The Peroxisome Proliferator-activated Receptor γ Regulates Expression of the Perilipin Gene in Adipocytes*

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Recent studies have shown that lipid droplets are covered with a proteinaeous coat, although the functions and identities of the component proteins have not yet been well elucidated. The first identified lipid droplet-specific proteins are the perilipins, a family of proteins coating the surfaces of lipid droplets of adipocytes. The generation of perilipin-null mice has revealed that although they consume more food than control mice, they have normal body weight and are resistant to diet-induced obesity. In one study (Martinez-Botas, J., Anderson, J. B., Tessier, D., Lapillonne, A., Chang, B. H. J., Quast, M. J., Gorenstein, D., Chen, K. H., and Chan, L. (2000) Nat. Genet. 26, 474–479) it was reported that in an animal model obesity was reversible by breeding perilipin−/− allels into Lepr db/db obese mice, ostensibly by increasing the metabolic rate of the mice. To understand the exact mechanisms that drive the exclusive expression of the perilipin gene in adipocytes, we analyzed the 5′-flanking region of the mouse gene. Treatment of differentiating 3T3-L1 adipocytes with an agonist of proliferator-activated receptor (PPAR) γ, the putative “master regulator” of adipocyte differentiation, significantly augmented perilipin gene expression. Reporter assays using the −2.0-kb promoter revealed that this region contains a functional PPARγ-responsive element. Gel mobility shift and chromatin immunoprecipitation assays showed that endogenous PPARγ protein binds to the perilipin promoter. PPARγ2, an isoform exclusively expressed in adipocytes, was found to be the most potent regulator from among the PPAR family members including PPARα and PPARγ1. These results make evident the fact that perilipin gene expression in differentiating adipocytes is crucially regulated by PPARγ2, providing new insights into the adipogenic action of PPARγ2 and adipose-specific gene expression, as well as potential anti-obesity pharmaceutical agents targeted to a reduction of the perilipin gene product.

Adipocytes are the major reservoir of energy stored in the form of triacylglycerol in the body. Triacylglycerol is stored within intracellular lipid droplets covered by a monolayer of phospholipids, free cholesterol, and proteins. In times of energy need, for example, as brought about by activities such as fast-}

* This work was supported by research grants from the Ministry of Education, Science, Sports, and Culture of Japan and the program for promotion of Basic Research Activities for Innovative Biosciences. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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1 The abbreviations used are: PKA, cAMP-dependent protein kinase; PPAR, peroxisome proliferator-activated receptor; FBS, fetal bovine serum; PPRE, PPAR-responsive element.

** This paper is available on line at http://www.jbc.org
perilipin, and anti-mouse β-actin antibodies were from Santa Cruz, Prepro, and ICN, respectively.  

**Cell Culture**—3T3-L1 fibroblasts (obtained from Health Science Research Resources Bank, Osaka, Japan) were differentiated into adipocytes after they reached confluency (day 0) by the addition of differentiation medium (Dulbecco’s modified Eagle’s medium plus 10% fetal bovine serum (FBS), 100 units/ml penicillin, 100 μg/ml streptomycin, 0.5 mM 3-isobutyl-1-methylxantine, 1 μM dexamethasone, 100 μM ascorbic acid, and 10 μg/ml insulin). After 2 days, the 3T3-L1 cells were transferred to adipocyte growing medium (Dulbecco’s modified Eagle’s medium plus 10% FBS, 100 units/ml penicillin, 100 μg/ml streptomycin, 100 μM ascorbic acid, and 5 μg/ml insulin) and refed every 2 days. Differentiation of 3T3-L1 cells to mature adipocytes was confirmed by Oil Red O staining of lipid vesicles. PPARγ-expressing NIH-3T3 cells were cultured as described previously (10).  

**Plasmid Constructs**—Expression plasmids for mouse PPARγ1 (11), mouse PPARγ2 (11), human RXRα (12) human SREBP-1α (13), and rat C/EBPα (14) were described previously. An expression plasmid for mouse PPARγ2 was made by inserting a fragment coding amino acids 1-169 of mouse PPARγ2 into the HindIII sites of pcCMX-PPARγ1. To generate a perilipin promoter-reporter plasmid (pPlin-2.0), the BamHI-HindIII PCR fragments from mouse genomic DNA were ligated to the BglII-HindIII sites of a pG3L basic vector (Promega).  

Mutant versions of perilipin promoter-reporter plasmids were constructed by a PCR-assisted method using a site-directed mutagenesis kit following the instructions provided by the supplier (Stratagene).  

**Northern Blot Analysis**—Total RNA was isolated using an RNA preparation kit (Isogen; Nippon Gene Corp.). The RNA was fractionated by electrophoresis in an 1% formaldehyde–agarose gel and transferred to nylon membranes (Hybond-N; Amersham Biosciences). Probes for perilin, PPARγ, aP2, human LPL, and 36B4 (15) were labeled with γ[32P]ATP (3000 Ci/μmol; Amersham Biosciences) using a random-primed DNA labeling kit (Megaprime DNA labeling system; Amersham Biosciences). The membrane was hybridized with radioactive cDNA probes, and the signals on the membrane were quantified using an image-analyzing system (FLA-3000; Fuji Film Inc.).  

**Luciferase Assay**—3T3-L1 adipocytes cultured in a 12-well plate were transfected with 2 μg of a reporter plasmid and 0.02 μg of pRL-TK (Promega) complexed with LipofectAMINE™ (Invitrogen) according to the manufacturer’s instructions. 3T3-L1 preadipocytes cultured in a 12-well plate were transfected with 1 μg of a reporter plasmid, 0.01 μg of pRL-TK and expression plasmids complexed with LipofectAMINE™. The cells were incubated with a medium containing 10% charcoal-stripped FBS and 10 μg/ml pioglitazone. Twenty-four hours later both firefly and Renilla luciferase activities were quantified using a Dual-Luciferase™ reporter system (Promega) according to the manufacturer’s instructions (16, 17). HEK293 cells were cultured and transfected as described previously (13, 16).  

**Western Blot Analysis**—A double-stranded DNA fragment corresponding to the PPAR-responsive element (PPRE) of the aP2 gene (ARE7) (18) and nucleotides –992 to –968 of the mouse perilipin gene were 3′-end labeled with 32P-γ-ATP (Amersham Biosciences) using T4 polynucleotide kinase (Takara, Japan). A 20-μl reaction solution containing 50 μl of radiolabeled fragment (1.5 × 106 cpm) and 1 μl each of recombinant PPARγ and RXRα (10) was incubated for 20 min at room temperature and for 15 min at 4°C in a buffer containing 10 mM Tris-HCl, pH 7.9, 40 mM KC1, 1 mM dithiothreitol, 0.05% Nonidet P-40, 10% glycerol, and 1 mg of poly(dI-dC). The DNA-protein complexes were subjected to electrophoresis on 4% polyacrylamide gel in 0.25°Tris-HCl, pH 7.9, 40 mM KCl, 1 mM dithiothreitol, 0.05% Nonidet P-40, 0.1°borate/EDTA buffer at 4°C for 1 h and for 15 min at 4°C. The DNA-protein complexes were subjected to electrophoresis and blot hybridization with the indicated 32P-labeled probe. The gels were dried, and the signals on the gel were detected using an image-analyzing system (FLA-3000; Fuji Film Inc.).  

**Lipid Analysis**—3T3-L1 cells were washed with cold phosphate-buff ered saline, and lipids were extracted by chloroform/methanol (2:1, v/v). The lower organic phase was dried, and the lipids were dissolved in 2-propanol. Triacylglycerol content was determined using Triglyceride E-test Wako (Wako, Japan) according to the manufacturer’s instructions.  

**Western Blot Analysis**—3T3-L1 preadipocytes were differentiated into adipocytes by the addition of differentiation medium containing 10 μg pioglitazone at day 0 and were cultured for 4 days. Total cellular proteins were fractionated by SDS-10% PAGE. Western blot analysis was carried out using anti-human perilipin or anti-mouse β-actin antibodies with ECL (Amersham Biosciences). The signals on the membrane were quantified with a LuminoImage (LAS-3000; Fuji Film Inc.).

**RESULTS**

A **PPARγ Ligand Enhances Perilipin Gene Expression in Adipocytes**—Fig. 1A shows that perilipin gene expression was low to almost the zero point level in preadipocytes but was induced markedly at later stages of differentiation. This perilipin expression pattern was quite similar to those for PPARγ, known to be a central regulator of adipocyte differentiation (18), and aP2, a target gene of PPARγ. Therefore, we hypothesized that PPARγ participates in the induced expression of the perilipin gene during differentiation. As expected, treatment of 3T3-L1 cells for 48 h with a PPARγ agonist, pioglitazone, raised expression of the mRNA for perilipin and LPL, another PPARγ gene target (20), but only in adipocytes (Fig. 1B). This suggests that PPARγ, which is highly expressed after adipocyte differ-
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When pioglitazone was added to the culture medium at an early stage of differentiation, the enhancing effect of the drug was significant (Fig. 2, day 2). In contrast, as a result of treatment of the cells with a PPARγ antagonist, GW9662, perilipin gene expression was inhibited for 4 days. Because a longer treatment with pioglitazone gradually suppressed perilipin gene expression (21), the maximal drug effect was observed at day 2, and no effect was seen after day 6 (data not shown). Fig. 2B clearly shows that forced expression of PPARγ in both adipogenic and nonadipogenic cells enhanced the luciferase activities ~40-fold as long as the reporter gene containing the segment around −2.0-kb was present (the transcription start site is position +1). Deletion of −100 and −300 bp (pPlin-1.9 and pPlin-1.7, respectively) dramatically reduced this effect. We obtained the same results using nonmammalian cells, Drosophila SL2 cells (data not shown). It is likely that the 5- and 10-fold induction of the promoter activity of pPlin-1.9 observed in 3T3-L1 preadipocyte and HEK293 cells, respectively, is largely attributable to overexpression of PPARγ and RXRa. We cannot rule out the possibility that the 1.9-kb promoter contains several weak PPARγ responsive elements. The luciferase activities of pPlin-2.0 were greatly stimulated only when both PPARγ and RXRa were expressed in 3T3-L1 preadipocyte cells in the presence of the agonist (Fig. 3C). When only RXRa was expressed, no effect was observed, suggesting that the pioglitazone-mediated effect is not caused by a combination of RXR and some nuclear receptors, other than PPARγ. The luciferase activities of pPlin-1.9 were slightly augmented by PPARγ/RXRα. Next we performed further luciferase assays using pPlin-2.0 and pPlin-1.9 in differentiated 3T3-L1 adipocytes. Endogenous PPARγ activated by pioglitazone markedly enhanced the luciferase activities of pPlin-2.0, whereas deletion of −100 bp completely abolished this effect (Fig. 3D). Even when PPARγ/RXRα were overexpressed in 3T3-L1 adipocytes, the PPRE-1.9 promoter did not respond to pioglitazone. These results demonstrate that the 5′-flanking region of mouse perilipin gene contains PPRE(s), which responds to endogenous PPARγ, located in a region of approximately −2.0-kb.

The Element Responsible for the PPARγ-mediated Transcriptional Regulation of the Perilipin Gene—We identified two putative PPREs of approximately −2.0-kb (PPRE and PPRE-like in Fig. 3A). To confirm that these motifs are recognized by a PPARγ/RXRα heterodimer, gel mobility shift assays were performed with recombinant PPARγ/RXRα. A single-shifted DNA-protein complex was observed in the presence of a control 32P-labeled fragment corresponding to the PPRE of the aP2 gene and recombinant PPARγ/RXRα (Fig. 4A, lane 2) and gradually disappeared after the addition of increasing amounts of the nonlabeled PPRE DNA fragment but not the PPRE-like fragment. Fig. 4B shows that a single-shifted perilipin PPRE-PPRE/RXRα complex was formed (lane 2). The band almost completely disappeared in the presence of an excess amount of an unlabeled wild type fragment but not a mutant fragment (lanes 3–6). These results clearly demonstrate that PPARγ is capable of binding to the TCACCTTCACCC sequence in the perilipin promoter. As shown in Fig. 4C, the identical two repeats in the PPRE are conserved in the promoters of both the mouse and human genes. To determine whether this PPRE is involved in the PPARγ-mediated regulation of perilipin gene expression, luciferase assays using wild type and mutant versions of reporter genes were carried out. Mutation of the PPRE sequence (~1977 to ~1983 bp) resulted in a remarkable suppression of the PPARγ-dependent induction of luciferase activities in preadipocyte cells (Fig. 4D). These results provide evidence that the PPRE motif (~1974 to ~1986 bp) is crucially responsible for the transcriptional regulation of the perilin gene during adipocyte differentiation.

To investigate whether PPARγ binds to the endogenous perilipin promoter, we performed chromatin immunoprecipitation. As shown in Fig. 5, endogenous PPARγ protein bound to the promoter of the perilipin gene as well as that of another PPARγ target, the aP2 gene. These data show that PPARγ-mediated expression of the perilipin gene involves the binding of endogenous PPARγ to the PPRE in chromatin.
**PPARγ Regulates Perilipin Gene Expression**

**Fig. 3. Activation of the perilipin promoter by PPARγ-2.** A, mouse perilipin promoter sequence (31). The transcription start site is +1. The PPRE is boxed. The PPRE-like sequence is underlined. The mutant sequence in the PPRE is shown by italic letters under the individual original sequence. B, 3T3-L1 preadipocytes or HEK293 cells were co-transfected with the indicated mouse perilipin promoter-luciferase reporter gene together with pRL-TK and expression plasmids for PPARγ and RXRα (solid bar). pGL3 is a promoter-less reporter gene. The cells were incubated with a medium containing 10% charcoal-stripped FBS and 10 μM pioglitazone for 24 h, and then luciferase assays were performed. Luciferase activities in the absence of PPARγ and RXRα were considered as 1. The data are shown as the means ± S.D. All of the values given are the averages of data from three experiments performed in triplicate. 

**PPARγ Is a Major Regulator for Perilipin Gene Expression in Adipocytes**—To verify that PPARγ is a major regulator for perilipin gene expression in adipocyte cells, we established a stable NIH-3T3 cell line (NIH-y2) expressing PPARγ-2, an isoform expressed exclusively in adipose tissue (10). When these PPARγ-2-expressing cells were cultured in a differentiation medium, more than 60% of the cells were stained with Oil Red O, whereas no lipid-containing cells were observed among the control NIH-vector cells (10). These two stable (NIH-vec and NIH-y2) cells were cultured with a normal medium containing 10 μM pioglitazone for 48 h, and perilipin gene expression was analyzed by the reverse transcription-PCR method (Fig. 6A). Expression of adipogenic marker aP2, a PPARγ-responsive gene, was markedly induced, but perilipin gene expression was only slightly enhanced in NIH-y2 cells. Indeed, we performed an reverse transcription-PCR analysis to confirm perilipin gene expression after we failed to observe it in Northern blot analysis. Although perilipin expression in NIH-y2 cells was induced at the detectable level during adipocyte differentiation, the expression level was much lower than that in differentiated 3T3-L1 adipocytes, probably because of an attenuated expression of the endogenous PPARγ gene (Fig. 6B).

Next we determined which isoform of PPARγ preferentially regulates the perilipin promoter activity. 3T3-L1 preadipocyte cells transfected with pPlin-2.0 and one of the expression plasmids for PPARγ1 and y2 were cultured with various concentrations of pioglitazone for 24 h. Both PPARγ1 and y2 expression levels were analyzed by immunoblotting. When equal
FIG. 4. A PPARγ-RXR complex binds to the PPRE in the perilipin promoter and regulates the gene expression. A, a double-stranded DNA fragment corresponding to the PPRE of the aP2 gene (15) was 3' end-labeled with [γ-32P] ATP. 32P-Radiolabeled fragments were incubated with recombinant PPARγ and RXRα. In competition assays, 40-, 80-, and 200-fold molar excesses of unlabeled double-stranded DNA fragments derived from the wild type (PPREwt) or perilipin PPRE (see Fig. 3A) or PPRE-like sequence (see Fig. 3A, underlined) were added. DNA-protein complexes were subjected to electrophoresis on 4% polyacrylamide gel. B, a double-stranded DNA fragment corresponding to the PPRE of the perilipin gene was 3' end-labeled with [γ-32P] ATP. 32P-Radiolabeled fragments were incubated with recombinant PPARγ and RXRα. In competition assays, 40-, 80-, and 200-fold molar excesses of unlabeled double-stranded DNA fragments derived from the wild type (PPREwt) or the mutant (PPREmut) of perilipin PPRE (see Fig. 3A) were added. DNA-protein complexes were subjected to electrophoresis on 4% polyacrylamide gel. C, comparison of conserved PPRE sequences in the promoters of both the mouse and human (119460–119472 in AC079075) genes. D, 3T3-L1 preadipocytes were co-transfected with either the wild type or mutant version of reporter gene (pPlin-2.0 or pPlin-mut) together with pRL-TK and the expression plasmids for PPARγ2 and RXRα (solid bar). The cells were incubated with a medium containing 10% charcoal-stripped FBS and 10 μM pioglitazone for 24 h, and then luciferase assays were performed. Luciferase activities in the absence of PPARγ2 and RXRα were considered as 1. The data are shown as the means ± S.D. The inset shows an immunoblot (100 μg of protein/lane) of whole cell extracts using anti-PPARγ antibodies. The signals were quantified with a LuminoImager (LAS-3000; Fuji Film Inc.). E, 3T3-L1 preadipocytes were co-transfected with pPlin-2.0 together with pRL-TK and one of the expression plasmids for C/EBPα, SREBP-1a, LXRα, PPARα, and PPARγ2. The cells were incubated with a medium containing 10% charcoal-stripped FBS and each ligand (1 μM T0901317 for LXRα, 50 μM WY14463 for PPARα, and 10 μM pioglitazone for PPARγ2) for 24 h, and then luciferase assays were performed. Luciferase activities in the absence of expression vectors were considered as 1. The data are shown as the means ± S.D. All of the values given are the averages of data from three experiments performed in triplicate.

FIG. 5. Chromatin immunoprecipitation assays of the perilipin promoter in 3T3-L1 adipocytes. Chromatin immunoprecipitation assays were performed as described under “Experimental Procedures.” Soluble chromatin was immunoprecipitated with mouse IgG (lane 2), antibodies against mouse PPARγ (lane 3), or acetyl-histone H3 (lane 4). Immunoprecipitates were analyzed by PCR with specific primers for the mouse perilipin or aP2 promoter. PCR was performed with total chromatin input (lane 1).

amounts of both isoforms were expressed (Fig. 7A, inset, 1.00 versus 1.08), PPARγ2 was more potent than PPARγ1 at every concentration of pioglitazone, suggesting that perilipin expression being exclusively limited to adipose tissue is partly attributable to PPARγ2 expression in this tissue. We then examined whether other transcription factors might be involved in perilipin expression during adipogenesis. Forced expression of C/EBPα, SREBP1a, and LXRα (with a synthetic ligand), which are highly expressed and regulate the expression of several adipogenic genes during adipocyte differentiation (22–24), did not enhance the activities of the perilipin promoter (~2.0 kb) (Fig. 7B). PPARα together with a synthetic ligand slightly augmented perilipin promoter activity but was still a much weaker regulator as compared with PPARγ2. Taken together,
it is likely that PPARγ is a major regulator of perilipin gene expression in adipocyte cells.

**DISCUSSION**

The major finding of this study is that perilipin is a novel, adipocyte-specific target gene of PPARγ. Perilipin mRNA in undifferentiated 3T3-L1 preadipocytes is not detectable but is remarkably increased during 3T3-L1 adipocyte differentiation. A recent paper showed that perilipin gene expression was very specifically regulated, the expression occurring concomitantly with changes in PPARγ gene expression induced by treatment of 3T3-L1 preadipocytes with a mitogen-activated protein kinase inhibitor and/or fibroblast growth factor-2 (25). The current finding can offer a mechanistic explanation of these observations.

We further report that the perilipin gene has a functional PPRE in its 5′-flanking region and that its expression in adipocytes is predominantly regulated by PPARγ in adipocytes. Reporter assays revealed that the segment from −2.0 to −1.9 kb of the mouse perilipin gene is essential for PPARγ-mediated gene expression (Figs. 3 and 4). There indeed exists a PPRE in this region, and the TCACCTTTCACCC sequence is both recognized by a PPARγ/RXRα heterodimer and is indispensable for the activation of the promoter (Figs. 3 and 4). We confirmed a 74% nucleotide homology in the 300-bp promoter region (−2.0 to −1.7 kb for the mouse gene) and a 100% match of two direct repeats (TCACCT and TCACCC) in the PPRE in the mouse and human forms (Fig. 4), suggesting that a regulation likely occurs in humans highly similar to what has been found in the mouse model.

PPARγ is present in two major isoforms, PPARγ1 and PPARγ2, resulting from alternate promoter utilization (26, 27). PPARγ2 contains an additional 30 amino acids at the N-terminal end in comparison with PPARγ1. PPARγ2 expression is limited exclusively to adipose tissue, where it plays a pivotal role in adipogenesis, whereas PPARγ1 is ubiquitously expressed in various tissues. Recently, two reports presented quite different data on the adiogenic action of the two isoforms (28, 29). Ren et al. (28) demonstrated that PPARγ2 isoforms can drive the differentiation of fully functional fat cells. The data presented here show that both PPARγ2 and PPARγ1 are capable of enhancing perilipin promoter activity (Fig. 7), favoring the latter finding. However, a modest expression of PPARγ2 in stable NIH-3T3 (NIH-2) cells was not sufficient for inducing perilipin gene expression, even in the presence of a PPARγ ligand, pioglitazone (Fig. 6).

Once these cells were cultured with a differentiation medium containing pioglitazone, perilipin mRNA was enhanced concomitantly with the increase in endogenous PPARγ, suggesting that a high expression of PPARγ including both isoforms is required for augmenting perilipin gene expression. Alternatively, other as yet unidentified factors activated during adipocyte differentiation might be involved in this event. During the period of this investigation, several transcription factors other than PPARγ2 known to be involved in adipocyte differentiation, e.g. C/EBPα, SREBP-1a, and LXRα, were not able to stimulate perilipin promoter activity. It remains, therefore, to be precisely elucidated how perilipin gene expression is restricted to the adipose tissue. It is possible that the levels of PPARγ1 and endogenous as yet unidentified ligands in extra-adipose tissues are insufficient to induce perilipin gene expression, whereas in adipose tissues there are sufficiently high levels of the PPARγ isoforms, their ligands, and the several functional co-activators required for transcriptional activity (30). Further investigation should bring these issues into better focus.

The perilipin proteins are the most abundant PKA substrates in adipocytes (1, 5, 6) and play an important role in PKA-mediated lipolysis. Several reports have provided evidence that the perilipins protect stored triacylglycerol from hydrolysis by cellular lipases. Two reports describing the phenotype of the perilipin-null mouse also have demonstrated that these mice have both greatly diminished adipose stores and constitutively high levels of basal lipolysis (7, 8). These findings suggest perilipin to be an attractive target for anti-obesity medications. Although caution would expect reduced perilipin gene expression in adipocytes by the administration of a PPARγ antagonist, according to the findings described here, which strongly suggest that PPARγ plays a crucial role in the expression of perilipin, this approach might not be practical for reasons similar to the complications of side effects in the usage of PPARγ agonists against type 2 diabetes. As yet unidentified determinants of adipose-specific perilipin gene expression in addition to PPARγ could provide further targets for pharmaceutical intervention. Further analysis of the regulation of perilipin gene expression should make the elucidation of such targets possible, as well as provide greater insights into the underlying mechanisms controlling adipose-specific gene expression in general.

**Acknowledgment**—We thank Dr. Kevin Boru of Advanced Clinical Trials for review of the manuscript.

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J. Biol. Chem. 2004, 279:10070-10076.
doi: 10.1074/jbc.M308522200 originally published online January 2, 2004

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