Regulation of Peroxisome Proliferator-activated Receptor γ Activity by Mitogen-activated Protein Kinase*

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Adipocyte differentiation is regulated both positively and negatively by external growth factors such as insulin, platelet-derived growth factor (PDGF), and epidermal growth factor (EGF). A key component of the adipocyte differentiation process is PPARγ, peroxisomal proliferator-activated receptor γ. To determine the relationship between PPARγ activation and growth factor stimulation in adipogenesis, we investigated the effects of PDGF and EGF on PPARγ activity. PDGF treatment decreased ligand-activated PPARγ transcriptional activity in a transient reporter assay. In vivo 

[32P]orthophosphate labeling experiments demonstrated that PPARγ is a phosphoprotein that undergoes EGF-stimulated MEK/mitogen-activated protein (MAP) kinase-dependent phosphorylation. Purified PPARγ protein was phosphorylated in vitro by recombinant activated MAP kinase. Examination of the PPARγ1 sequence revealed a single MAP kinase consensus recognition site at Ser82. Mutation of Ser82 to Ala inhibited both in vitro and in vivo phosphorylation and growth factor-mediated transcriptional repression. Therefore, phosphorylation of PPARγ1 by MAP kinase contributes to the reduction of PPARγ1 transcriptional activity by growth factor treatment.

Peroxisomal proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily (1). These receptors heterodimerize with retinoic acid-like receptor, RXR, and become transcriptionally active when bound to ligand. The three PPAR isoforms (α, δ, and γ) differ in their C-terminal ligand binding domains, and each appears to bind and respond to a specific subset of agents including hypolipidemic drugs, long chain fatty acids, aracacidonic acid metabolites, and anti diabetic thiazolidinediones (2–4). PPARγ is expressed predominantly in mouse white and brown fat, with lower levels in liver, whereas PPARα is present in heart, kidney, and liver (5, 6). PPARδ expression is ubiquitous (7, 8).

Ectopic expression of either PPARα or PPARγ in NIH-3T3 cells is sufficient to induce adipocyte differentiation in the presence of PPARγ activators (9, 10). The rapid induction of PPARγ during adipocyte differentiation and its enriched expression in adipose tissues suggest that PPARγ is responsible for the initiation and maintenance of the adipocyte phenotype in vivo (9). Previously two isotypes of PPARγ (PPARγ1 and PPARγ2) have been identified in 3T3-L1 adipocytes (11). Zhu et al. (12) have demonstrated that these two isotypes are derived from a single PPARγ gene by alternative promoter usage and RNA splicing. However, thus far, no functional difference has been found between the two isotypes.

Adipogenesis is a complex process; multiple hormones and factors regulate the conversion of progenitor cells to adipocytes. Insulin and/or insulin-like growth factor enhance the ability of PPAR ligand to induce differentiation of both 3T3-L1- and PPARγ-overexpressing cell lines (9, 13). In contrast, growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and fibroblast growth factor inhibit adipocyte conversion (14–18). In this report, we find that activation of EGF and PDGF receptors and subsequent phosphorylation of PPARγ by the MAP kinase signaling pathway decreases PPARγ transcriptional activity. This repression is mediated by MAP kinase phosphorylation of Ser82 on PPARγ. These studies identify PPARγ as a substrate of MAP kinase and provide evidence for regulation of PPARγ activity by phosphorylation.

EXPERIMENTAL PROCEDURES

Chemicals and Materials—Cell culture reagents were purchased from Life Technologies, Inc. The ECL detection system and carrier-free 
[32P]orthophosphate were obtained from Amersham Corp. The PDGF was purchased from Intercigen, while EGF was from Harlan. PD98059 and BRL49653 were synthesized at Parke-Davis Pharmaceutical Research Division of Warner-Lambert Co.

Vector Constructs and Transient Transfection—For eukaryotic expression of PPARγ1 and RXRα, the entire PPARγ1 or RXRα cDNA was inserted 3′ to the cytomegalovirus promoter in pSG5 (Stratagene). Constitutively active MAP kinase kinase (CA-MEK), which contains mutations at Ser21/22 to Glu and Ser21/22 to Glu was obtained from Dr. S. Decker (Parke-Davis). Site-directed mutagenesis of PPARγ1/pSG5 was conducted using the MBRP site-specific plasmid DNA mutagenesis system (5 Prime → 3 Prime, Inc., Boulder, CO). The oligonucleotide used in mutagenesis was CAAAGTAGAAGCTGAGCTCACCTTATTTCTGAAAAAGC and changed Ser22/23 to Ala. The reporter construct used in the transfections contained three copies of the PPRE site from the n2 enhancer (ARE7) inserted upstream of a minimal thymidine kinase (TK) promoter in the pGL3 basic luciferase vector (a gift from Dr. R. Wyborski). All constructs were sequenced prior to use. For the transient transfection, NIH 3T3 cells were grown in 10% fetal calf serum/Dulbecco’s modified Eagle’s medium and co-transfected with various expression plasmids and pCMV β-galactosidase plasmid (Clontech) using Lipofectamine (Life Technologies, Inc.). After recovery, cells were placed in 0.5% bovine serum albumin/Dulbecco’s modified Eagle’s medium for 6 h and then treated with 25 μM BRL49653 and/or 100 ng/ml PDGF for 16 h. Luciferase and β-galactosidase activities were determined using a Luciferase assay (Promega) and the Galacto-light system (Tropix, Inc.).

Production of PPAR Fusion Proteins and in Vitro Phosphorylation

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1 The abbreviations used are: PPAR, peroxisomal proliferator-activated receptor; MAP, mitogen-activated protein; RXR, retinoic acid-like receptor; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; MEK, MAP kinase kinase; CA-MEK, constitutively active MEK; MBP, maltose-binding protein; TK, thymidine kinase; PPRE, peroxisome proliferator response element; ARE7, adipocyte regulatory factor response element.
To express the maltose-binding protein (MBP) fusion proteins in *Escherichia coli*, the coding regions of PPARγ1, PPARδ, and RXRα were inserted downstream of the isopropyl-β-D-thiogalactopyranoside-inducible MalE-tacZa gene fusion in the pMAL-C2 plasmid (New England Biolabs). Protein expression was induced with isopropyl-β-D-thiogalactoside, and the fusion proteins were partially purified by amylose affinity chromatography (19). In vitro phosphorylation of MBP, MBP-PPARγ1, and MBP-PPARδ by MAP kinase was performed as described previously (20) using a bacterially expressed glutathione S-transferase fusion protein of 44-kDa MAP kinase (GST-MAP kinase) and the 45-kDa MEK (GST-MEK1). Using a PPARγ-specific polyclonal antibody (produced using the MBP-PPARγ fusion protein) in vitro translated PPARγ1 and the mutant PPARγ1 (S82A) were immunoprecipitated and phosphorylated by active GST-MAP kinase as described above.

**Mobility Shift Assays**—Approximately 0.5 μg of the partially pure MBP-PPARγ1, phosphorylated or unphospho, and 0.5 μg of MBP-RXRα protein were preincubated for 15 min in 1× mobility shift assay buffer (15 mM Hepes, pH 7.0, 80 mM KCl, 10% glycerol, 1 μg of poly(dil-dc), 0.2 mM EDTA, and 0.4 mM dithiothreitol) to allow heterodimer formation, or MBP-PPARγ1 was phosphorylated prior to heterodimerization with MBP-RXRα. Approximately 20 fmol of a 32P-labeled double-stranded ARE7 PPRE-containing oligonucleotide probe (5′-AATTCAGGCAGAAGTGAACTCTGATCCAGTAAGAAG-3′) was added to the protein mix and incubated at room temperature for 20 min. Protein-DNA complexes were analyzed in 5% TBE polyacrylamide gels.

**Cell Transfection and in Vivo Radiolabeling**—293T cells were maintained in Dulbecco's modified Eagle's medium containing 10% fetal calf serum (Life Technologies, Inc.) and transfected using a calcium phosphate transfection protocol according to the manufacturer (Stratagene). For in vivo labeling, transfected cells were serum-starved overnight in 0.5% bovine serum albumin/Dulbecco's modified Eagle's medium, pretreated with phosphate-free medium for 1 h, and subsequently incubated in 0.8 mCi of [32P]orthophosphate at 37 °C for 3 h. Cells were preincubated with either BRL49653 (25 μM) or PD98059 (40 μM) for 15 min followed by the addition of EGF (100 ng/ml). EGF stimulation proceeded for 5 or 15 min prior to removal of the media and cell lysis.

Cells were harvested in radioimmune precipitation lysis buffer (10% glycerol, 137 mM NaCl, 1% Nonidet P-40, 0.5% deoxycholate, 0.1% SDS, 0.1% SDS, 20 mM Tris, pH 8.0, 2 mM EDTA, complete protease inhibitors, and 20 mM NaVO₄). Whole cell extracts were immunoprecipitated with anti-PPARγ antibody and protein A-Sepharose (Life Technologies, Inc.) for 16 h at 4 °C and resolved in 10% SDS-PAGE. To detect MAP kinase phosphorylation, proteins were transferred to nitrocellulose and probed with an antibody to phospho-threonine 202 and tyrosine 204 of MAP kinase. The phosphorylation status of PPARγ1 and RXRα was determined by Western blot analysis using an anti-active MAP kinase antibody (Promega) and ECL system (Amersham).

**RESULTS**

**Growth Factors Decrease the Transcriptional Activity of PPARγ1**—Transcription reporter assays were used to determine the effect of growth factors on the transcriptional activity of PPARγ1. The luciferase reporter constructs used in NIH3T3 cells contained the TK promoter (TKpGL3) or three copies of ARE7 PPRE elements upstream of the TK promoter (ARE7-TKpGL3). In the absence of co-transfected PPARγ1 and RXRα expression plasmids, no PPARγ1 ligand (BRL49653)-dependent transcription was observed from either the TKpGL3 or ARE7-TKpGL3 (Fig. 1A). In the presence of PPARγ1 and RXRα, a 2-fold increase in transcription was observed from ARE7-TK promoter after 16 h of treatment with BRL49653. The addition of 100 ng/ml PDGF to these cells decreased both the basal and BRL49653-activated transcription from the ARE7. This suggests that at least a fraction of the activity from the ARE7-TKpGL3 plasmid in the absence of exogenously added ligand is due to the activation of the PPARγ-RXR heterodimer by endogenous ligands. This activity was also reduced by PDGF treatment.

Close examination of the PPARγ amino acid sequence revealed that PPARγ contains one serine residue, Ser325, whose surrounding amino acids correspond to the consensus phosphorylation site for MAP kinase (Fig. 2A) (22). This site is absolutely conserved between human and mouse PPARγ. A variation of the MAP kinase consensus site is also found in mouse PPARα at a similar position in the amino acid sequence. PPARδ lacks this site altogether (Fig. 2A). Since both EGF and PDGF are known to activate MAP kinase in vivo, a CA-MEK that constitutively activates MAP kinase was co-transfected with ARE7-TKpGL3, PPARγ1, and RXRα expression plasmids. As shown in Fig. 1B, CA-MEK decreased both the basal and the ligand-dependent PPARγ1 transcriptional activity in a dose-dependent manner. No significant effect was seen with the TKpGL3 parental reporter construct. This suggests that the intracellular signaling pathways activated by PDGF or EGF can modulate PPARγ1-dependent transcriptional activity.

**MAP Kinase Phosphorylates PPARγ1 but Not PPARδ in Vitro**—To determine if PPARγ1 can be phosphorylated by MAP
kinase in vitro, partially purified MBP, MBP-PPARγ1, or MBP-PPARδ fusion proteins were incubated with preactivated GST-MAP kinase and [γ-32P]ATP under conditions that phosphorylate myelin basic protein, a known MAP kinase substrate. As shown in Fig. 2B, MAP kinase efficiently phosphorylated PPARγ1 but not MBP-PPARδ or maltose-binding protein (data not shown). Coomassie staining verified that nearly equal amounts of intact proteins were loaded (Fig. 2C). To determine if Ser82 is the residue phosphorylated in vitro, a mutation was introduced into PPARγ1 that changed Ser82 to Ala. Both the wild type PPARγ1 and the mutant PPARγ1 (S82A) were in vitro translated using rabbit reticulocyte lysates and immunoprecipitated with a PPARγ-specific antibody followed by in vitro kinase assay using active GST-MAP kinase. E, Western blot analysis of the in vitro translated wild type and mutant Ser82 → Ala PPARγ1 using the PPARγ antibody.

Phosphorylation of PPARγ by MAP Kinase

**Fig. 2.** MAP kinase phosphorylates PPARγ but not PPARδ or mutant PPARγ1 (S82A) in an in vitro kinase assay. A, schematic diagram of PPARγ structure (A/B region-putative ligand-independent transactivation domain, DBD-DNA binding domain, and LBD-ligand binding domain). A comparison of mouse and human PPAR isoforms containing the putative MAP kinase phosphorylation site (PASP) is shown. B, approximately 0.5 μg of MBP-PPARγ1 or 0.5 μg of MBP-PPARδ fusion proteins were phosphorylated with active GST-MAP kinase. C, Coomassie-stained gel of the autoradiogram shown in B. D, both the wild type and the mutant PPARγ1 were in vitro translated using rabbit reticulocyte lysates and immunoprecipitated with a PPARγ-specific antibody followed by in vitro kinase assay using active GST-MAP kinase. E, Western blot analysis of the in vitro translated wild type and mutant Ser82 → Ala PPARγ1 using the PPARγ antibody.
In response to EGF treatment, the Ser 82 phosphorylation site on PPARγ mutant was introduced into 293T cells, and phosphorylation of the wild type PPARγ was performed in the presence and absence of 100 ng/ml EGF (Fig. 4, lane 2) alone did not bind to the ARE7 element (6). However, in the presence of RXRα, both the phosphorylated and unphosphorylated forms of PPARγ bound equally well to the ARE7 probe (Fig. 6, lanes 3 and 5). In addition, phosphorylation of preformed PPARγ-RXRα heterodimer prior to mobility shift assay did not alter PPARγ DNA binding.

DISCUSSION

The complexity of gene expression requires the utilization of multiple regulatory mechanisms to control both the quantity and activity of all components of the transcription machinery including upstream enhancer proteins. In this study, we have shown that activation of the MAP kinase signaling pathway by EGF and PDGF induces the phosphorylation of PPARγ on Ser82 and that this event decreases the ability of PPARγ to activate transcription. Mutation of the phosphorylated residue (Ser82) prevents PPARγ phosphorylation as well as the growth factor-mediated repression of PPARγ-dependent transcription. This phosphorylation-mediated transcriptional repression is not due to a reduced capacity of the PPARγ-RXRα complex to heterodimerize or recognize its DNA binding site but is due to its ability to become transcriptionally activated by ligand.

The activity of several nuclear hormone receptors is regulated by phosphorylation. Okadaic acid-induced phosphorylation of the human β1 thyroid receptor enhances the DNA binding capacity of the protein and increases the ligand-mediated transcription (23). Phosphorylation of retinoic acid receptor α and RXRα modulates heterodimerization of the receptors and consequently increases DNA binding activity (24). In addition, the MAP kinase-dependent phosphorylation of Ser118 on RXRα on the estrogen receptor causes a 1.8–2.3-fold increase in transcriptional activation by the AF1 domain (25). Taken together, these data suggest that in general phosphorylation of nuclear receptors enhances their transcriptional activity. In contrast, our data suggest that MAP kinase phosphorylation of PPARγ negatively regulates its function.

EGF, PDGF, and fibroblast growth factor inhibit the conversion of 3T3-L1 preadipocytes to adipocytes (15, 17, 18). Moreover, primary rat adipogenic precursor cells are also inhibited from becoming adipocytes in the presence of EGF (14), and EGF-treated animals show retardation of the development of adipose tissue (16). Although the precise mechanism of this
inhibition is unknown, growth arrest is required for adipogenesis. It is presumed that activation of the intracellular signaling cascades by growth factors must interfere with the activity of the factors involved in differentiation. We suggest that this interference occurs with the activation of MAP kinase. The activation of MAP kinase by EGF or PDGF induces the phosphorylation of PPARγ, which negatively regulates its activity, thereby preventing the progression of adipocyte differentiation.

The one piece still missing in this puzzle is how insulin promotes adipocyte differentiation. Insulin, like other growth factors, induces MAP kinase activity in 3T3-L1 adipocytes. In fact, two recent publications suggest that insulin stimulation does induce the PPARγ, PPARα, and PPARδ phosphorylation (26, 27). However, in contrast to our data, both groups present data suggesting that the insulin induced phosphorylation enhances the transcriptional activity of the PPARs. The use of different growth factors and different cell lines may explain this discrepancy. Yet, Zhang et al. (27) reported that mutation of the phosphorylated serine does not prevent the activation of PPARγ by insulin. In addition, expression of dominant negative MEK blocks the activity of PPARδ that is not phosphorylated by MAP kinase. This suggests that the activation of transcription by insulin in their system occurs through a mechanism independent of the MAP kinase-induced phosphorylation of PPARγ. Tontonoz et al. (9) have shown that deletion of the N-terminal portion of PPARγ, which lacks Ser282, enhances the ability of PPARγ to induce adipocyte differentiation. Moreover, recently Hu et al. (28) demonstrated that the ectopic expression of a mutant PPARγ (a serine to alanine mutation at position 112 in PPARγ, which is equivalent to Ser282 of PPARγ) enhanced sensitivity to ligand-induced transcription repression.

Additional studies on adipocyte function show that although insulin activates MAP kinase in 3T3-L1 adipocytes, insulin-dependent metabolic responses such as glucose uptake, glycogen synthesis, and lipogenesis are unaffected by the inhibition of MAP kinase with the MEK inhibitor PD98059 (29, 30). In addition, the MEK inhibitor does not prevent or delay 3T3-L1 adipocyte differentiation (data not shown). Since many of the effects of insulin in adipocytes do not utilize the MAP kinase signaling cascade, we suggest that other signaling events induced by insulin during adipogenesis more strongly regulate PPARγ activity than direct phosphorylation by MAP kinase.

The molecular mechanism of inhibition of PPARγ via phosphorylation is yet to be determined. Data presented here show that under equilibrium conditions DNA binding of recombinant PPARγ-RXRα complexes is unaffected by phosphorylation, implying that heterodimerization of the complex is also unaffected. This suggests that transcriptional activation by PPARγ is regulated by phosphorylation. Transcriptional activation by nuclear receptors is modulated upon the association of the receptors with co-activators (31, 32) and co-repressors (21, 33–34). Because of allosteric changes in the receptor, ligand-bound receptor has a greater affinity for the co-activator than the co-repressor and thus enhances transcription (21, 33). Since pretreatment with BRL49653 decreased receptor phosphorylation in cell culture, we speculate that phosphorylation, possibly by hindering ligand binding or preventing changes in receptor conformation, plays a role in the selectivity and/or affinity of PPARγ for the cofactors.

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FIG. 5. Mutant Ser282→Ala PPARγ is resistant to growth factor-mediated transcription repression. NIH 3T3 cells were cotransfected with reporter (ARE7-KpGL3) and either PPARγ1 or Ser282→Ala PPARγ1 expression plasmids as described in Fig. 1. Serum-starved cells were stimulated with appropriate treatments as indicated. Open bar, MeSO2; hatched bar, BRL49653; solid bar, BRL49653 plus PDGF. WT, wild type.

FIG. 6. Phosphorylation of PPARγ does not alter its DNA binding activity. A gel shift assay was performed using approximately 20 fmol of the [32P]labeled oligonucleotide probe containing the ARE7 alone (lane 1), with purified PPARγ1 alone (lane 2), PPARγ1 and RXRα heterodimer complex (lane 3), PPARγ1 and RXRα heterodimer complex in MAP kinase buffer without active GST-MAP kinase (lane 4), phosphorylated PPARγ1 and RXRα heterodimer complex with active GST-MAP kinase (lane 5), or phosphorylated PPARγ1 prior to heterodimerization with RXRα (lane 6).
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