Peroxisome Proliferator-activated Receptor γ as a Novel Target in Cancer Therapy: Binding and Activation by an Aromatic Fatty Acid with Clinical Antitumor Activity¹

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ABSTRACT

Aromatic fatty acids, of which phenylacetate is a prototype, constitute a class of low toxicity drugs with demonstrated antitumor activity in experimental models and in humans. Using in vitro models, we show here a tight correlation between tumor growth arrest by phenylacetate and activation of peroxisome proliferator-activated receptor γ (PPARγ), a member of the nuclear receptor superfamily. In support are the following observations: (a) the efficacy of phenylacetate as a cytostatic agent was correlated with pretreatment levels of PPARγ, as documented using established tumor lines and forced expression models; (b) in responsive tumor cells, PPARγ expression was up-regulated within 2–9 h of treatment preceding increases in p21waf1, a marker of cell cycle arrest; (c) inhibition of mitogen-activated protein kinase, a negative regulator of PPARγ, enhanced drug activity; and (d) phenylacetate interacted directly with the ligand-binding site of PPARγ and activated its transcriptional function. The ability to bind and activate PPARγ was common to biologically active analogues of phenylacetate and corresponded to their potency as antitumor agents (phenylacetate < phenylbutyrate < p-chloro-phenylacetate < p-iodo-phenylbutyrate), whereas an inactive derivative, phenylacetylglutamine, had no effect on PPARγ. These findings point to PPARγ as a novel target in cancer therapy and provide the first identification of ligands that have selective antitumor activity in patients.

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INTRODUCTION

The search for compounds that can reverse the characteristic cellular dedifferentiation of neoplasms, inhibit their growth, and hence be added to the therapeutic armamentarium has led to the identification of aromatic fatty acids as a promising new class of antitumor agents (1, 2). The prototypic compound, PA, is a naturally occurring growth regulator highly conserved in evolution. In experimental models, the aromatic fatty acids induce cytostasis and differentiation of various hematological and solid neoplasms, including multidrug resistant tumors (1, 3–8). Early clinical trials with PA documented activity in high-grade gliomas, hormone-independent prostatic carcinoma, and lymphoid malignancies (1, 9–11).

PB, which is metabolized to PA in humans, was also shown recently to benefit cancer patients who have failed conventional therapies (12–15). For both drugs, large drug doses are required to reach therapeutic plasma concentrations (mm range); these are well tolerated, with the dose-limiting toxicity being somnolence. The mechanisms of action are, however, unclear.

In the preclinical models, changes in tumor biology induced by PA and PB have consistently been associated with alterations in lipid metabolism, exemplified by the intracellular accumulation of fat droplets and by declines in cholesterol synthesis. The latter are accompanied by major changes in gene expression occurring at both the transcriptional and posttranslational levels. Declines in protein prenylation appear to be attributable to inhibition of mevalonate-PP decarboxylase, a key enzyme controlling the mevalonate pathway of de novo cholesterol metabolism (3, 16). Changes in gene transcription, on the other hand, have been linked to increased DNA availability for interaction with transcriptional factors through inhibition of histone deacetylation (17) and of DNA methylation (18). Our studies aiming to identify transcriptional factors involved have recently documented the activation of PPARα (19), a member of the nuclear hormone receptor superfamily implicated in growth control and differentiation.

PPARs is one of three distinct gene isoforms isolated to date from human cells; the other two are designated PPARγ and PPARδ (also known as NUC1 and PPARβ; Refs. 20 and 21). These are ligand-activated transcriptional factors capable of interacting with genes that contain consensus PPRE as a direct

The abbreviations used are: PA, phenylacetate; PB, phenylbutrate; PPAR, peroxisome proliferator-activated receptor; hPPAR, human PPAR; PPRE, PPAR response element; PAG, phenylacetylglutamine; PGD2, prostaglandin D2; PGI2, prostaglandin I2; CPA, cis-parinaric acid; β-gal, β-galactosidase; MAP, mitogen-activated protein; LBD, ligand-binding domain; TZD, thiazolidinedione; NSAID, nonsteroidal anti-inflammatory drug; PUFA, polyunsaturated fatty acid.

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repeat of two AGGTCA half-sites separated by a single intervening nucleotide (DR-1). PPARs recognize their cognate response element through heterodimerization with the retinoid X receptor α, a characteristics shared with their closely related nuclear receptors activated by retinoids (retinoic acid receptors), vitamin D (vitamin D receptor), and thyroid hormone (thyroid receptor). Among the compounds known to activate PPARα are fibrate hypolipidemic agents. Considering the structural similarity to clofibrate, we first examined the effect of PA and its analogues on PPARα. The aromatic fatty acids were found to stimulate the production and transcriptional function of the nuclear receptor, and the effect was correlated with their potency as inhibitors of tumor cell proliferation. Our earlier findings indicating that PA is a very effective inducer of adipocyte differentiation (1), a biological process dependent on PPARγ activation (22), led us to expand the scope of our investigation and speculate that this nuclear receptor subtype might also be a target of anticancer therapy.

The studies reported herein were thus undertaken to examine the effect of PA on PPARγ in human tumor cells. Using breast carcinoma and glioma cultures, we show here that pharmacological concentrations of PA increase PPARγ expression and transcriptional function and provide evidence for a biological role of this nuclear receptor in tumor cytostasis induced by aromatic fatty acids.

MATERIALS AND METHODS

Cell Cultures and Reagents. MCF7 and MCF7ADR breast carcinoma lines were obtained from Dr. Richard Camaliar (National Cancer Institute, Frederick, MD). The glioblastoma lines A172 and U251 and the monkey kidney CV-1 cells were purchased from the American Type Culture collection (Rockville, MD). Cultures of human tumor cells were maintained in RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, and 0.1% penicillin, streptomycin, neomycin antibiotics (Life Technologies, Inc., Gaithersburg, MD). The growth medium for CV-1 was DMEM (Life Technologies). The sodium salts of PA and PB (provided by the Cancer Treatment Evaluation Program, National Cancer Institute, Bethesda, MD) were dissolved in distilled water (pH 7.4). PAG, p-chloro-PB, and p-iodo-PB were synthesized as described previously (3). PGD2 and 15-deoxy-D12,14-PGJ2 were purchased from Cayman Chemical Co. (Ann Arbor, MI) and dissolved in absolute ethanol. G418 was purchased from Life Technologies. PD98059 was from Biomol, Inc. (Plymouth Meeting, PA). CPA was obtained in 10-mg aliquots from Molecular Probes (Eugene, OR).

Cytostasis Assays. To determine the antiproliferative effects of drugs, cells were seeded at a density of 2 × 10^4 cells/well in 24-well plates (Costar Co., Cambridge, MA) 24 h prior to the addition of test drugs. On day 5 of the treatment, cells were harvested by trypsinization and counted using a Coulter Counter. The IC50 s were determined from dose-response curves.

Northern Blot Analysis. mRNA was extracted from exponentially growing cells using the Fast Track 2.0 kit (Invitrogen, San Diego, CA). The RNA species were separated on 1.2% agarose-formaldehyde gels and were transferred to a Dura-
Lon-UV membrane, UV-cross-linked, and prehybridized and hybridized with [α-32P]CTP-labeled probes according to the supplier’s instructions (Stratagene, La Jolla, CA). The probes were: hPPARγ-LBD 1.6 kb cDNA; 1.8 kb XhoI-KpnI fragment of pBKCMVhPPARγ; 0.9 kb BsmI-BamHI fragment of the 3′-end coding sequences of hPPARα; a synthetic oligomer complementary to the mouse p21waf1 (23); and β-actin cDNA (Oncor, Gaithersburg, MD). Probes were labeled using a random primed DNA labeling kit (Ready-To-Go; Pharmacia Biotech, Piscataway, NJ), and 50 μCi [32P]CTP (specific activity, 6000 Ci/mmol; DuPont NEN, Boston, MA). Hybridization of the membranes followed the protocol provided by Stratagene for Quick Hyb. Autoradiography was performed using Kodak XAR5 film at −70°C with intensifying screen. For quantification, the relative intensity of signal bands was determined by densitometric analysis of the radiographs.

**Gene Transfer and Transactivation Experiments.** Transient expression assays were performed with minor modifications to established methods (24). Briefly, CV-1 cells were plated in six-well plates at a density of 4 × 10⁴ cells/well in DMEM. Two days later, the medium was changed, and cells were transfected by N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammoniummethyl sulfate (Boehringer Mannheim) with plasmids in the following amounts: 1.4 μg/well of pcDNA-hPPARγ [hPPARγ1 (21) in the mammalian expression vector pcDNA] or the empty vector pcDNA (Invitrogen); 0.7 μg/well

**Fig. 2** Time-dependent changes in PPARγ and p21waf in PA-treated cells. MCF7ADR cells were exposed to 8 mM PA for the indicated time periods, and their mRNA was subjected to Northern blot analysis. For quantification, the blot was rehybridized with 32P probes for PPARγ, p21, and β-actin; the relative intensity of bands was determined by densitometric analysis of the autoradiographs, and the changes in PPARγ and p21 were corrected for β-actin. A graphic representation of the relative changes in gene expression occurring during the first 72 h after treatment is shown. Note the earlier rise in PPARγ, preceding that of p21waf1. After 120 h of treatment, the expression of PPARγ and p21waf1 increased by about 90- and 20-fold, respectively, over untreated controls.
of pPPRE-3-TK-LUC (a reporter plasmid containing three copies of PPRE of the rat acyl-CoA oxidase promoter upstream the heterologous promoter of thymidine kinase) or empty reporter TK-LUC (a gift from Ron M. Evans, Salk Institute, La Jolla, CA); and 0.3 μg/well of pSV-β-gal (Promega). After 18–20 h, the medium was again changed, and the ligand/activator drugs were added. Cells were lysed after ~24 h in 300 μl of Promega β-gal reporter lysis buffer, and supernatants were homogenized and split: 100 μl for the luciferase assay and 150 μl for the Promega β-gal assay. Luciferase production was assayed according to the standard Analytical Luminescence protocol and measured as light units, normalized for transfection efficiency by β-gal results expressed as absorbance at 420 according to the Promega β-gal kit. Results from three experiments, each in triplicate, were averaged and expressed as fold activation over the indicated control, with the SD indicated by the error bar, using the Graph Pad (Prism) statistics program.

To obtain stable transformants, MCF7 cells were seeded in 35-mm dishes at a density of 2 × 10^5 cells/well in 3 ml of growth medium. After 24 h, a DNA mix containing 300 ng of pcDNA-hPPARγ, 150 ng pSV-neo, and 2 μg of calf thymus carrier DNA were transfected as described above. Forty-eight h after DNA transfections, cells were subcultured in selection medium composed of RPMI 1640 supplemented with 10% FBS, 2 mM l-glutamine, 0.1% penicillin, streptomycin, neomycin antibiotics, and G418 (500 μg/ml). Individual neo-positive col-
Biologically active aromatic fatty acids bind directly to hPPARγ LBD. Increasing concentrations of tested drugs were added to cuvettes containing 1.5 μM CPA and 3 μM hPPARγ. A, PA; B, PB; C, p-chloro-PA (4-ClPA); D, p-iodo-PB (4-IPB); E, PAG. Shown is the relative increase in the 319:329-nm ratio compared with CPA fully bound to PPAR. Each plot is a representative experiment of two to four independent experiments.

Ligand Binding Studies. The binding of PA and derivatives to hPPARγ was measured using a spectrophotometric assay based on the displacement of CPA, as described previously (25). CPA (1.5 μM) was added to 25 mM Tris-HCl (pH 7.5) at room temperature and scanned against buffer between 312 and 340 nm using a Shimadzu UV-3000 scanning spectrophotometer demonstrating a 319:329-nm ratio of 3. Highly purified recombinant hPPARγ ligand binding domain (3 μM) was then added to both the sample and reference cuvettes, and the 319:329-nm ratio was determined (~1.2). Subsequently, increasing concentrations of drug were added to both cuvettes, and the 319:329-nm ratio was measured until the 319:329-nm ratio reached a plateau (at around 2.6–2.8). Binding constants were calculated using a single binding site curve fitting with Ultrafit for the

RESULTS

PPARγ Expression Correlates with Tumor Sensitivity to Growth Arrest by PA. In previous studies, we identified malignant cell lines with varying sensitivity to PA (7). Of these, cultures of closely related breast carcinoma cell lines, MCF7 and its subclone MCF7ADR, were now used to examine the status of PPARγ. Consistent with previous findings, PA concentrations required to cause 50% growth arrest at 5 days of treatment were 10.5 and 3.7 mM for MCF7 and MCF7ADR, respectively. Because drug concentrations of up to 4–5 mM can be achieved in humans, MCF7ADR can be defined as a clinically sensitive cell line and MCF7, a resistant one. Northern blot analysis revealed marked differences in the constitutive and PA-induced levels of PPARγ in these cell lines. Resistant MCF7 cells exhibited low pretreatment levels, which were only slightly up-regulated by PA (<2 fold), whereas the sensitive MCF7ADR had ~5-fold higher base levels of PPARγ, and these further increased by ≥3 fold after 24 h exposure to PA (Fig. 1A). A similar difference in transcript levels, although less marked, was noted for PPARδ in Fig. 1A. As would be expected if PPARγ played a role in cytostasis, the two cell lines also differed in their vulnerability to natural ligands of PPARγ. Over 90% growth arrest was noted in MCF7ADR cultures treated with either 7 μM of 15-deoxy-Δ12,14-PGJ2 or 30 μM PGD2, whereas similar treatments of MC7 cells caused only 55 ± 5% and 37 ± 2% inhibition, respectively. The correlation between PPARγ expression and PA sensitivity was not limited to the breast carcinoma cells.

A differential expression and up-regulation of the nuclear receptor at baseline and after treatment with PA was noted also in brain cancer cells (Fig. 1B), specifically in PA-responsive glioblastoma A172 (IC50, 4.6 mM) and the resistant U251 line (IC50, 11.0 mM).

Up-Regulation of PPARγ by PA Precedes Increases in p21waf1. To characterize the temporal sequence of drug effect on PPARγ and its relation to growth arrest, MCF7ADR cultures were treated with PA for various durations of time and examined for expression of the nuclear receptor and of p21waf1, a marker of G1 arrest in these cells (23). As shown in Fig. 2, PPARγ levels increased within 9 h of treatment, followed by increases in p21waf1 1 day later. The latter could not be explained by changes in cell density, as evidenced by the low levels of both PPARγ and p21waf1 transcripts in control cells grown in the absence of drug. The effect of PA on PPARγ was time dependent (Fig. 2 shows up to 90-fold increase after 5 days of treatment), dose dependent (no significant up-regulation noted at <1 mM PA), and reversible upon cessation of treatment (data not shown).

Inhibition of MAP Kinase-mediated Phosphorylation of PPARγ Increases Tumor Sensitivity to PA. Although transcriptional activity of nuclear receptors is typically enhanced by phosphorylation, MAP kinase phosphorylation of PPARγ negatively regulates its function (26). In an attempt to establish a causal relationship between PPAR activity and tumor cytostasis, PA-resistant MCF7 breast cancer cells with low PPARγ expres-
sion were exposed to PA in the presence of PD98059, an inhibitor of MAP kinase. The combination of 5 μM PD98059 with 5 mM PA resulted in 42 ± 2% decline in the cell proliferation, versus 17 ± 1% for PA alone. By itself, PD98059 had no significant antiproliferative effect (<5%).

**Forced Expression of PPARγ in Resistant Tumor Cells Restores Responsiveness.** To further characterize the correlation between hPPARγ and antitumor activity, we cotransfected the gene together with a selectable marker (neo) into the PA-resistant MCF7 cells. Stable transformants were selected and tested for PPARγ expression and their sensitivity to growth arrest by PA. Compared with parental cells, clonal lines 2A/A4 and 1B/A2 were found to have significantly higher baseline and induced levels of PPARγ; they were also significantly more sensitive to cytostasis by PA (Fig. 3). The IC_{50}s of the stable transformants were 4.8 mM for 2A/A4 and 5.2 mM for 1B/A2, versus 17 ± 1% for PA alone. By itself, PD98059 had no significant antiproliferative effect (<5%).

**Biologically Active Aromatic Fatty Acids Interact with the LBD of PPARγ and Activate Transcriptional Function.** PA and analogous aromatic fatty acids, but not PAG (a derivative in which the carboxylic acid is blocked), share in common the ability to induce tumor cytostasis and differentiation (see “Introduction”). Because the concentrations required for antitumor activity (mM range) vastly exceed those of common nuclear receptor ligands, we investigated whether they can be consid-
binding and activation of PPARγ and tumor cytostasis by the aromatic fatty acids.

**DISCUSSION**

The PPAR family of nuclear receptors has been the subject of intensive research since the cloning of its first member, PPARα, in 1990 (27). Receptor activation was associated with cell differentiation and regulation of lipid metabolism in a wide spectrum of cell types (19, 20, 28, 29). Quite unexpectedly, PPARs seem to be activated by a wide array of structurally diverse ligands, ranging from prostaglandins and TGDs to fatty acids, eicosanoids, nonsteroidal NSAIDs, glucocorticoids, PUFAs, and aromatic fatty acids (19, 22, 24, 30). Targeting PPARs pharmacologically is thus believed to have implications in the treatment of clinical disorders as diverse as hyperlipidemia, atherosclerosis, hypertension, obesity, diabetes, inflammation, autoimmunity, skin disorders, and cancer.

Exploring the mechanisms of action of aromatic fatty acids, the prototype of which is PA, we first documented a correlation between antitumor activity and the ability of these compounds to activate PPARα (19). Our earlier observations, indicating that PA induces adipocyte differentiation in preadipocyte fibroblasts (Ref. 1; a process depending on PPARα activation) and up-regulates PPARγ in glioma cells (31), suggested that this PPAR isoform might also mediate tumor cell differentiation. In support of this hypothesis, other groups reported selective tumor cytostasis and differentiation induced by PPARγ activators such as PGs, TGDs, and PUFAs, observed in cultures of human liposarcoma (32) and various adenocarcinomas (33–35). Consistent with the in vitro findings, troglitazone reduced tumor growth in mouse models of prostate (35) and colon (33) cancer without causing any significant toxicity to the host. These studies, however, did not establish a biological role for PPARγ in the antineoplastic process. In the present report, we address this question focusing on aromatic fatty acids with a low toxicity and antitumor activity in humans (10–15).

Our in vitro studies with PA indicate that it up-regulates the expression of PPARγ in responsive human tumor cells, interacts with the ligand-binding site of the PPARγ receptor, and activates its transcriptional function. The link between PPARγ and antitumor activity was documented several ways:

(a) Tumor sensitivity to growth arrest by PA was correlated with pretreatment levels of PPARγ transcripts in breast carcinoma and glioma cell lines. It is unlikely that this reflects a chance occurrence, because the cells with higher PPARγ expression were also more vulnerable to cytostasis induced by the natural ligands, 15-deoxy-Δ12,14-PGJ2 and PGD2.

(b) Studies carried out in initially resistant cells established that sensitivity to PA can be restored either by forced expression of PPARγ (gene transfer) or by interfering with receptor phosphorylation through inhibition of MAP kinase, a negative regulator of PPARγ.

(c) PPARγ expression increased in responsive cells within the first 9 h of PA treatment, preceding increases in p21waf1, a cyclin-dependent kinase inhibitor associated with G1 arrest in these tumor cells (23). Receptor binding and activation were common to aromatic fatty acids with antitumor activity and corresponded to their potency as antitumor agents (PA < PB < p-chloro-PA < p-iodo-PB). PAG, a biologically inactive metabolite, failed to bind PPARγ.

These findings, although not precluding the contribution of other mechanisms (see “Introduction”), establish a tight link between PPARγ and antitumor activity and provide the first documentation of drugs with selective clinical anticancer activity being identified as ligands of PPARγ.

The expression of PPARγ in treated patients is yet to be determined. Of interest are recent studies with PB (a precursor of PA), which show increases in histone acetylation in monocellular cells of a child with acute promyelocytic leukemia, who achieved complete clinical and cytogenetic remission upon treatment with this drug (15). Histone acetylation is critical to the function of transcriptional factors, such as the PPARs (36). The interaction of histone deacetylases with nuclear receptors has been implicated in transcriptional repression. In addition to removing such repression, increases in histone acetylation induced by the aromatic fatty acids can facilitate the binding of nuclear receptors by relaxing specific segments in the tightly coiled DNA. Of note is also the fact that the large doses (20–30 g/day) of the aromatic fatty acids required for therapeutic benefit achieve plasma drug levels in the millimolar range sufficient to activate PPARγ in vitro. Similar to other PPAR activators, notably the NSAIDs (37), the metabolic effects seen with PA and PB include sustained decreases in glucose concentrations, hyperammonemia, and symptoms reminiscent of acute hypoglycemia. Elevation in hepatic transaminases has been documented in children (but not in adults) with cancer treated by continuous infusion of PA (38). Most of these side effects, however, were not dose-limiting and could be controlled by dose reduction. These may belong to and help define a “PPAR activation toxicity syndrome,” consistent with the widespread tissue distribution of the receptors.

Earlier studies with PPAR ligands focusing on cancer in rodent models first implicated PPARα in hepatocarcinogenesis in rats (39). More recently, PPARγ agonists were also shown to promote cancer, specifically of the colon, in genetically susceptible mice (40, 41). Such findings raise concerns regarding the carcinogenic potential of PPAR activators in general, several of which are already in wide clinical use (42, 43). It must be kept in mind, however, that carcinogenesis by PPARα activators has thus far been restricted to rodents, and no significant increase in liver cancer has been noted in patients treated with clofibrate or NSAIDs. The latter may be attributable to the fact that human liver contains a very low level of functional PPARα, insufficient to mediate the hyperplastic responses seen in rodents (44). The promotion of colon cancer by PPARγ ligands, on the other hand, was described only in susceptible mice harboring a mutated APC gene. To date, no definitive increase in colon cancer has been documented in diabetic patients subjected to chronic treatment with troglitazone, although a nonsignificant increase in gastrointestinal cancer has been reported with clofibrate in large population studies (45). Continuous use of NSAIDs, on the other hand, lowers the risk of colon cancer in humans (46). Although the risk posed by PPAR activators to healthy or genetically susceptible humans remains unclear, there is compelling evidence suggesting that PPARs might serve as novel targets for anticancer therapy.

Are the aromatic fatty acids carcinogenic? The safety of
PA and PB has been well established in individuals with nonmalignant diseases (urea cycle disorders and β-chain hemoglobinopathies) who were subjected to chronic treatment with large drug doses (20 or more g/day; Refs. 47–49). No increases in the incidence of cancer were noted in these patient populations. The aromatic fatty acids activate more than one PPAR subtype; it is possible that a specific ratio of activated PPAR isoforms leads to tumor growth arrest, whereas another may induce carcinogenesis in predisposed cells. In this respect, the biological activity of highly specific PPAR ligands remains to be characterized, whereas genetic heterogeneity in the expression of the nuclear receptors may underlie an individual response to dietary and pharmacological agonists.

Should a correlation be established between PPAR expression and antitumor activity in humans, the present in vitro findings may have implications that range from therapeutic guidance to validating a novel target for drug discovery. PPARγ status may prove to have a predictive value with respect to therapeutic outcome; patient screening on that basis might therefore serve to guide the choice of therapy in a population with severely limited treatment options. Without excluding potential complementation with conventional cytotoxic chemo- and radiotherapy, combination therapy protocols can also be conceived involving the coadministration of aromatic fatty acids with compounds that either target PPARs themselves [e.g., TZDs, PUFAs, and vastatins (50)] or their heterodimer partner, retinoid X receptor (retinoids). Finally, similar to the evolution of TZDs, PUFAs, and vastatins (50) or their heterodimer partner, retinoid X receptor (retinoids). Finally, similar to the evolution of PPARs, phenylbutyrate and sodium phenylacetate have been shown to have a therapeutic effect in cancers (46) make it a therapeutic target of choice that could potentially transcend histological categorizations and justify studies to establish the value of PPARs in the molecular profiling of tumors, shifting the basis of therapeutic strategies from their microscopic phenotype to their genotype.

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