The Peroxisome Proliferator-activated Receptor δ Promotes Lipid Accumulation in Human Macrophages*

Helen Vosper‡, Lisa Patel§, Tracey L. Graham‡, Guennadi A. Khoudolii, Alexander Hill§, Colin H. Macphee§, Ivan Pinto§, Stephen A. Smith§, Keith E. Suckling§, C. Roland Wolf‡, and Colin N. A. Palmer‡**

From the ‡Biomedical Research Centre, Imperial Cancer Research Fund, Molecular Pharmacology Unit, and the ¶Department of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland and §GlaxoSmithKline, New Frontiers Science Park North, Third Avenue, Harlow, Essex CM19 5AW, United Kingdom

The peroxisome proliferator-activated receptors (PPARs) are a family of fatty acid-activated transcription factors which control lipid homeostasis and cellular differentiation. PPARα (NR1C1) controls lipid oxidation and clearance in hepatocytes and PPARγ (NR1C3) promotes preadipocyte differentiation and lipogenesis. Drugs that activate PPARα are effective in lowering plasma levels of lipids and have been used in the management of hyperlipidemia. PPARγ agonists increase insulin sensitivity and are used in the management of type 2 diabetes. In contrast, there are no marketed drugs that selectively target PPARδ (NR1C2) and the physiological roles of PPARδ are unclear. In this report we demonstrate that the expression of PPARδ is increased during the differentiation of human macrophages in vitro. In addition, a highly selective agonist of PPARδ (compound F) promotes lipid accumulation in primary human macrophages and in macrophages derived from the human monocytic cell line, THP-1. Compound F increases the expression of genes involved in lipid uptake and storage such as the class A and B scavenger receptors (SRA, CD36) and adipophilin. PPARδ activation also represses key genes involved in lipid metabolism and efflux, i.e. cholesterol 27-hydroxylase and apolipoprotein E. We have generated THP-1 sublines that overexpress PPARδ and have confirmed that PPARδ is a powerful promoter of macrophage lipid accumulation. These data suggest that PPARδ may play a role in the pathology of diseases associated with lipid-filled macrophages, such as atherosclerosis, arthritis, and neurodegeneration.

Peroxisome proliferator-activated receptors (α, δ, and γ) are ligand-activated transcription factors that control lipid and glucose homeostasis (1). They are members of the nuclear receptor family and form obligate heterodimers with the retinoid X receptor (2). PPARα is highly expressed in the rodent liver,

where its activation up-regulates β-oxidation and thus promotes lipid clearance. PPARα agonists, such as the fibrates, are effective lipid-lowering drugs. PPARγ, which is activated by 15-deoxy-Δ12,14-PGJ₂ and the thiazolidinedione class of insulin-sensitizing drugs, is expressed particularly in adipose tissue, where it initiates the differentiation cascade (3, 4). Among its known target genes are adipocyte fatty acid-binding protein and fatty acid synthase, which are effectors of lipid accumulation during adipogenesis.

PPARγ has also been studied for its role in the formation of the atherosclerotic plaque, a lesion consisting of an accumulation of lipid-laden macrophages within the intima of the arterial wall. These studies started with the observation that PPARγ up-regulates CD36 (scavenger receptor-class B) expression in macrophages. This facilitates uptake of modified plasma low density lipoproteins into the macrophages potentially leading to the formation of foam cells (5, 6). However, plaque formation is also appreciated to be an inflammatory response and it has been shown that activators of PPARγ inhibit the production of inflammatory cytokines such as tumor necrosis factor-α, interleukin-6 and interleukin-1β (7–11). Although the PPAR dependence of these effects is controversial (12, 13), the mechanism of this inhibition appears to be via repression of AP-1, NF-κB, and STAT-1 activity (8, 14, 15).

Furthermore, it has recently been shown that activation of PPARγ by the thiazolidinedione, rosiglitazone, decreases scavenger receptor A expression (16) and increases ABCA1 expression (17). ABCA1 is a member of the ATP-binding cassette transporter family and it is involved in the control of the apoA1-mediated cholesterol efflux from macrophages and other peripheral lipid stores. Mutations in this protein occur in patients with Tangiers disease, a syndrome that is characterized by the pathological accumulation of cholesterol esters in many tissues. Up-regulation of ABCA1 may promote cholesterol clearance, and overall, PPARγ appears to be a negative regulator of cholesterol accumulation (16, 17). Indeed, in vivo studies using animal models and preliminary clinical data have suggested that PPARγ agonists oppose atheroma progression (18–22).

In contrast to PPARα and -γ, the function of PPARδ is relatively unknown. PPARδ, also known as PPARβ, NC1, and FAAR, has been shown to be expressed in a wide range of tissues, but progress in understanding the function of this protein has been hampered by the lack of selective ligands. PPARδ has recently been implicated in a wide range of physiological and pathophysiological processes such as embryonic implantation, wound healing, inflammation, cancer, and osteoporosis (23–29). In this report, we show that PPARδ mRNA and protein levels are dramatically elevated during macrophage

Received for publication, September 4, 2001
Published, JBC Papers in Press, September 13, 2001, DOI 10.1074/jbc.M108422200

*This work was supported by a grant from SmithKline Beecham Pharmaceuticals (to H. V.) and by The British Heart Foundation (to G. K.). 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 1754 solely to indicate this fact.

**To whom correspondence should be addressed. Tel.: 44-0-1382-632774; Fax: 44-0-1382-669993; E-mail: palmer@icrf.icnet.uk.

The abbreviations used are: PPAR, peroxisome proliferator-activated receptor; RXR, 9-cis-retinoic acid receptor; FABP, fatty acid-binding protein; PMA, phorbol 12-myristate 13-acetate; apo, apolipoprotein; LDL, low density lipoprotein; ABC, ATP binding cassette; SR, scavenger receptor.
differentialiation and provide both genetic and pharmacological evidence that PPARε is a positive effector of lipid accumulation in human macrophage cultures. We also show that PPARδ coordinates a complex pattern of gene expression controlling lipid uptake, transport, storage, metabolism, and efflux.

**EXPERIMENTAL PROCEDURES**

**Isolation of Human Monocytes and in Vitro Monocyte/Macrophage Differentiation**—Human monocytes were isolated from buffy coat preparations of whole blood taken from healthy volunteers. In brief, the buffy coat was mixed with Optiprep® (Robbins Scientific Div.) to a ratio of 2.5:1 and then overlaid with a discontinuous Optiprep™ gradient, prepared according to the reagent datasheet. Following centrifugation for 25 min at 600 × g the monocyte layer formed within the top 5–10 ml of the gradient was removed, washed with phosphate-buffered saline, and resuspended in RPMI 1640, supplemented with 2 mM glutamine and 10% human serum (Sigma). Cell viability was assessed by the ability to exclude trypan blue and was typically >95%. Monocyte purity was determined by differential counts of DiffQuik (Porvair Sciences Ltd.) stained cell preparations and was typically >95%. For monocyte-macrophage differentiation, monocytes isolated as above were resuspended in culture medium at a density of 2.5 × 10⁶/ml and seeded into 12-well tissue culture plates; medium was changed every 48 h. LDL, oxidized LDL, and lipid-depleted serum was obtained from Intracel Corporation.

**Transient Transfection**—COS-1 cells were transfected by a DEAE-dextran method as previously described (30). The reporter construct pFABPLUC contains 4 copies of the peroxisome proliferator response element from the human liver FABP gene in front of the herpes simplex virus-thymidine kinase promoter, cloned immediately upstream of the cDNA encoding firefly luciferase in pGL3 Basic (Promega). The PPAR expression vectors contained the coding sequence for human PPARα, -δ, and -γ under the control of the enhancer/promoter of the human cyto-megalovirus. PSVβGal was co-transfected with each sample to act as an internal control for transfection. Cell lysates were prepared and luciferase and β-galactosidase activities were assayed using kits as described by the manufacturer (Promega). Data are presented as the relative light units obtained with the luciferase assay divided by the absorbance obtained at 405 nm in the β-galactosidase assays.

**Culture and Differentiation of THP-1 Cells**—THP-1 cells were obtained from ATCC. Cultures were grown in RPMI supplemented with 10% heat-inactivated fetal calf serum. Differentiation was initiated by the addition of 5 ng/ml PMA in the above medium. All drugs were added to cultures using a 10% human serum (Fig. 2, A, 6, 8, 10) (Fig. 1A). Interestingly, we also found that PPARδ levels are markedly increased during macrophage differentiation. PPARα protein was also detectable, but was not greatly altered during differentiation. This pattern of regulation was confirmed at the mRNA level (Fig. 1B).

**Lipid Extraction and Measurement**—primary human macrophages in vitro. We confirmed previous observations that PPARγ protein levels are increased during this process (5, 6, 8, 10) (Fig. 1A). We observed that rosiglitazone (1 μM) partially inhibited the accumulation of lipid under such conditions. We also found that rosiglitazone (1 μM) partially inhibited the accumulation of lipid in primary human macrophages under normal culture conditions (10% human serum) (Fig. 2, A versus B). We observed that rosiglitazone (1 μM) partially inhibited the accumulation of lipid under such conditions. We also found that rosiglitazone did not stimulate lipid accumulation in primary macrophages in lipid-depleted serum alone, or supplemented with 100 μg/ml normal or oxidized low density lipoproteins (Fig. 2C, nLDL and oxLDL, respectively).

**Activation of PPARδ Promotes Lipid Accumulation in Primary Human Macrophages**—in view of the marked induction of PPARδ during human macrophage differentiation, we investigated whether it may be a regulatory factor in the process of lipid accumulation. Investigations into the role of PPARδ in lipid metabolism have been hampered by the lack of PPAR selective agonists. A series of compounds has recently been described as having selectivity for PPARδ (33, 34), and we have synthesized one of these compounds (compound F) that has an EC₅₀ of 2 nM for hPPARδ, 400 nM for hPPARγ, and >1 μM for hPPARα (Fig. 3A). Interestingly, this compound has no selectivity between mouse PPAR and -δ (data not shown). Human macrophages were therefore treated with compound F (100 nM) in the presence of serum, resulting in a profound increase in

---

2 L. Patel and C. Macphee, manuscript in preparation.
lipid accumulation (Fig. 3B). The formation of foam cells is thought to be promoted by modified lipoproteins in vivo. We therefore tested the ability of compound F to facilitate lipid accumulation in the presence of oxidized LDL (Fig. 3C). Oxidized LDL is a stimulus for lipid accumulation in human macrophages and addition of increasing concentrations of compound F stimulates further increases in lipid accumulation. The dose response of this lipid accumulation was very similar to the concentrations required for activation of PPARδ in COS-1 cells and occurred at concentrations well below those required for the activation of PPARγ and -α. Importantly, lipid loading was not observed with normal LDL or lipid-depleted serum at any concentration of compound F (data not shown). This demonstrates that the action of compound F is dependent on the nature and availability of the lipid donors in the culture medium.

**FIG. 1.** PPARδ expression is increased during macrophage differentiation. A, protein was prepared from cultures of human monocytes at day 0, 1, and 4 after the plating. The lysates were analyzed by Western blotting for the presence of PPARγ, -δ, and -α. B, RNA was prepared from PPARα, -γ, and -δ expression using TaqMan™ procedures. All results show the mean ± S.E., n = 3.

**FIG. 2.** Activation of PPARγ does not promote lipid accumulation in human macrophages. A, macrophages cultured in 10% human serum and stained with Oil red O. B, rosiglitazone (1 μM) inhibits lipid accumulation in macrophages cultured with 10% human serum. C, rosiglitazone (1 μM) inhibits lipid accumulation in the presence of oxidized LDL (100 μg/ml). All results show the mean ± S.E., n = 3.

**FIG. 3.** A selective agonist of human PPARδ promotes lipid accumulation in human monocytes. A, dose response of activation of human PPARs by compound F in COS-1 cells. COS-1 cells were transfected with a PPARδ expression vector and a reporter construct containing the luciferase cDNA under the control of the PPRE found in the human FABP gene. B, compound F (100 nM) stimulates macrophage lipid accumulation in the presence of serum. C, low concentrations of compound F stimulate lipid accumulation in the presence of oxidized LDL supplemented (100 μg/ml) and lipid-depleted serum. All results show the mean ± S.E., n = 3.
PPARδ in Macrophages

Fig. 4. Activation of PPARδ promotes lipid accumulation in a human monocytic cell line. A, THP-1 cells were treated with PMA for 3 days and analyzed for PPAR mRNA levels by TAQMAN™ procedures. B, the effects of PPAR agonists on lipid accumulation were assessed by Oil red O staining. MeSO (0.5%), rosiglitazone (40 μM), Wy14,463 (25 μM), and compound F (1 μM). C, low concentrations of compound F promote lipid accumulation. The effects of increasing concentrations of compound F on lipid accumulation are shown. D, compound F and LG100268 co-operate in lipid accumulation. Shown is the lipid accumulation after treatment with solvent alone (Me2SO), LG100268 (LG268, 10 nM), compound F (CompF, 1 μM), or a combination of LG100268 and compound F (LG+F). DMSO, dimethyl sulfoxide.

increased upon differentiation (50- and 34-fold, respectively). These findings are similar to those obtained during the differentiation of primary macrophages (Fig. 1). To determine whether the PPARs were involved in lipid accumulation, THP-1 cells were treated with activators of PPARα, -γ, and -δ in the presence of serum. No change in lipid accumulation was observed on the addition of the PPARα activator, Wy14,643, or the PPARγ activator, rosiglitazone (Fig. 4B). However, when THP-1 cells were treated with compound F, a marked increase in intracellular lipid was observed (Fig. 4B). The EC50 of compound F for this effect was higher than that observed for the primary monocytes (~400 nM, Fig. 4C). The effect of compound F was further enhanced by the addition of the RXR agonist, LG100268 (Fig. 4D); further supporting the action of a PPAR/RXR heterodimer in this process. There was a high degree of similarity in the findings with those obtained in primary macrophages indicating that THP-1 cells provide a good model for studying the role of PPARδ in macrophage lipid accumulation.

PPARδ Is a Potent Regulator of Genes Involved in Lipid Accumulation—The lipid accumulation phenotype observed with compound F may reflect regulation of a number of aspects of lipid transport and metabolism in these cells. Recent studies have shown that rosiglitazone modulates lipid uptake by transcriptional regulation of the class B scavenger receptor CD36, but that this is balanced by increases in efflux via ABCA1 and decreases in the class A scavenger receptor, SRA (16). We therefore investigated the effects of compound F on the expression of a range of genes known to determine lipid balance in macrophages. We performed a dose-response experiment with PPARδ selective concentrations of compound F and compared these treatments to a saturating dose of rosiglitazone (500 nM) (Fig. 5A). We observed that CD36 is effectively induced (6-fold) by 10 nM compound F, and that this induction is greater than that seen with 500 nM rosiglitazone (2-3-fold). This suggests that CD36 is a target gene for both PPARδ and PPARγ. The class A scavenger receptor was also slightly increased by 10 nM compound F (2.5-fold), whereas rosiglitazone does not modify the expression of this gene. The gene encoding the adipocyte-type fatty acid-binding protein (AFLBP) is highly regulated by both rosiglitazone and 10 nM compound F, again showing an overlapping set of target genes. However, the gene encoding the lipid-vesicle coat protein, adipophilin is very selectively regulated by compound F (10-fold versus 3-fold with rosiglitazone). The selectivity for activation of SRA, CD36, and adipophilin was confirmed in a time course study (Fig. 5B) where it was clear that compound F mediates a larger and more sustained induction of these gene products relative to rosiglitazone. The induction of SRA was very modest but sustained, in contrast no significant induction with rosiglitazone was seen at any time point. CD36 induction by compound F appeared to be diminished at longer time points but adipophilin was highly induced throughout the experiment.

Overexpression of PPARδ Results in Increased Lipid Accumulation—To obtain evidence for a direct role for PPARδ in macrophage lipid accumulation, we generated THP-1 sublines that overexpressed PPARδ (PPARδSENSE). Constitutive expression of PPARδ in the PPARδSENSE cells was confirmed by Western blotting (Fig. 6A). In agreement with the effects of the PPARδ agonist, PPARδ SENSE cell lines were extremely lipid-laden when compared with the wild type cells, even in the absence of added PPAR ligand (but in the presence of serum).
FIG. 5. PPARδ regulates genes involved in lipid uptake, transport, storage, and efflux. A, PMA-differentiated THP-1 cells were treated with increasing concentrations of compound F (CF) or 500 nM rosiglitazone (Ros) for 48 h and analyzed for several mRNA levels by TAQMAN™ procedures. B, PMA differentiated THP-1 cells were treated with 100 nM compound F or 500 nM rosiglitazone and RNA was prepared at 2, 4, 8, 16, 48, 72, and 125 h and analyzed for several mRNA levels by TAQMAN™ procedures. The values obtained relative to Me2SO (DMSO) at each time point are shown. All results show the mean ± S.E., n = 3.

FIG. 6. Overexpression of PPARδ promotes lipid accumulation. A, Western blotting reveals high levels of PPARδ protein in PPARδSENSE cell lines. Constant protein loading is confirmed by an antibody to aflatoxin reductase (AFAR). B, THP-1 cells and PPARδ SENSE cells were treated with PMA for 3 days, fixed, and stained with Oil red O. C, THP-1 cells were treated with PMA and Me2SO or 100 nM compound F for 10 days. PPARδ cells were treated with PMA for 10 days. Lipids were extracted and analyzed for cholesterol by GC-MS; D, lipids were analyzed for triglyceride content. E, cells growing in medium without PMA were analyzed for expression of the AFABP by TAQMAN™ procedures. F, cells growing in medium without PMA were analyzed for expression of adipophilin by TAQMAN™ procedures. All results show the mean ± S.E., n = 3. DMSO, dimethyl sulfoxide.
apoA1-mediated efflux from cells treated with this compound and PPARδ overexpression (Fig. 7E) in agreement with our observation that ABCA1 is up-regulated and with the study of Oliver et al. (33). In contrast, total efflux from the cells was significantly attenuated by compound F treatment or PPARδ overexpression (Fig. 7F). This data supports our gene expression data in suggesting that PPARδ may have opposing effects on different lipid efflux pathways. The rank order of efflux inhibition correlated well with the rate of lipid accumulation i.e. SENSE > compound F > control THP-1.

DISCUSSION

We have demonstrated that the expression of PPARδ is increased dramatically during the differentiation of human primary macrophages and upon differentiation of THP-1 cells with phorbol ester. This has suggested a potential role for PPARδ in the modulation of atherosclerosis and inflammation. The awareness of coincedent expression of PPARγ and PPARδ is important in the interpretation of studies exploring macrophage biology that have used poorly selective PPAR agonists (5, 6, 10, 39). In the current study we have used highly selective agonists to demonstrate that both PPARδ and PPARγ differentially regulate the lipid accumulation in macrophages, with PPARδ activation promoting lipid accumulation and PPARγ promoting lipid clearance. These findings are in contrast with studies that suggested PPARγ may promote macrophage lipid accumulation; however, these studies utilized compounds that are not as selective for PPARγ as rosiglitazone (5, 6). Indeed, several publications, which were published during the preparation of this manuscript (7, 16, 17), support our finding that PPARγ activation by rosiglitazone opposes lipid accumulation in macrophages. This role for PPARγ in lipid clearance is in distinct contrast to its role in adipocyte differentiation, but is similar to the proposed role for PPARγ in the clearance of lipid from pancreatic β cells (40). We have found that PPARδ selectively promotes the accumulation of lipid in both THP-1 cells and ex vivo human macrophage cultures. This lipid accumulation occurs because of a complex regulation of gene products that control many aspects of lipid homeostasis (Fig. 8). PPARδ controls lipid uptake, via the class A and class B scavenger receptors (SR-A, CD36). Transport is mediated by increases in lipid-binding proteins such as AFABP. Storage is facilitated by the production of large amounts of lipid vesicle coating proteins such as adipophilin, while metabolism of cholesterol to bile acids is regulated by the repression of CYP27. Lipid efflux is modulated in a contrasting manner by the induction of ABCA1 and the repression of apolipoprotein E. It is clear that this list of PPARδ-regulated genes is incomplete and that the dramatic lipid storage phenotype that we have observed is determined by a complex interplay of such target genes. Importantly, we have characterized the novel repression of two gene products that are intimately involved in lipid storage disorders, i.e. apoE and CYP27. It is clear that both of these proteins are important in human lipid homeostasis. Indeed, genetic studies have shown that functional polymorphisms of the human apoE gene are associated with atherosclerosis (41–44) and mutations in the CYP27 gene are seen in patients with cerebrotendinous xanthomatosis (45). This is a severe cholesterol storage disorder where cholesterol is deposited throughout the body, but is primarily targeted to the vasculature and brain. The metabolism of cholesterol by this enzyme in the macrophage directs cholesterol to bile acid synthesis and export, independent of apoA1 lipid acceptors (46–49). Therefore the profound repression of CYP27 and apoE expression by activation or overexpression of PPARδ might contribute to the lipid accumulation observed in these cells in culture. Importantly, although PPARδ and PPARγ have some common target genes, apoE and CYP27 are not repressed by PPARγ agonists such as rosiglitazone.
PPARγ agonists have been consistently shown to reduce the atherogenic profile of serum lipids (50, 51) and have inhibitory effects on atheroma formation (18–22). We and others have shown that this is reflected in the modest ability of rosiglitazone to promote lipid clearance in human monocytes in vitro and it is likely that the anti-inflammatory nature of PPARγ agonists also contribute to inhibition of atherosclerotic processes. In contrast, PPARδ agonists have been shown to have complex effects on serum lipids in different animal models, with a common feature of raising total serum cholesterol (33, 50, 52). The relevance to man of studies of PPARs on lipids in small animals is often limited. One of these studies, using the highly selective PPARδ agonist, GW501516, has also shown a potent raising of serum high density lipoprotein and lowering of serum triglycerides in obese rhesus monkeys (33). The mechanism of triglyceride lowering by GW501516 was distinct from the mechanism of lipid lowering seen in the use of PPARγ ligands such as bezafibrate. The repression of apoC-III expression by fibrates is considered to be an important factor in lipid lowering and bezafibrate treatment of obese rhesus monkeys produces marked decreases in serum apoC-III, whereas GW501516 produced a marked increase in serum apoC-III. GW501516 has no effects on apoC-III gene expression in cultured human hepatocytes and the mechanism of lipid lowering by GW501516 is yet to be determined. It is therefore important that future studies address the effects that PPARδ agonists have on both the processing of lipid in specific lipid depots, and whole body lipid balance. However, it is clear that PPARδ agonists behave differently in different animal models and such studies will have to be chosen with great care. Our study has focused on the pharmacology and molecular biology of the human receptor in human cells and we have demonstrated that PPARδ mediates a complex program of gene expression for the
control of lipid accumulation in human macrophages. Further investigations will be required to determine the usefulness of PPARδ agonists and antagonists in the management of human metabolic and vascular disease.

Acknowledgments—We thank Gary Moore for help with the TAQMAN reagents, Dr. David Bell for the antisem for PPARδ, and Professor John Haynes for the antisem against aflatoxin reductase. We also thank Dr. Roger Tatoud for help with graphic design (Fig. 8) and helpful discussions during the preparation of this manuscript.

REFERENCES

1. Kersten, S., Desvergne, B., and Wahli, W. (2000) Nature 405, 421–424
2. Kliewer, S. A., Unesno, K., Noonan, D. J., Heyman, R. A., and Evans, R. M. (1992) Science 257, 714–717
3. Tontonoz, P., Hu, E., and Spiegelman, B. M. (1994) Cell 79, 1147–1156
4. Forman, B. J., Ten, R. P., Chen, J., Brun, R. P., Spiegelman, B. M., and Evans, R. M. (1995) Cell 83, 803–812
5. Nagy, L., Tontonoz, P., Alvarez, J. G., Chen, H., and Evans, R. M. (1998) Cell 92, 229–240
6. Tontonoz, P., Nagy, L., Alvarez, J. G., Thomassy, A. M., and Evans, R. M. (1998) Cell 93, 241–252
7. Chawla, A. Barak, Y., Nagy, L., Liu, D., Tontonoz, P., and Evans, R. M. (2001) Nat. Med. 7, 48–52
8. Ricote, M., Li, A. C., Willson, T. M., Kelly, C. J., and Glass, C. K. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 7614–7619
9. Jiang, C., Ting, A. T., and Seed, B. (1998) Nature 391, 82–86
10. Jiang, C. Ting, A. T., and Seed, B. (1998) Nature 391, 82–86
11. Shu, H., Wong, B., Zhou, G., Li, Y., Berger, J., Woods, J. W., Wright, S. D., and Hegele, R. A. (1997) J. Clin. Invest. 100, 252–259
12. Peters, J. M., Lee, S. S., Li, W., Ward, J. M., Gavriloa, O., Everett, C., Reitman, M. L., Hudson, L. D., and Gonzalez, F. J. (2000) Mol. Cell. Biol. 20, 5109–5129
13. Lim, H., and Dey, S. K. (2000) Trends Endocrinol. Metab. 11, 137–142
14. Forman, B. M., Tontonoz, P., Nagy, L., Alvarez, J. G., Thomazy, V. A., and Evans, R. M. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 2598–2603
15. Mano, H., Kimura, C., Fujisawa, Y., Kameda, T., Watanabe-Mano, M., Kameko, H., Kameda, T., Hakeda, Y., and Kumegawa, M. (2000) J. Biol. Chem. 275, 8126–8132
16. Michalik, L., Desvergne, B., Tan, N. S., Basu-Mokad, S., Escher, P., Rieusset, J., Peters, J. M., Kaya, G., Gonzalez, F. J., Zakany, J., Metzger, D., Chambon, P., Duboule, D., and Wahli, W. (2001) J. Cell Biol. 154, 799–814
17. Cullen, B. R. (1987) Methods Enzymol. 132, 629–693
18. Brighty, D. W., Rosenberg, M., Chen, I. S., and Ivey-Hoyle, M. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 7802–7805
19. Wu, H., Moulton, K., Horvai, A., Park, S., and Glass, C. K. (1994) Mol. Cell. Biol. 14, 2129–2130
20. Oliver, W. R., Shen, J. K., Snaith, M. R., Russell, K. D., Bodkin, N. L., Lewis, M. C., Winer, B. A., Sznajdman, M. M., Lambert, M. H., Xu, H. E., Sternbach, D. D., Kliever, S. A., Hansen, B. C., and Willson, T. M. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 5306–5311
21. Leibowitz, M. D., Berger, J. P., Moller, D. E., Auwerx, J., and Berger, G. D. (1997) Compound F. International Patent Publication No. WO 97/28149
22. Charrides, L., Christian, A., Stoudt, G., Morel, D., and Rothblat, G. H. (1998) Arterioscler. Thromb. Vasc. Biol. 18, 1589–1599
23. Buechler, C., Ritter, M., DuBois, R. N., Trzaskos, J. M., and Dey, S. K. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 4832–4837
24. Menzel, H. J., Kladetzky, R. G., and Assmann, G. (1983) FEBS Lett. 136, 312–315
25. Kim, S. H., and Hegele, R. A. (1997) Mutat. Res. 382, 57–65
26. Utermann, G., Harwas, A., and Zimmer, F. (1984) Hum. Genet. 63, 237–241
27. Mennel, H. J., Kludetzky, R. G., and Assmann, G. (1988) Arteriosclerosis 8, 310–315
28. Davidson, J., Gregg, R. E., and Sing, C. F. (1988) Arteriosclerosis 8, 1–21
29. Cali, J. J., Hsieh, C. L., Francke, U., and Russell, D. W. (1991) J. Biol. Chem. 266, 7779–7785
30. Babiker, A., Andersson, O., Lund, E., Xiu, R. J., Deeb, S., Reshef, A., Leitersdorf, E., Diczfalusy, U., and Bjorkhem, I. (1997) J. Biol. Chem. 272, 26253–26261
31. Shimabukuro, M., Zhou, Y. T., Lee, Y., and Unger, R. H. (1998) J. Biol. Chem. 273, 27504–27509
32. Connelly, P. W., and Hegele, R. A. (1997) J. Clin. Invest. 100, 523–531
33. Sina, M. G. (2000) Trends Endocrinol. Metab. 11, 47–55
34. Koshiyama, H., Shimono, D., Watanabe-Mano, M., and Nakamura, Y. (2001) J. Clin. Invest. 108, 1581–1587
35. Lim, H., Gupta, R. A., Ma, W. G., Paria, B. C., Moller, D. E., Morrow, J. D., Dubois, R. N., Terasaki, J. M., and Dey, S. K. (1999) Genes Dev. 13, 1581–1587
The Peroxisome Proliferator-activated Receptor δ Promotes Lipid Accumulation in Human Macrophages

Helen Vosper, Lisa Patel, Tracey L. Graham, Guennadi A. Khoudoli, Alexander Hill, Colin H. Macphee, Ivan Pinto, Stephen A. Smith, Keith E. Suckling, C. Roland Wolf and Colin N. A. Palmer

J. Biol. Chem. 2001, 276:44258-44265.
doi: 10.1074/jbc.M108482200 originally published online September 13, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M108482200

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 51 references, 23 of which can be accessed free at http://www.jbc.org/content/276/47/44258.full.html#ref-list-1