Constitutive Activation of Peroxisome Proliferator-activated Receptor-γ Suppresses Pro-inflammatory Adhesion Molecules in Human Vascular Endothelial Cells

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Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a ligand-activated nuclear receptor that has an essential role in adipogenesis and glucose homeostasis. PPAR-γ is expressed in vascular tissues including endothelial cells (ECs). PPAR-γ activity can be regulated by many pathophysiological and pharmacological agonists. However, the role of PPAR-γ activation in ECs remains unclear. In this study, we examined the effect of the constitutive activation of PPAR-γ on the phenotypic modulation of ECs. Adenovirus-mediated expression of a constitutively active mutant of PPAR-γ resulted in significant ligand-independent activation of PPAR-γ and specific induction of the PPAR-γ target genes. However, PPAR-γ activation significantly suppressed the expression of vascular adhesion molecules in ECs and the ensuing leukocyte recruitment. Furthermore, constitutive activation of PPAR-γ resulted in simultaneous repression of AP-1 and NF-κB activity, which suggests that PPAR-γ may reduce pro-inflammatory phenotypes via, at least in part, suppression of the AP-1 and NF-κB pathways. Therefore, using a gain-of-function approach, our study provides novel evidence showing that constitutive activation of PPAR-γ is sufficient to prevent ECs from converting into a pro-inflammatory phenotype. These results also suggest that, in addition to pharmacological agonists, the genetic modification of the PPAR-γ activity in ECs may be a potential approach for therapeutic intervention in various inflammatory disorders.

The abbreviations used are: PPAR, peroxisome proliferator-activated receptor; EC(s), endothelial cell(s); TZD, thiazolidinedione; HUVECs, human umbilical cord vein endothelial cell(s); ICAM, intercellular adhesion molecule; VCAM, vascular adhesion molecule; EMSA, electrophoretic mobility shift assay; TNF, tumor necrosis factor; PMA, phorbol 12-myristate 13-acetate; HSV, herpes simplex virus; Ad, adenovirus; GFP, green fluorescence protein; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PPRE, PPAR-responsive element.

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However, the role of PPAR-γ activation in ECs remains unclear. Previous studies have shown that PPAR-γ agonists such as 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) and the thiazolidinedione (TZD) class of insulin-sensitizing drugs can modulate the expression of many pro-inflammatory cytokines (2), chemokines (3), and adhesion molecules (4) in macrophages and many other cell types including ECs. However, the observed anti-inflammatory effects often vary according to the agonists used and are not always consistent with their capacity for receptor binding (5). Furthermore, recent studies indicate that the receptor-independent effects exist both for 15d-PG-J2 and TZDs (6, 7). Therefore, whether constitutive activation of the PPAR-γ per se, regardless of pleiotropic ligand-specific effects, has an anti-inflammatory effect remains to be investigated.

The aim of this study was to examine whether a constitutively active PPAR-γ can modulate the endothelial expression of pro-inflammatory phenotype such as the induction of adhesion molecules and recruitment of leukocytes. The constitutively active mutant of PPAR-γ (VP-PPAR-γ) was constructed by fusing the herpes virus VP16 activation domain to wild-type PPAR-γ, and delivered into human umbilical cord vein endothelial cells (HUVECs) with use of a tetracycline-controlled adenoviral system. The overexpression of VP-PPAR-γ resulted in the ligand-independent activation of PPAR-γ and specific induction of the PPAR-γ target genes. However, the induced expression of intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and E-selectin was significantly suppressed in the VP-PPAR-γ-transduced ECs. Consequently, endothelial recruitment of monocytes was markedly attenuated by constitutive activation of the PPAR-γ. Results from electrophoretic mobility shift assays (EMSA) and reporter transfection assays demonstrated that VP-PPAR-γ in ECs resulted in a simultaneous decrease in AP-1 and NF-κB activity. These results demonstrate that activation of endothelial PPAR-γ has a potent anti-inflammatory role.

EXPERIMENTAL PROCEDURES

Cells and Reagents—HUVECs were harvested by collagenase treatment of umbilical cord veins and cultured on plates coated with collagen. Cells were maintained in M199 supplemented with 20% fetal bovine serum, 20 mM HEPES (pH 7.4), 1 mg/ml of recombinant human fibroblast growth factor, and 90 μg/ml of heparin and antibiotics. In all the experiments, cells within three passages were used. THP-1, a human monocytic cell line (ATCC), was grown in RPMI 1640 containing 10% fetal bovine serum. Recombinant human tumor necrosis factor (TNF-α) was from Becton-Dickinson. Phorbol 12-myristate 13-acetate (PMA) and tetracyncline were purchased from Sigma.

Adenoviral Vectors and Infection—VP-PPAR-γ contains the 78 amino...
acid herpes simplex virus (HSV) VP16 transactivation domain fused to the N terminus of mouse PPAR-γ (GenBank accession number U10374). To generate the adenoviruses expressing VP-PPAR-γ (Ad-VP-PPAR-γ), the cDNA fragment containing VP-PPAR-γ was subcloned into a shuttle plasmid pAdlox and recombined with an E1- and E3-deleted adenovirus DNA in CRE8 cells (8). The expression of the inserted gene was driven by a 7 x tet/minimal cytomegalovirus promoter that was further under the control of an artificial tetracycline-responsive transactivator (tTA). The adenoviruses expressing green fluorescence protein (Ad-GFP) and tTA were previously described (9). The adenoviruses were plaque-purified, expanded, titrated in 293 cells, and purified by cesium chloride methods. For adenovirus-mediated gene transfer, confluent HUVECs were exposed to adenoviral vectors at a multiplicity-of-infection of ~50–100 for 2 h (Ad-tTA was co-infected to induce the tetracycline controllable expression). After the viruses were washed off, infected cells were further incubated for the indicated time in the presence or absence of tetracycline.

**Plasmids, Transfection, and Reporter Assay**—The PPRE-TK-Luc is a luciferase reporter containing the herpes virus thymidine kinase promoter (−105/+51) downstream of three copies of PPAR response elements from the acyl-CoA oxidase gene. The pCMX-VP16 is a plasmid encoding the VP16 transactivation domain (9). Plasmids for the yeast PPRE-TK-Luc reporter (Promega) (9). Mutagenesis of the AP-1-NF-κB site in the human ICAM-1 promoter region was performed with the QuikChange™ polymerase chain reaction-based method (Stratagene) as described previously (9). Mutagenic primers were used to introduce mutations (lowercase letters) at the AP-1-like site (−321, in relation to the start codon) and the NF-κB-like site (−223) (underlined) in the ICAM-1 promoter region: AP-1m, 5′-GGCGTGTAGACCTGGTGGAGCTGCTTATAAGGTCGAGCTGCCG-3′ and NF-κBm, 5′-CAGATTGTTTACTGTTGAAAT-3′. Following transformation, amplification, selection, and screening, the mutagenic exchanges were confirmed by sequencing. Plasmids were introduced into HUVECs with use of a cationic lipid-based transfection reagent vitrogen, fractionated on a formaldehyde-agarose gel, transferred to a nitrocellulose membrane, and immunoblotted with use of a rabbit polyclonal antibody to PPAR-γ (H-100, Santa Cruz, California) and an horseradish peroxidase-conjugated secondary antibody (sheep anti-rabbit, 1:5000, Sigma) followed by ECL detection (Amer sham Biosciences).

**Electrophoretic Mobility Shift Assay (EMSA)**—The nuclear extracts were first mixed with 1 μg of poly (dI-dC) in DNA binding buffer and incubated at room temperature for 10 min. **32**P-labeled oligonucleotides were then added to the reaction and incubated for 20 min at room temperature. The oligonucleotides were end labeled with use of T4 polynucleotide kinase and [γ-**32**P]adenosine triphosphate (ICN). The sequences of oligonucleotides are as follows (sequences of the complementary strands are omitted): 1) PPRE (Aco oxidoase), 5′-GGGGGACCGAGGAGTTTCAACAGACAGGGAGCT-3′; 2) AP-1 (consensus), 5′-AGACAGACAGGGAGCT-3′; and 3) NF-κB (consensus), 5′-AAGGAGGAGCTTCCAGGGC-3′.

**Leukocyte Adhesion Assay**—Human monocyte cells, THP-1, were infected with Ad-GFP and Ad-tTA. Twenty-four hours post-infection, the THP-1 cells were washed and co-incubated for 30 min with control or activated HUVECs. Unbound leukocytes were removed by washing, the adhered cells were fixed with 4% paraformaldehyde, and the number of adhered cells was visualized by fluorescence microscopy as described previously (9). To quantify the THP-1 adhesion, the cells (THP-1 and HUVECs) were harvested, solubilized, and measured with use of a fluorescence concentration analyzer (Pandex, IDEXX) as previously described (13).

**Statistical Analysis**—Quantitative data are expressed as mean ± S.E. Statistical analysis was performed with use of the Student’s *t* test. Differences were considered significant when probability values were less than 0.05.

**RESULTS**

**Conditional Expression of the Constitutively Active Mutant of PPAR-γ in ECs**—To examine the role of PPAR-γ in EC phenotypic modulation, we constructed a constitutively active form of PPAR-γ by fusing a herpes virus VP16 transactivation domain to the wild-type PPAR-γ cDNA. A recombinant adenovirus expressing VP-PPAR-γ was made to ensure a ubiquitous yet controllable expression of VP-PPAR-γ in ECs (Fig. 1A). As shown by RNA hybridization and immunoblotting (Fig. 1B), overexpression of VP-PPAR-γ was achieved by infection of HUVECs with Ad-VP-PPAR-γ and Ad-tTA and switched off by the addition of tetracycline in the culture medium. Furthermore, the overexpression of VP-PPAR-γ specifically induced DNA binding to Aco-PPRE, which could be blocked by a specific cold competitor (Fig. 2A). VP-PPAR-γ did not bind to the sequences for other transcription factors such as AP-1, NF-κB, AP-2, and GATA (data not shown). In addition, a transient reporter assay was performed to assess the functionality of VP-PPAR-γ to induce the PPRE-dependent gene expression. As shown in Fig. 2B, adenovirus-mediated expression of VP-PPAR-γ caused a more than 10-fold increase in the PPRE-driven luciferase expression in the absence of exogenous PPAR-γ ligands. It is thus demonstrated that adenovirus-mediated expression of VP-PPAR-γ can be used as a model for constitutive PPAR-γ activation in ECs.

**Constitutive Activation of PPAR-γ Inhibits the Expression of Adhesion Molecules in ECs and Endothelial-Leukocyte Adhesion**—Because the induced expression of adhesion molecules is a phenotypic hallmark of EC activation and a critical step of many pro-inflammatory processes, we next examined the effect of the PPAR-γ constitutive activation on the gene expression of ICAM-1, VCAM-1, and E-selectin in response to known pro-inflammatory agonists PMA and TNF-α. Northern blotting results (Fig. 3) reveal that overexpression of the VP-PPAR-γ significantly suppressed the induction of these adhesion molecules by PMA and TNF-α, whereas expression of the housekeeping gene GAPDH was not affected. In contrast, the expression of CD36, an endogenous target gene of PPAR-γ, was clearly induced. Thus, constitutive activation of PPAR-γ selectively down-regulated the pro-inflammatory genes in ECs.

The induction of adhesion molecules is essential for leukocyte trafficking to the vessel wall and for eliciting inflammatory reactions in various physiological and pathological processes. Therefore, we carried out the endothelial-leukocyte adhesion assay to investigate whether the constitutive activation of PPAR-γ functionally modulates such a process in vitro. The mononuclear cells (THP-1) were infected to express a green fluorescence protein for use in visualization and quantification by fluorescence microscopy or fluorescence analyzer. As shown in Fig. 4, massive EC-leukocyte adhesion was induced by pre-stimulating HUVECs with either TNF-α or PMA. However, constitutive activation of PPAR-γ in ECs significantly attenuated the recruitment of leukocytes provoked by either pro-inflammatory agonist. Thus, it is plausible that an increase in PPAR-γ activity is sufficient to down-regulate the expression of adhesion molecules and, as a result, to prevent the endothelium from converting into a pro-inflammatory state.

**Constitutive Activation of PPAR-γ Inhibits AP-1 and NF-κB Pathways in ECs**—To understand how the constitutive activation...
tion of PPAR-γ causes the transcriptional repression of the adhesion molecules, we examined the effect of VP-PPAR-γ on the activation of AP-1 and NF-κB, which are known to be the most important transcription factors governing endothelial activation. As seen in Fig. 5A, the constitutive activation of PPAR-γ markedly inhibited both AP-1- and NF-κB-mediated gene expression in the transient reporter assays. However, it did not affect the yeast transcription factor Gal4-mediated gene expression. This trans-repressive effect was also demonstrated in results from EMSA. In the VP-PPAR-γ expressing cells, the AP-1 and NF-κB binding activity clearly decreased (Fig. 5B). Further, ICAM-1 promoter assays were performed to address whether the simultaneous inhibition of AP-1 and NF-κB by the constitutively active PPAR-γ can account for the transcriptional suppression of the vascular adhesion molecules. As shown in Fig. 6, the induced ICAM-1 promoter activity was significantly repressed by co-expression of the VP-PPAR-γ but not the VP16 activation alone. However, abolishing the AP-1 and NF-κB binding sites virtually eliminated the ICAM-1 promoter induction as well as the suppressive effect of the VP-PPAR-γ. Thus, it demonstrated that a simultaneous inhibition of AP-1 and NF-κB activity is sufficient to block the ICAM-1 induction and may contribute to the inhibitory effect of VP-PPAR-γ on the induction of the adhesion molecules and the ensuing endothelial-leukocyte interaction.

**DISCUSSION**

Recently, an anti-inflammatory role for PPAR-γ has been suggested because many of the PPAR-γ ligands effectively reduce inflammatory processes in vitro and in vivo (3, 4). Both endogenous and synthetic PPAR-γ ligands such as 15d-PG-J2 and TZDs were shown to inhibit the expression of pro-inflammatory genes in monocyte and other cell types. Moreover, these ligands have been demonstrated to be effective in animal models of many inflammatory disorders including atherosclerosis (14), arthritis (15) and inflammatory bowel disease (16). However, because the anti-inflammatory potency of the PPAR-γ ligands does not parallel their affinity to the receptor and these ligands often possess pleiotropic activities other than being PPAR-γ agonists, receptor-independent mechanisms have been suggested. For instance, deletion of the gene expressing PPAR-γ in stem cell-derived macrophages did not alter basal or stimulated cytokine production. Furthermore, high concentrations of PPAR-γ ligands can inhibit cytokine production in macrophages lacking PPAR-γ (6). Thus, the question is whether PPAR-γ activation, excluding the various receptor-independent effects of a rapidly expanding pool of ligands, is by itself sufficient to revert a pro-inflammatory phenotype. In this study, using a tightly regulated adenoviral system to express the constitutively active PPAR-γ in HUVECs, we demonstrated a potent inhibitory effect of this receptor on the endothelial expression of pro-inflammatory adhesion molecules and the ensuing leukocyte recruitment. This observation provides novel evidence for a receptor-dependent role in modulating endothelial phenotypic activation, which suggests that modification of the PPAR-γ receptor may be a potential anti-inflammatory strategy.

The EC expression of adhesion molecules and recruitment of leukocytes to the vessel wall are critical steps in the immune response and in inflammatory disorders (17). The expression of these adhesion molecules has been found to be regulated by
various agonists for PPAR-γ, which is expressed in vessel tissues including the endothelium. However, with respect to a role for PPAR-γ ligands in the induction of endothelial adhesion molecules, data have been inconsistent. Pasceri et al. found that 15d-PG-J2 (20 μM) and troglitazone (100 μM) markedly attenuated the TNF-α-induced expression of VCAM-1 and ICAM-1 but not E-selectin and PECAM-1 in HUVECs (4). Jackson et al. found that, in aortic ECs, the PMA- or LPS-induced VCAM-1 was partially inhibited by the PPAR-γ activators 15d-PG-J2, ciglitazone and troglitazone, but unaffected by BRL 49653 (rosiglitazone) (18). Chen et al. described troglitazone as enhancing both basal and oxidized LDL-induced ICAM-1 expression in ECV-304, an endothelial-like tumor cell line (19). At the moment, there is no obvious explanation for these seemingly conflicting results. It is plausible that differences in cell types and stimuli may account for the observed discrepancies. In addition, the inconsistent results may also be attributed to the receptor-independent effects. However, because we have shown that constitutive activation of PPAR-γ in ECs sufficiently inhibited the expression of these adhesion

FIG. 3. VP-PPAR-γ suppresses the expression of adhesion molecules in ECs. Confluent HUVECs were infected with Ad-VP-PPAR-γ and Ad-tTA in the presence or absence of tetracycline. After 24 h, cells were treated with control, PMA (50 ng/ml), or TNF-α (2 ng/ml) for 4 h. The RNA blot was sequentially hybridized to the cDNA probes for ICAM-1, VCAM-1, E-selectin, CD36, and GAPDH. Data represents three independent experiments.

FIG. 4. VP-PPAR-γ prevents recruitment of leukocytes to ECs. Confluent HUVECs were infected with Ad-VP-PPAR-γ and Ad-tTA in the presence or absence of tetracycline. After 24 h, cells were treated with control, TNF-α (2 ng/ml), or PMA (50 ng/ml) for 16 h and then incubated with GFP-expressing THP-1 cells for 30 mins. A, after fixation, the THP-1 cells (with green fluorescence) bound to ECs and were visualized under fluorescence microscopy. B, fluorescent intensities in cellular lysates were assessed with use of a fluorescence concentration analyzer. Bars represent mean ± S.E. of three independent experiments, each performed in triplicate. *, p < 0.05; VP-PPAR-γ (−Tc) versus mock infection (+Tc).
molecules challenged by either PMA or TNF-α, it can be speculated that pharmacological activation of PPAR may exert an anti-inflammatory net effect if the receptor-independent non-specific effects are minimized.

As a transcription factor, the primary mechanism for PPAR-γ to regulate gene expression is through binding to the specific recognition site, the PPAR-responsive element (PPRE), in the promoter region of a target gene. Thus, as expected, the constitutively active PPAR-γ induced the gene expression of CD36, which has a consensus PPRE in its promoter and is considered to be a PPAR-γ-specific target gene (20). Induction of the CD36 expression demonstrated both functionality and specificity of the adenovirally expressed VP-PPAR-γ. However, because the consensus PPRE motif was not identified in the 5'-flanking regions of the ICAM-1, VCAM-1, and E-selectin genes, the regulatory mechanisms for the down-regulation of these vascular adhesion molecules by VP-PPAR-γ may not be the same as that for the CD36 induction. We have found that the constitutive activation of PPAR-γ inhibited the AP-1 and NF-κB transactivation. In addition, the VP-PPAR-γ reduced AP-1 and NF-κB DNA binding, which may lead to decreases in their transactivation. It is well known that both AP-1 and NF-κB play pivotal roles in the transcriptional regulation of ICAM-1 and other pro-inflammatory genes (21). Especially, AP-1- and NF-κB-like cis-elements have been identified in the

**FIG. 5.** VP-PPAR-γ inhibits AP-1 and NF-κB activation in ECs. A, constitutive activation of PPAR-γ inhibits transactivation of AP-1- and NF-κB-dependent gene expression in ECs. VP-PPAR-γ-infected HUVECs were transfected with AP-1-, NF-κB, or UAS-driven reporter plasmids respectively. The AP-1 or NF-κB-reporter gene expression was induced by PMA or TNF-α; the UAS-reporter was induced by co-transfection of the Gal4 expression plasmid. Bars represent fold induction (mean ± S.E.; n = 3) of basal activity. *, p < 0.05; **, p < 0.01; VP-PPAR-γ (−Tc) versus mock infection (+ Tc). B, constitutive activation of PPAR-γ decreases the AP-1 and NF-κB DNA binding activity in ECs. EMSA was performed with 32P-labeled double-strand oligonucleotides with the sequences corresponding to PPRE, AP-1, or NF-κB. The VP-PPAR-γ-infected cells were maintained in the medium with or without tetracycline and treated with control or PMA (50 ng/ml) for 2 h before extraction of nuclear protein.

**FIG. 6.** VP-PPAR-γ suppresses ICAM-1 induction via AP-1 and NF-κB pathway. Promoter-reporter assays were performed by co-transfection of ICAM-1 (−445)-luc or ICAM-1 (−445)-AP-1/NF-κBm-luc with pCMX-VP-PPAR-γ, pCMX-VP16 or pCMX blank vector, respectively. After transfection, HUVECs were exposed to PMA (50 ng/ml) or control medium for 16 h before being harvested for luciferase and β-galactosidase assay. Bars represent fold induction (mean ± S.E.; n = 3) of basal activity. **, p < 0.01; VP-PPAR-γ versus vector control.
proximal 445-bp of the 5‘-flanking region of the ICAM-1 gene and found to be responsible for ICAM-1 induction by PMA and TNF-α (10, 12). In this study, we demonstrated that mutations at these two sites are sufficient to abrogate the ICAM-1 induction as well as the suppressive effect elicited by VP-PPAR-γ. Therefore, it is conceivable that the simultaneous trans-repression of AP-1 and NF-κB may account for one of the mechanisms by which the constitutively active PPAR-γ negatively regulates endothelial adhesion molecules and pro-inflammatory processes. In the present study, the constitutively active PPAR-γ is a chimeric construct containing the VP16 activation domain from HSV. Expression of this construct in ECs leads to PPAR-γ activation in the absence of exogenous ligands or activators. This approach is to circumvent the receptor-independent effects that individual PPAR agonists may have. The anti-inflammatory effect described is unlikely to be attributed to a nonspecific effect of the VP16 transactivation domain because VP-PPAR-γ did not affect the basal transcription as demonstrated by the use of a Gal4-responsive reporter gene (Fig. 5A) and, more importantly, because gene induction of ICAM-1 was inhibited by the VP-PPAR-γ but not by the VP16 activation domain (Fig. 6). In addition, other studies showed that HSV infection induces pro-inflammatory vascular adhesion molecules and MAPK/AP-1 activity (22–25). Taken together, these observations support the conclusion that the anti-inflammatory effect is associated with the constitutive activation of PPAR-γ. Interestingly, PPAR-γ ligands such as 15d-PGJ2 are known to inhibit AP-1 and NF-κB DNA binding via both the receptor-dependent and -independent mechanisms (7). In this respect, the PPAR-γ constitutive activation model described in this study may mimic the PPAR-γ-dependent action in a ligand-activated context. The receptor-independent mechanisms may account for pleiotropic effects of individual pharmacological PPAR agonists. For the time being, the exact pathways leading to a trans-repression of these transcription factors remain unclear. These are clearly important issues for future study. Nevertheless, the conditional expression of VP-PPAR-γ established in this study will be helpful in elucidating the pathophysiological functions of this receptor in vessel walls. Most importantly, our finding that a constitutively active form of PPAR-γ prevents endothelial activation and leukocyte recruitment may represent an approach to control the vascular inflammatory processes.

In conclusion, we have demonstrated a direct anti-inflammatory role for PPAR-γ. Specifically modifying PPAR-γ activity in ECs may have potential application in the treatment of various pro-inflammatory disorders, including arthritis, atherosclerosis, and inflammatory bowel disease.

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