2 element. To determine the relative binding affinity of the PPARγ/RXRα heterodimer for the Rev-DR2 site, cross-competition EMSA experiments were performed comparing binding of PPARγ/RXRα to the natural DR-1 site in the aP2 promoter (5) and the Rev-DR2 site. As shown in Fig. 5B, competition with the cold Rev-DR2 site decreased PPARγ/RXRα binding to both the radiolabeled Rev-DR2 and aP2 DR-1 sites. These experiments demonstrate that PPARγ binds as a heterodimer with RXRα to the Rev-DR2 site of the Rev-Erbα promoter, albeit with significantly lower affinity compared with the aP2 PPRE site (Fig. 5B).

Rev-Erbα Increases the Adipogenic Activity of PPARγ Agonists—To assess a potential role of Rev-Erbα in adipogenesis, full-length human Rev-Erbα was cloned into a retroviral vector, and 3T3-L1 preadipocytes were infected with the resulting virus (MFG-Rev) or the control MFG-Neo virus. Pools of cells stably transduced, but not clonal selected 3T3-L1 cells were subsequently cultured with an incomplete differentiation mixture, which requires PPARγ activation with rosiglitazone for optimal differentiation, and either rosiglitazone (1 μM) or vehicle was added from day 2 to day 8. The presence of Rev-Erbα in MFG-Neo or MFG-Rev infected cells was analyzed by Western blot (Fig. 6A) and Northern blot analysis (Fig. 6B) of 3T3-L1 cells treated for 6 days with the differentiation mixture. Western blot analysis demonstrated the presence of ectopic expressed human Rev-Erbα protein in MFG-Rev infected, but not in the control cells (Fig. 6A). Since the antibody used was raised against a peptide, its affinity was too low to detect endogenous Rev-Erbα protein. However, both ectopic and endogenous Rev-Erbα expression was detected by Northern blot analysis in MFG-Rev cells, whereas MFG-Neo cells only expressed endogenous Rev-Erbα (Fig. 6B).

The effect of ectopic Rev-Erbα on adipocyte differentiation
Fig. 6. Ectopic expression of Rev-Erbα enhances rosiglitazone-induced lipid accumulation. 3T3-L1 cells were infected with a retrovirus containing either Rev-Erbα (MFG-Rev) or not (MFG-Neo). The resulting cells were induced to differentiate in the presence of insulin and IBMX with or without RSG (1 μM) for 8 days. The cells were subsequently fixed and stained with Oil Red O. Ectopic expression of Rev-Erbα protein was determined by Western blot analysis (A) using a rabbit polyclonal anti-Rev-Erbα antibody raised against a synthetic peptide (amino acids 263–365 of the human sequence) that recognizes Rev-Erbα protein. Northern blot analysis (B) (left lane, 3T3-L1 MFG-Neo; right lane, 3T3-L1 MFG-Rev-infected cells) of infected 3T3-L1 cells demonstrating ectopic (Ecto-Rev) and endogenous (Endo-Rev) Rev-Erbα mRNA expression. Microscopic views of the Oil Red O-stained cells (C) and macroscopic views of the Oil Red O-stained dishes (D).

was investigated using Oil Red O staining to assess triglyceride accumulation in 3T3-L1 cells induced to differentiate in incomplete medium (Insulin and IBMX, but no dexamethasone). Under these conditions, full differentiation is dependent on the presence of the PPARγ agonist rosiglitazone. In the absence of rosiglitazone, ectopic expression of Rev-Erbα induced only a slight increase in triglyceride accumulation (Fig. 6, C and D). However, when rosiglitazone was added, a major increase in triglyceride accumulation was observed in the cells expressing Rev-Erbα compared with control cells. These morphological changes were accompanied by a pronounced induction of mRNA levels of the adipocyte-specific marker, and PPARγ target gene, aP2, whose expression was strongly induced by rosiglitazone and Rev-Erbα (Fig. 7). Moreover, a strong increase in PPARγ mRNA levels was observed in MFG-Rev compared with MFG-Neo cells, which may be a reflection of the differentiation status of the cells. In addition, rosiglitazone treatment induced PPARγ expression due to PPARγ auto-induction (39). Similarly, mRNA levels of C/EBPα, another differentiation marker, were also induced by Rev-Erbα over-expression. Moreover, as expected, C/EBPα mRNA level was induced by rosiglitazone in MFG-Neo cells, likely due to the cross regulation of PPARγ and C/EBPα (40). However, in Rev-Erbα expressing cells, rosiglitazone treatment did not further enhance C/EBPα expression. Although the expression levels of C/EBPβ, an early inducer of adipocyte differentiation, and SREBP-1/ADD1 were higher upon rosiglitazone treatment, likely due to the optimal differentiation status of the cells under these conditions, the mRNA levels of these transcription factors were not influenced by Rev-Erbα expression (Fig. 7).

Next, the influence of Rev-Erbα on the expression of aP2, PPARγ and C/EBPα was determined when 3T3-L1 cells were differentiated under classical conditions (insulin, IBMX, and dexamethasone). As expected, induction levels of aP2, PPARγ, C/EBPα, and endogenous Rev-Erbα were more pronounced in the complete compared with the incomplete mixture without dexamethasone (compare Fig. 7 to Fig. 8). Induction levels of these adipogenic markers were identical between non-infected cells and MFG-Neo cells indicating that the retrovirus-infected cells differentiate normally (data not shown). Interestingly, Rev-Erbα infected cells expressed Rev-Erbα mRNA levels similar to those present in 3T3-L1 cells differentiated in complete mixture containing rosiglitazone, indicating that the Rev-Erbα retrovirus system produced Rev-Erbα levels within the physiological range (Fig. 8). Rev-Erbα over-expression further enhanced aP2, PPARγ, and C/EBPα expression although the effect was less pronounced than in the presence of incomplete mixture. Finally, no change was observed in C/EBPβ and SREBP-1/ADD1 mRNA levels under these conditions (Fig. 8). Altogether, these data support a role of Rev-Erbα as an enhancer of adipogenesis likely acting downstream PPARγ.

**DISCUSSION**

The expression of the nuclear receptor Rev-Erbα has previously been reported to be transcriptionally up-regulated during adipocyte differentiation (18). However, the mechanisms of this induction and the physiological role of Rev-Erbα in adipogenesis remained unexplored. In the present report, we demonstrate that PPARγ activation by rosiglitazone induces Rev-Erbα mRNA expression both in vivo in adipose tissue of rats and in vitro in 3T3-L1 adipocytes. Transfection experiments revealed that the regulation of human Rev-Erbα expression by rosiglitazone occurs at the transcriptional level via activation of PPARγ. Mutation of the Rev-DR2 site located in the Rev-Erbα promoter prevented PPARγ-induced Rev-Erbα transcription identifying this site as a novel type of PPRE. Finally, we show that ectopic Rev-Erbα promotes adipocyte differentiation induced by PPARγ activators.

Recent structure-function analysis and three-dimensional modeling of Rev-Erbα indicated that the structure of the putative ligand cavity is occupied by side chains, suggesting that this receptor may not have any endogenous ligands (41). Therefore, the regulation of Rev-Erbα expression constitutes a crucial level of control of receptor activity. Rev-Erbα expression...
has been reported to be controlled by a variety of stimuli. Human Rev-Erbα represses its own expression via a Rev-DR2 site located in its promoter (29). In rat liver, as well as in cultures of human primary hepatocytes (42) and rat fibroblasts (43), Rev-Erbα expression oscillates in a circadian rhythm. In addition, rat and human hepatic Rev-Erbα expression is also under control of other nuclear receptors, such as the glucocorticoid receptor (42). Interestingly, we previously demonstrated that fibrates induce human Rev-Erbα expression in liver via PPARγ binding to the Rev-DR2 site (23). Here, we find that activation of PPARγ induces Rev-Erbα gene expression in adipose tissue. This induction occurs at the transcriptional level through binding of PPARγ to the Rev-DR2 site (23). Here, we find that activation of PPARγ induces Rev-Erbα gene expression in adipose tissue. This induction occurs at the transcriptional level through binding of PPARγ to the Rev-DR2 site, in a manner as described for PPARα. This identifies Rev-Erbα as a new PPARγ target gene in adipose tissue. Moreover, since all PPARγ elements so far identified are DR-1 elements composed of a direct repeat of the canonical AGGTCA sequence separated by one base, our data identify the DR-2 element as a novel type of PPARγ response element. PPARα and PPARγ share a number of common target genes. Indeed fibrates, which activate preferentially PPARα, induce LPL, ACS, and CD36 expression in liver, whereas glitazones, which selectively activate PPARγ, have little effect on liver, but induce similar target genes in adipose tissue of rats (44–46). Therefore, Rev-Erbα is another example of a gene whose expression is induced specifically by PPARα in liver and by PPARγ in adipose tissue.

The molecular mechanisms regulating the initial steps of adipogenesis have been thoroughly studied. The transcription cascade triggering adipogenesis requires a fine orchestration of sequential expression of different transcription factors. The sequential activation of C/EBPs and PPARs are central in the adipogenic process. C/EBPβ and C/EBPδ are induced early during differentiation in 3T3-L1 preadipocytes and therefore appear to play an important role in the initiation of the adipogenic cascade. C/EBPβ and C/EBPδ play a crucial role in further promoting adipocyte differentiation. C/EBPγ and C/EBPα mutually activate the expression of the other, leading to a sustained expression of these transcription factors (40, 48). Our results show that Rev-Erbα is a target gene of PPARγ (Fig. 9). Whether Rev-Erbα is also a target gene for C/EBPs awaits further studies.

Since Rev-Erbα is a transcription factor, we studied whether...
it might participate in the adipogenic program. Rev-Erbα significantly promoted adipogenesis especially under conditions where the differentiation is dependent on PPARγ activation. Thus, Rev-Erbα is not only a PPARγ target gene, but also potentiates the adipogenic activity of this receptor. The observation that ectopic expression of Rev-Erbα increases the expression of the PPARγ target genes, aP2, and C/EBPα, indicates that Rev-Erbα enhances the adipogenic function of PPARγ. The fact that Rev-Erbα also induces PPARγ expression could be an indirect reflection of the pronounced stimulation of adipocyte differentiation, since this effect is also observed under conditions independent of rosiglitazone treatment (Fig. 8). Alternatively, Rev-Erbα could indirectly enhance PPARγ expression by interfering negatively with the expression or activity of a transcription factor that represses PPARγ expression. Since, Rev-Erbα over-expression does not change C/EBPβ and SREBP-1/ADD1 mRNA levels, it appears to play a role as an enhancer of adipogenesis acting downstream of PPARγ (Fig. 9).

Since Rev-Erbα is a repressor of gene transcription, it may also promote adipocyte differentiation indirectly via the down-
regulation of anti-adipogenic factors or via negative interference with anti-adipogenic cytokine cascades (49). Such anti-adipogenic factors may include the Glucocorticoid-induced leucine zipper (GILZ) protein (50), Pref-1 (51), Resistin (51), Resistin-like molecule α (52), Wnt protein (53, 54), Kruppel-like factor (KLF2) (55), Foxo1 (56), Retinoblastoma (RB) (57), and/or calcineurin (37). Further studies are required to determine whether any of these factors are potential target genes of Rev-Erbα.

In conclusion, we have identified Rev-Erbα as a new target gene for PPARγ in the adipogenic cascade of transcription factors and as an important factor modulating adipocyte function, at least in part, by enhancing the adipogenic action of PPARγ. The exact molecular mechanisms by which Rev-Erbα enhances adipogenesis await further studies.

Acknowledgments—We thank O. Vital, B. Derudas, Y. Delplace, C. Boulain, C. Duham for technical assistance. GP+ E6 cells (31) were kindly provided by Dr. Arthur Bank (Columbia University, New York) and the pMFG plasmid (32) by Dr. Richard Mulligan (Massachusetts Institute of Technology, Cambridge). The Rev-Erbα cDNA and promoter (29) constructs were a kind gift of Dr. Vincent Lauden. We would like to thank Dr. Olivier Barbier for helpful comments on the manuscript.

REFERENCES

1. Cornelius, P., MacDougall, O. A., and Lane, M. D. (1994). Annu. Rev. Nutr. 14, 99–129
2. Spiegelman, B. M., and Flier, J. S. (1996). Curr. Opin. Lipidol. 7, 377–398
3. Rosen, E. D., Walker, C. J., Puigserver, P., and Spiegelman, B. M. (2000). Genes Dev. 14, 1293–1307
4. Tontonoz, P., Hu, E., and Spiegelman, B. M. (1994) Cell 79, 1147–1156
5. Tontonoz, P., Hu, E., Graves, R. A., Budavari, A. I., and Spiegelman, B. M. (1994) Genes Dev. 8, 1224–1234
6. Christy, R. J., Yang, V. W., Ntambi, J. M., Geiman, D. E., Landschulz, W. H., Friedman, A. D., Nakabeppu, Y., Kelly, T. J., and Lane, M. D. (1989) Genes Dev. 3, 1323–1335
7. Freytag, S. O., Geddes, T. J. (1992) Science 256, 379–382
8. Freytag, S. O., Paelli, D. L., and Gilbert, J. D. (1994) Genes Dev. 8, 1645–1663
9. Wu, Z., Xie, Y., Bucher, N. L., and Farmer, S. R. (1995) Genes Dev. 9, 2350–2360
10. Wu, Z., Bucher, N. L., and Farmer, S. R. (1996) Mol. Cell. Biol. 16, 4128–4136
11. Yeh, W. C., Cao, Z., Classon, M., and McKnight, S. L. (1995) Genes Dev. 9, 169–181
12. Havel, D., and Grimaldi, P. A. (2002) Curr. Opin. Lipidol. 13, 241–245
13. Kim, J. B., and Spiegelman, B. M. (1996) Genes Dev. 10, 1096–1107
14. Tontonoz, P., Kim, J. B., Graves, R. A., and Spiegelman, B. M. (1993) Mol. Cell. Biol. 13, 4753–4759
15. Kim, J. B., Wright, H. M., Wright, M., and Spiegelman, B. M. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 4333–4337
16. Barbier, O., Torra, I. P., Duguay, Y., Blanquart, C., Fruchart, J. C., Glineur, C., and Staels, B. (2002) Arterioscler. Thromb. Vasc. Biol. 22, 717–726
17. Willson, T. M., Lambert, M. H., and Kliwer, S. A. (2001) Annu. Rev. Biochem. 70, 341–367
18. Chawla, A. and Lazar, M. A. (1993) J. Biol. Chem. 268, 16265–16269
19. Forman, B. M., Chen, J., Blumberg, B., Kliwer, S. A., Henshaw, R., Ong, E. S., and Evans, R. M. (1994) Mol. Endocrinol. 8, 1253–1261
20. Lazar, M. A., Hodin, R. A., Darling, D. S., and Chin, W. W. (1989) Mol. Cell. Biol. 9, 1128–1136
21. Miyajima, N., Horuchi, R., Shibuya, Y., Fukushige, S., Matsubara, K., Tsuchihama, Y., and Yamamoto, T. (1989) Cell 57, 31–39
22. Lauden, V., and Adelmant, G. (1995) Curr. Opin. Biol. 5, 124–127
23. Gervais, P., Chopin-Delannoy, S., Fadel, A., Dubois, G., Kosykh, V., Fruchart, J. C., Najib, J., Laudeit, V., and Staels, B. (1999) Mol. Endocrinol. 13, 409–409
24. Staels, B., van Tol, A., Andreu, T., and Auwerx, J. (1992) Arterioscler. Thromb.