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Review Article

PPARα Ligands as Antitumorigenic and Antiangiogenic Agents

Ambra Pozzi and Jorge H. Capdevila

Department of Medicine, Division of Nephrology and Hypertension, S-3223 Medical Center North, Vanderbilt University, Nashville, TN 37232, USA

Correspondence should be addressed to Ambra Pozzi, ambra.pozzi@vanderbilt.edu

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Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor family of ligand-activated transcription factors. This subfamily is composed of three members—PPARα, PPARδ, and PPARγ—that differ in their cell and tissue distribution as well as in their target genes. PPARα is abundantly expressed in liver, brown adipose tissue, kidney, intestine, heart, and skeletal muscle; and its ligands have been used to treat diseases such as obesity and diabetes. The recent finding that members of the PPAR family, including the PPARα, are expressed by tumor and endothelial cells together with the observation that PPAR ligands regulate cell growth, survival, migration, and invasion, suggested that PPARs also play a role in cancer. In this review, we focus on the contribution of PPARα to tumor and endothelial cell functions and provide compelling evidence that PPARα can be viewed as a new class of ligand activated tumor "suppressor" gene with antiangiogenic and antitumorigenic activities. Given that PPAR ligands are currently used in medicine as hypolipidemic drugs with excellent tolerance and limited toxicity, PPARα activation might offer a novel and potentially low-toxic approach for the treatment of tumor-associated angiogenesis and cancer.

1. THE PEROXISOMAL PROLIFERATOR-ACTIVATED RECEPTORS (PPARs)

PPARs nuclear receptors that regulate many physiological processes, including lipid and glucose homeostasis, inflammation, and wound healing [1]. Three PPAR isotypes have been identified: α, δ (or β), and γ. Upon ligand binding, PPARs form heterodimers with the retinoic acid receptor and interact with specific response elements in the promoter region of target genes [2]. Although PPARs share extensive structural homology, each isotype appears to possess distinct functions. PPARγ is expressed mainly in adipose tissue and at lower levels in intestine and immune cells [3–5]. It controls adipocyte differentiation, glucose and lipid homeostasis [5–7] and has been implicated in the pathophysiology of insulin resistance and atherosclerosis [1, 8]. PPARγ ligands include long-chain fatty acids, prostaglandins, and other eicosanoids [4]. Among the synthetic PPARγ ligands, the thiazolidinediones are currently used as insulin sensitizers in patients with type-2 diabetes [9]. PPARδ is ubiquitously expressed and it is most abundant in brain, colon, and skin [10, 11], and binds molecules such as fatty acids and prostaglandins [4].

PPARα is primarily expressed in liver, brown adipose tissue, kidney, intestine, heart, and skeletal muscle. This receptor controls fatty acid metabolism and transport, peroxisomal and mitochondrial β-oxidation [3, 4]. Moreover, this receptor has been implicated in the pathophysiology of inflammation and cardiovascular diseases [12]. Several compounds bind PPARα, including fatty and phytanic acids [4], as well as the fibric acid derivatives used in medicine for the treatment of hyperlipidemias [1].

2. PPARs AND CANCER

The observation that members of the PPAR family are expressed by tumor and endothelial cells [13, 14] together with the finding that PPAR ligands regulate cell growth, survival, migration, and invasion [15, 16] prompted investigators to determine whether these receptors play a role in the pathophysiology of tumorigenesis and angiogenesis [17, 18].

The anticancer effects of PPARγ agonists have been extensively studied because of their antiproliferative, proapoptotic, antiapoptotic, and differentiation-promoting activities [19]. In this context, activation of PPARγ has been reported to reduce tumor cell proliferation and invasion [20] and to enhance apoptosis [21]. PPARγ ligands also regulate endothelial cell growth, migration, and angiogenesis [22–25], and influence the progression of vascular inflammation and tumorigenesis [26, 27]. Moreover, disruption of the PPARγ gene in the intestine enhances tumorigenesis in Apc$^{Min/+}$ mice [28]. Although these studies suggest that PPARγ functions as a tumor suppressor factor and its activation might be beneficial for patients with tumors, PPARγ agonists have been shown also to increase the frequency of colon tumors [29] and to promote edema [30].

In contrast to PPARγ, PPARδ has been described as protumorigenic as its ligand-mediated activation increases tumor-associated angiogenesis [31]. Moreover, treatment of Apc$^{Min/+}$ mice with PPARδ antagonists or crossing these mice with PPARδ-null mice prevents tumor growth and angiogenesis [31]. However, a recent study showed that activation of this receptor attenuates chemically-induced colon carcinogenesis, and that PPARδ-null mice exhibit increased colon polyp multiplicity, suggesting that ligand activation of this receptor can also inhibit carcinogenesis [32].

The analysis of the antitumorigenic properties of PPARα ligands has been less studied mostly due to the observation that long-term administration of certain PPARα agonists (Clofibrateand WY14643) induces hepatocarcinogenesis in rodents [33–35], despite the fact that PPARα ligands are widely used in medicine as antilipidemic drugs with excellent tolerance and little or no reported side effects. The finding that fenofibrate decreases VEGF levels in patients with hyperlipidemiaand atherosclerosis [36] provided a rationale for analyzing PPARα and its ligands as a molecular target for cancer therapy. In this review, we highlight some of the key functions attributed to PPARα in the context of endothelial and tumor cell biology.

3. PPARα TARGETS IN ANGIOGENESIS

PPARα controls the transcription of many genes involved in cell functions such as lipid metabolisms, inflammation, cell cycle progression, and angiogenesis. Among the angiogenic targets, PPARα has been shown to regulate the expression of the vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), members of the arachidonic acid P450 monooxygenases, thrombospondin and endostatin to name few (see also Figure 1 and Table 1). Biscetti et al. have recently shown that the selective PPARα agonist WY14643 promotes cornea angiogenesis in vivo and enhances endothelial tubulogenesis in vitro [37]. Interestingly, WY14643 can enhance endothelial cell tubulogenesis in vitro only when endothelial cells are cocultured with interstitial cells and this effect is accompanied by upregulation of interstitial-derived VEGF synthesis [37]. However, WY14643 does not directly promote endothelial cell migration or proliferation, and when used at 10–20 μM range it reduces both endothelial cell proliferation and migration [37]. Thus, this study indicates that while WY14643 might directly prevent endothelial cell functions, it might also promote angiogenesis by stimulating the production of nonendothelial VEGF. The observation that activation of PPARα prevents endothelial cell proliferation/migration parallels our findings that WY14643 prevents—in a PPARα-dependent fashion—endothelial cell proliferation in vitro and tumorigenesis in vivo [38]. The antiangiogenic properties of WY14643 are associated with a PPARα-dependent downregulation of the epoxygenase branch of the cytochrome P450 arachidonic acid monooxygenases [38]. The arachidonic acid epoxygenases are expressed by endothelial cells both in vitro and in vivo [39–41] and catalyze the oxidation of arachidonic acid to four regioisomeric epoxyeicosatrienoic acids (EETs) [42, 43]. EETs have been shown to possess proangiogenic activities [39, 44–47] and we have demonstrated that WY14643-mediated PPARα activation directly prevents endothelial cell migration and proliferation by downregulating endothelial arachidonate epoxygenase expression and EET biosynthesis [38]. Most importantly, in vivo treatment with WY14643 prevents primary tumor growth and tumor-associated angiogenesis by downregulating the levels of circulating EETs [38].

Consistent with the observation that PPARα ligands might act as potent direct and/or indirect antiangiogenic factors, Panigrahy et al. have recently shown that fenofibrate suppresses VEGF-mediated endothelial cell proliferation as well as tumor cell-derived VEGF and FGF2 synthesis with concomitant stimulation of tumor-cells derived thrombospondin and endostatin [48]. Moreover, fenofibrate and WY14643 prevent VEGF-mediated endothelial cell migration by inhibiting Akt phosphorylation [24] and fenofibrate prevents endothelial cell proliferation by inhibiting cyclooxygenase-2 expression [25]. Finally, PPARα agonists were found to inhibit endothelial VEGFR2 expression by preventing Sp1-dependent promoter binding and transactivation [23]. Some of the major PPARα targets known to control endothelial cell functions and the effects of PPARα ligands on angiogenesis are summarized in Figure 1 and Table 1.

In conclusion these studies strongly suggest that by preventing endothelial cell functions PPARα ligands may protect the vasculature from pathological alterations associated with either metabolic disorders (i.e., atherosclerosis, diabetes) or cancer. Thus, PPARα can be considered as a new class of "antiangiogenic" gene, and suggest that its ligands may function as effective antiangiogenic drugs.

4. PPARα TARGETS IN CANCER

The observation that PPARα is expressed by tumor cells [59–61] started studies of the role of this nuclear receptor and its ligands on the prevention of tumor cell proliferation in vitro and in vivo. In this context it has been shown that PPARα ligands suppress the growth of several cancer lines—including colon, liver, breast, endometrial, and skin—in vitro [62–66], as we all inhibit the metastatic potential of melanoma cells in vitro and in vivo [67, 68]. Furthermore, PPARα ligands decrease colon carcinogenesis [62] and the growth of human ovarian cancer in mice [49]. Although the mechanisms whereby PPARα directly prevents tumor cell functions have not been investigated

Table 1: Effect of PPARα activation on angiogenesis and tumorigenesis.

Ligand	Cell type	Effect	Target	Reference
WY14643	Endothelial cells	Inhibition of cell proliferation and tubulogenesis in vitro Antiangiogenic activity in vivo	Downregulation of arachidonate epoxygenase synthesis	[38]
WY14643	Endothelial cells	Enhanced endothelial tube formation in vitro Proangiogenic activity in vivo	Upregulation of VEGF production	[37]
Fenofibrate WY14643 ETYA	Endothelial cells	Inhibition of VEGF- or FGF2-mediated cell proliferation in vitro Antiangiogenic activity in vivo	Downregulation of VEGF production Upregulation of thrombospondin and endostatin production	[48]
Fenofibrate WY14643	Endothelial cells	Reduced cell migration	Inhibition of Akt activation	[24]
Fenofibrate	Endothelial cells	Reduced cell proliferation	Inhibition of cyclooxygenase-2 expression	[25]
Fenofibrate	Endothelial cells	Reduced cell proliferation	Inhibition of VEGFR2 expression	[23]
Clofibrate	Ovarian cancer cells	Reduced cell proliferation in vitro Antitumorigenic activity in vivo	Reduced prostanoid and VEGF levels via upregulation of carbonyl reductase expression	[49]
Methylclofenapate	Colonic adenocarcinoma	Reduced cell proliferation	Not investigated	[50]
Methylclofenapate	$Apc^{Min/+}$ mice	Reduced number of intestinal polyps	Not investigated	[50]
Bezafibrate	APC^{1309}mice $Apc^{Min/+}$ mice	Reduced number of intestinal polyps	Reduced serum level of triglycerides and increased lipoprotein lipase synthesis	[27, 51]
WY14643	Wild-type mice	Enhanced hepatocellular proliferation and tumorigenesis in vivo	Downregulation of the miRNA let-7C with increased c-myc expression	[52]

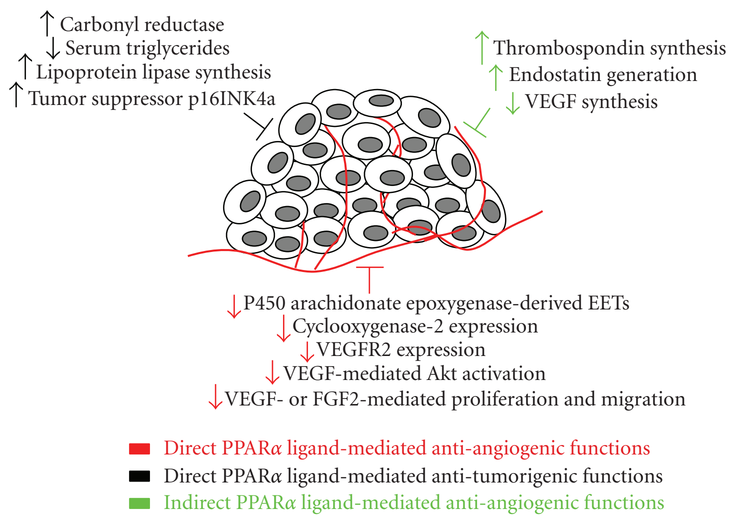

Figure 1: *Schematic representation of the antiangiogenic and antitumorigenic properties of PPARα*. PPARα ligands reduce tumor growth by direct inhibition of tumor cell functions (black pathway). In addition, they prevent tumor-associated angiogenesis via direct (red pathway) as well as indirect (green pathway) inhibition of endothelial cell functions.

Table 2: PPARα and tumorigenesis: lessons from the PPARα-null mice.

Ligand	Host	Challenge	Effect	Target	Reference
WY14643	PPARα-null mice		Resistant to the development of spontaneous hepatocarcinoma	Inability to downregulate the miRNA let-7C	[52]
WY14643 Fenofibrate	PPARα-humanized transgenic mouse		Resistant to the development of spontaneous hepatocarcinoma	Inability to downregulate the microRNA let-7C	[53, 54]
WY14643	PPARα-null mice	Injection of isogenic tumor cells	Resistant to the Wyeth-mediated antiangiogenic and antitumorigenic activities	Inability to downregulate arachidonate epoxygenase expression	[38]
DEHP	PPARα-null mice		Development of hepatocarcinoma	Increased PPARα-independent oxidative stress	[55]
WY14643 Fenofibrate	PPARα-null mice	Carotid arterial injury	Intimal hyperplasia	Inability to induce the expression of the tumor suppressor p16INK4a	[56]
	PPARα-null mice	Injection of isogenic tumor cells	Resistant to the development of primary and metastatic tumor growth	Increased recruitment of granulocyte responsible for thrombospondin production	[57]
	PPARα-null mice		Increased susceptibility to spontaneous adenomas and hepatocellular carcinomas	Not explored	[58]

in details, potential targets have been identified. Clofibrate, a PPARα ligand, significantly suppressed the growth of OVCAR-3 xenotransplanted tumors and inhibited ovarian tumor cell proliferation by increasing the expression of carbonyl reductase, an enzyme that promotes the conversion of protumorigenic prostaglandin E2 to inactive PGF2α [49]. Moreover, clofibrate reduced the levels of circulating VEGF in tumor-bearing mice [49], while bezafibrate, another PPARα ligand, decreased the number of intestinal polyps in $Apc^{Min/+}$ mice possibly by lowering serum level of triglycerides and upregulating lipoprotein lipase synthesis [27, 51]. Finally, PPARα activation has been shown to inhibit vascular smooth muscle cell proliferation underlying intimal hyperplasia by inducing the expression of the tumor suppressor p16INK4a [56].

Whereas these studies clearly suggest that PPARα activation might be beneficial in reducing cancer growth, studies from the Gonzales laboratory demonstrate that long-term administration of certain PPARα agonists (clofibrate and WY14643) induces liver adenoma and carcinomas in rats and mice [35, 52, 69, 70]. The ability of PPARα ligands to induce hepatocarcinoma is PPARα-dependent and mediated by the novel microRNA let-7C/c-myc axis [52]. Let-7C is a micro RNA that controls cell growth by directly downregulating c-myc expression [52]. Upon treatment of mice with WY14643, the hepatic expression of let-7C decreases with the concomitant induction of c-myc and the increased expression of the oncogenic mir-17-92 cluster [52]. Thus, this novel rodent specific PPARα-regulated pathway might be responsible for increased hepatocellular proliferation and tumorigenesis.

All together, these findings indicate that, with few exceptions, PPARα ligands can be viewed as antitumorigenic agents either by directly preventing tumor cell functions or by preventing tumor-derived production of proangiogenic molecules. Some of the potential PPARα targets that control tumor cell functions and the effects of PPARα ligands on tumorigenesis are summarized in Figure 1 and Table 1.

5. PPARα LIGANDS AND TUMORIGENESIS: LESSONS FROM MICE

The generation of PPARα null mice has provided an excellent tool not only to determine whether the effects exerted by PPARα ligand are indeed PPARα-dependent, but also for discerning between host versus tumor-mediated PPARα responses (see Table 2 for details). In this regard, we have shown that wild-type mice injected with isogenic PPARα expressing tumor cells respond to WY14643 treatment and develop fewer and smaller tumors than untreated wild-type mice [38]. In contrast, the growth of the same tumor cells is not prevented in WY14643-treated PPARα null mice [38]. In agreement with our finding, absence of PPARα in the host animals abrogated the potent antitumor effect of fenofibrate [48]. Finally whereas in vivo activation of PPARα prevents vascular smooth muscle cell proliferation underlying intimal hyperplasia, PPARα deficiency leads to hyperplasia [56]. Taken together, these results strongly suggest that activation of PPARα in the host is a key element in preventing unwanted pathological cell growth.

Although rodents are the only species in which activation of PPARα promotes liver cancer, for a long time it was thought that Di(2-ethylhexyl)phthalate (DEHP), a commonly used industrial plasticizer, might cause liver tumorigenesis presumably via activation of PPARα [55, 71]. The use of PPARα null mice has disproved this idea, as this plasticizer is able to induce tumorigenesis in both wild-type and PPARα-null mice [55, 71]. These results suggest the existence of pathways for DEHP-induced hepatic tumorigenesis that are independent of PPARα, but most likely dependent on DEHP-mediated oxidative stress [55].

PPARα null mice have been also instrumental to determine the role of rodent versus human PPARα in the promotion of liver carcinogenesis. Morimura et al. have generated a PPARα-humanized mouse in which the human PPARα is expressed in liver under control of the Tet-OFF system. Interestingly, prolonged exposure to WY14643 in these mice only led to a 5% incidence of liver tumors—including hepatocellular carcinoma—compared to the 71% observed in mice expressing the mouse PPARα [53]. More recently, Yanget al. generated a PPARα-humanized transgenic mouse where the complete human PPARα gene was introduced onto a PPARα-null background [54]. These PPARα-humanized mice express the human PPARα in liver as well as other tissues and respond to fenofibrate treatment by lowering serum triglycerides and by inducing the expression of enzymes involved in fatty acid metabolism [54]. However, in contrast to wild-type mice, treatment with fenofibrate did not cause significant hepatomegaly, hepatocyte proliferation, and most importantly hepatocarcinoma [54]. Thus, this study shows that the protumorigenic let-7C/c-myc pathway is activated only by the rodent, but not the human PPARα receptor. Most importantly, this work highlights the possibility that PPARα ligands might be used as safe drugs for the treatment of cancer in humans.

Although activation of PPARα in either endothelial or tumor cells has been proven to be beneficial in inhibiting cancer growth, it has also been shown that loss of host-derived PPARα can be advantageous as it prevents tumor growth and development [57]. The host cells responsible for this protection, however, are granulocytes rather than endothelial cells. Loss of PPARα leads to an increased infiltration to the side of injury of granulocytes that suppress tumor-associated angiogenesis via excess production of the endogenous angiogenesis inhibitor thrombospondin [57]. This study clearly indicates that both activation of PPARα in specific host cells (i.e., endothelia cells) and concomitant inhibition of PPARα in immuno cells (i.e., granulocytes) might lead to the same effects, namely protection from tumor growth.

6. CONCLUSIONS

The studies summarized in this review identify PPARα as a potential host-based target for the development of new antiangiogenic approaches to inhibit and/or prevent tumor growth. As an established modulator of gene transcription, PPARα regulates the expression of genes known to be involved in energy metabolism, cellular proliferation, and angiogenesis and to have positive effects on the control of dyslipidemia, inflammation, and cardiovascular diseases. Furthermore, several fibric acid derivatives bind to and activate human PPARα with limited or no documented unwanted consequences and have proven to be safe and effective hypolipidemic drugs. In this context, gemfibrozil safely reduced the risk of death from coronary heart disease, nonfatal myocardial infarction, or stroke by raising HDL cholesterol levels and lowering levels of triglycerides [72, 73].

The effects of PPARα ligands in animal models of tumor angiogenesis should help not only to stimulate further research of their usefulness as antitumorigenic agents, but also to facilitate their evaluation as valid tools for the treatment and/or prevention of human cancers. In this context, it is our hope that these studies will serve to encourage epidemiological studies of cancer incidence in patients using hypolipidemic drugs, and help to identify their potential beneficial effects as agents for tumor prevention and/or treatment. The urgency of new approaches for cancer treatment are indicated by the fact that most current antitumorigenic therapies are oriented towards a general inhibition of tumor cell growth and, as such, they suffer from lacking target selectivity and, in most cases, causing severe side effects and overall systemic toxicity. Thus, targeting PPARα may prove to be a potential therapeutic strategy—either alone or in combination with conventional chemotherapy—to inhibit and ideally prevent cancer with excellent tolerance and limited toxicity.

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REFERENCES

[1] S. Kersten, B. Desvergne, and W. Wahli, "Roles of PPARS in health and disease," *Nature*, vol. 405, no. 6785, pp. 421–424, 2000.

[2] S. A. Kliewer, K. Umesono, D. J. Noonan, R. A. Heyman, and R. M. Evans, "Convergence of 9-*cis* retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors," *Nature*, vol. 358, no. 6389, pp. 771–774, 1992.

[3] A. Aranda and A. Pascual, "Nuclear hormone receptors and gene expression," *Physiological Reviews*, vol. 81, no. 3, pp. 1269–1304, 2001.

[4] B. Desvergne and W. Wahli, "Peroxisome proliferator-activated receptors: nuclear control of metabolism," *Endocrine Reviews*, vol. 20, no. 5, pp. 649–688, 1999.

[5] R. K. Semple, V. K. K. Chatterjee, and S. O'Rahilly, "PPARγ and human metabolic disease," *Journal of Clinical Investigation*, vol. 116, no. 3, pp. 581–589, 2006.

[6] P. Tontonoz, E. Hu, and B. M. Spiegelman, "Stimulation of adipogenesis in fibroblasts by PPARγ2, a lipid-activated transcription factor," *Cell*, vol. 79, no. 7, pp. 1147–1156, 1994.

[7] M. Ricote, A. C. Li, T. M. Willson, C. J. Kelly, and C. K. Glass, "The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation," *Nature*, vol. 391, no. 6662, pp. 79–82, 1998.

[8] N. Kubota, Y. Terauchi, H. Miki, et al., "PPARγ mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance," *Molecular Cell*, vol. 4, no. 4, pp. 597–609, 1999.

[9] S. Schwartz, P. Raskin, V. Fonseca, and J. F. Graveline, "Effect of troglitazone in insulin-treated patients with type II diabetes mellitus," *The New England Journal of Medicine*, vol. 338, no. 13, pp. 861–866, 1998.

[10] S. A. Kliewer, B. M. Forman, B. Blumberg, et al., "Differential expression and activation of a family of murine peroxisome proliferator-activated receptors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, no. 15, pp. 7355–7359, 1994.

[11] O. Braissant, F. Foufelle, C. Scotto, M. Dauça, and W. Wahli, "Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-α, -β, and -γ in the adult rat," *Endocrinology*, vol. 137, no. 1, pp. 354–366, 1996.

[12] G. Rizzo and S. Fiorucci, "PPARs and other nuclear receptors in inflammation," *Current Opinion in Pharmacology*, vol. 6, no. 4, pp. 421–427, 2006.

[13] R. M. Touyz and E. L. Schiffrin, "Peroxisome proliferator-activated receptors in vascular biology-molecular mechanisms and clinical implications," *Vascular Pharmacology*, vol. 45, no. 1, pp. 19–28, 2006.

[14] S. Z. Duan, M. G. Usher, and R. M. Mortensen, "Peroxisome proliferator-activated receptor-γ-mediated effects in the vasculature," *Circulation Research*, vol. 102, no. 3, pp. 283–294, 2008.

[15] S. Theocharis, A. Margeli, P. Vielh, and G. Kouraklis, "Peroxisome proliferator-activated receptor-γ ligands as cell-cycle modulators," *Cancer Treatment Reviews*, vol. 30, no. 6, pp. 545–554, 2004.

[16] R. A. Roberts, S. Chevalier, S. C. Hasmall, N. H. James, S. C. Cosulich, and N. Macdonald, "PPARα and the regulation of cell division and apoptosis," *Toxicology*, vol. 181-182, pp. 167–170, 2002.

[17] C. Giaginis, A. Tsantili-Kakoulidou, and S. Theocharis, "Peroxisome proliferator-activated receptor-γ ligands: potential pharmacological agents for targeting the angiogenesis signaling cascade in cancer," *PPAR Research*, vol. 2008, Article ID 431763, 12 pages, 2008.

[18] Y. Yasui, M. Kim, and T. Tanaka, "PPAR ligands for cancer chemoprevention," *PPAR Research*, vol. 2008, Article ID 548919, 10 pages, 2008.

[19] L. Michalik, B. Desvergne, and W. Wahli, "Peroxisome-proliferator-activated receptors and cancers: complex stories," *Nature Reviews Cancer*, vol. 4, no. 1, pp. 61–70, 2004.

[20] J.-S. Annicotte, I. Iankova, S. Miard, et al., "Peroxisome proliferator-activated receptor γ regulates E-cadherin expression and inhibits growth and invasion of prostate cancer," *Molecular and Cellular Biology*, vol. 26, no. 20, pp. 7561–7574, 2006.

[21] M. Li, T. W. Lee, A. P. C. Yim, T. S. K. Mok, and G. G. Chen, "Apoptosis induced by troglitazone is both peroxisome proliterator-activated receptor-γ- and ERK-dependent in human non-small lung cancer cells," *Journal of Cellular Physiology*, vol. 209, no. 2, pp. 428–438, 2006.

[22] X. Xin, S. Yang, J. Kowalski, and M. E. Gerritsen, "Peroxisome proliferator-activated receptor γ ligands are potent inhibitors of angiogenesis in vitro and in vivo," *Journal of Biological Chemistry*, vol. 274, no. 13, pp. 9116–9121, 1999.

[23] M. Meissner, M. Stein, C. Urbich, et al., "PPARα activators inhibit vascular endothelial growth factor receptor-2 expression by repressing Sp1-dependent DNA binding and transactivation," *Circulation Research*, vol. 94, no. 3, pp. 324–332, 2004.

[24] S. Goetze, F. Eilers, A. Bungenstock, et al., "PPAR activators inhibit endothelial cell migration by targeting Akt," *Biochemical and Biophysical Research Communications*, vol. 293, no. 5, pp. 1431–1437, 2002.

[25] J. Varet, L. Vincent, P. Mirshahi, et al., "Fenofibrate inhibits angiogenesis in vitro and in vivo," *Cellular and Molecular Life Sciences*, vol. 60, no. 4, pp. 810–819, 2003.

[26] C. Blanquart, O. Barbier, J. C. Fruchart, B. Staels, and C. Glineur, "Peroxisome proliferator-activated receptors: regulation of transcriptional activities and roles in inflammation," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 85, no. 2–5, pp. 267–273, 2003.

[27] N. Niho, M. Takahashi, T. Kitamura, et al., "Concomitant suppression of hyperlipidemia and intestinal polyp formation in *Apc*-deficient mice by peroxisome proliferator-activated receptor ligands," *Cancer Research*, vol. 63, no. 18, pp. 6090–6095, 2003.

[28] C. A. McAlpine, Y. Barak, I. Matise, and R. T. Cormier, "Intestinal-specific PPARγ deficiency enhances tumorigenesis in $Apc^{Min/+}$ mice," *International Journal of Cancer*, vol. 119, no. 10, pp. 2339–2346, 2006.

[29] A.-M. Lefebvre, I. Chen, P. Desreumaux, et al., "Activation of the peroxisome proliferator-activated receptor γ promotes the development of colon tumors in C57BL/6J-Apc^{Min}/+ mice," *Nature Medicine*, vol. 4, no. 9, pp. 1053–1057, 1998.

[30] Y. Guan, C. Hao, D. R. Cha, et al., "Thiazolidinediones expand body fluid volume through PPARγ stimulation of ENaC-mediated renal salt absorption," *Nature Medicine*, vol. 11, no. 8, pp. 861–866, 2005.

[31] D. Wang, H. Wang, Y. Guo, et al., "Crosstalk between peroxisome proliferator-activated receptor δ and VEGF stimulates cancer progression," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 50, pp. 19069–19074, 2006.

[32] H. E. Marin, M. A. Peraza, A. N. Billin, et al., "Ligand activation of peroxisome proliferator-activated receptor β inhibits colon carcinogenesis," *Cancer Research*, vol. 66, no. 8, pp. 4394–4401, 2006.

[33] F. J. Gonzalez and Y. M. Shah, "PPARα: mechanism of species differences and hepatocarcinogenesis of peroxisome proliferators," *Toxicology*, vol. 246, no. 1, pp. 2–8, 2008.

[34] J. M. Peters, C. Cheung, and F. J. Gonzalez, "Peroxisome proliferator-activated receptor-α and liver cancer: where do we stand?" *Journal of Molecular Medicine*, vol. 83, no. 10, pp. 774–785, 2005.

[35] J. C. Corton, P. J. Lapinskas, and F. J. Gonzalez, "Central role of PPARα in the mechanism of action of hepatocarcinogenic peroxisome proliferators," *Mutation Research*, vol. 448, no. 2, pp. 139–151, 2000.

[36] A. D. Blann, F. M. Belgore, J. Constans, C. Conri, and G. Y. H. Lip, "Plasma vascular endothelial growth factor and its receptor Flt-1 in patients with hyperlipidemia and atherosclerosis and the effects of *fluvastatin* or *fenofibrate*," *The American Journal of Cardiology*, vol. 87, no. 10, pp. 1160–1163, 2001.

[37] F. Biscetti, E. Gaetani, A. Flex, et al., "Selective activation of peroxisome proliferator-activated receptor (PPAR)α and PPARγ induces neoangiogenesis through a vascular endothelial growth factor-dependent mechanism," *Diabetes*, vol. 57, no. 5, pp. 1394–1404, 2008.

[38] A. Pozzi, M. R. Ibanez, A. E. Gatica, et al., "Peroxisomal proliferator-activated receptor-α-dependent inhibition of endothelial cell proliferation and tumorigenesis," *Journal of Biological Chemistry*, vol. 282, no. 24, pp. 17685–17695, 2007.

[39] A. Pozzi, I. Macias-Perez, T. Abair, et al., "Characterization of 5,6- and 8,9-epoxyeicosatrienoic acids (5,6- and 8,9-EET) as potent in vivo angiogenic lipids," *Journal of Biological Chemistry*, vol. 280, no. 29, pp. 27138–27146, 2005.

[40] U. R. Michaelis and I. Fleming, "From endothelium-derived hyperpolarizing factor (EDHF) to angiogenesis: epoxyeicosatrienoic acids (EETs) and cell signaling," *Pharmacology & Therapeutics*, vol. 111, no. 3, pp. 584–595, 2006.

[41] I. Fleming, "Epoxyeicosatrienoic acids, cell signaling and angiogenesis," *Prostaglandins & Other Lipid Mediators*, vol. 82, no. 1–4, pp. 60–67, 2007.

[42] J. H. Capdevila, J. R. Falck, and R. C. Harris, "Cytochrome P450 and arachidonic acid bioactivation: molecular and functional properties of the arachidonate monooxygenase," *Journal of Lipid Research*, vol. 41, no. 2, pp. 163–181, 2000.

[43] J. H. Capdevila, J. R. Falck, E. Dishman, and A. Karara, "Cytochrome P-450 arachidonate oxygenase," *Methods in Enzymology*, vol. 187, pp. 385–394, 1990.

[44] M. Potente, U. R. Michaelis, B. Fisslthaler, R. Busse, and I. Fleming, "Cytochrome P450 2C9-induced endothelial cell proliferation involves induction of mitogen-activated protein (MAP) kinase phosphatase-1, inhibition of the c-Jun N-terminal kinase, and up-regulation of cyclin D1," *Journal of Biological Chemistry*, vol. 277, no. 18, pp. 15671–15676, 2002.

[45] M. Potente, B. Fisslthaler, R. Busse, and I. Fleming, "11,12-epoxyeicosatrienoic acid-induced inhibition of FOXO factors promotes endothelial proliferation by down-regulating p27^{Kip1}," *Journal of Biological Chemistry*, vol. 278, no. 32, pp. 29619–29625, 2003.

[46] U. R. Michaelis, J. R. Falck, R. Schmidt, R. Busse, and I. Fleming, "Cytochrome P4502C9-derived epoxyeicosatrienoic acids induce the expression of cyclooxygenase-2 in endothelial cells," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 25, no. 2, pp. 321–326, 2005.

[47] U. R. Michaelis, B. Fisslthaler, M. Medhora, D. Harder, I. Fleming, and R. Busse, "Cytochrome P450 2C9-derived epoxyeicosatrienoic acids induce angiogenesis via cross-talk with the epidermal growth factor receptor (EGFR)," *The FASEB Journal*, vol. 17, no. 6, pp. 770–772, 2003.

[48] D. Panigrahy, A. Kaipainen, S. Huang, et al., "PPARα agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 3, pp. 985–990, 2008.

[49] Y. Yokoyama, B. Xin, T. Shigeto, et al., "Clofibric acid, a peroxisome proliferator-activated receptor α ligand, inhibits growth of human ovarian cancer," *Molecular Cancer Therapeutics*, vol. 6, no. 4, pp. 1379–1386, 2007.

[50] L. Jackson, W. Wahli, L. Michalik, et al., "Potential role for peroxisome proliferator activated receptor (PPAR) in preventing colon cancer," *Gut*, vol. 52, no. 9, pp. 1317–1322, 2003.

[51] N. Niho, M. Mutoh, M. Takahashi, K. Tsutsumi, T. Sugimura, and K. Wakabayashi, "Concurrent suppression of hyperlipidemia and intestinal polyp formation by NO-1886, increasing lipoprotein lipase activity in Min mice," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 8, pp. 2970–2974, 2005.

[52] Y. M. Shah, K. Morimura, Q. Yang, T. Tanabe, M. Takagi, and F. J. Gonzalez, "Peroxisome proliferator-activated receptor α regulates a microRNA-mediated signaling cascade responsible for hepatocellular proliferation," *Molecular and Cellular Biology*, vol. 27, no. 12, pp. 4238–4247, 2007.

[53] K. Morimura, C. Cheung, J. M. Ward, J. K. Reddy, and F. J. Gonzalez, "Differential susceptibility of mice humanized for peroxisome proliferator-activated receptor α to Wy-14,643-induced liver tumorigenesis," *Carcinogenesis*, vol. 27, no. 5, pp. 1074–1080, 2006.

[54] Q. Yang, T. Nagano, Y. Shah, C. Cheung, S. Ito, and F. J. Gonzalez, "The PPARα-humanized mouse: a model to investigate species differences in liver toxicity mediated by PPARα," *Toxicological Sciences*, vol. 101, no. 1, pp. 132–139, 2008.

[55] Y. Ito, O. Yamanoshita, N. Asaeda, et al., "Di(2-ethylhexyl)phthalate induces hepatic tumorigenesis through a peroxisome proliferator-activated receptor α-independent pathway," *Journal of Occupational Health*, vol. 49, no. 3, pp. 172–182, 2007.

[56] F. Gizard, C. Amant, O. Barbier, et al., "PPARα inhibits vascular smooth muscle cell proliferation underlying intimal hyperplasia by inducing the tumor suppressor p16^{INK4a}," *The Journal of Clinical Investigation*, vol. 115, no. 11, pp. 3228–3238, 2005.

[57] A. Kaipainen, M. W. Kieran, S. Huang, et al., "PPARα deficiency in inflammatory cells suppresses tumor growth," *PLoS ONE*, vol. 2, no. 2, p. e260, 2007.

[58] P. Howroyd, C. Swanson, C. Dunn, R. C. Cattley, and J. C. Corton, "Decreased longevity and enhancement of age-dependent lesions in mice lacking the nuclear receptor peroxisome proliferator-activated receptor α (PPARα)," *Toxicologic Pathology*, vol. 32, no. 5, pp. 591–599, 2004.

[59] G. P. Collett, A. M. Betts, M. I. Johnson, et al., "Peroxisome proliferator-activated receptor α is an androgen-responsive gene in human prostate and is highly expressed in prostatic adenocarcinoma," *Clinical Cancer Research*, vol. 6, no. 8, pp. 3241–3248, 2000.

[60] K. M. Suchanek, F. J. May, J. A. Robinson, et al., "Peroxisome proliferator-activated receptor α in the human breast cancer cell lines MCF-7 and MDA-MB-231," *Molecular Carcinogenesis*, vol. 34, no. 4, pp. 165–171, 2002.

[61] K. M. Suchanek, F. J. May, W. J. Lee, N. A. Holman, and S. J. Roberts-Thomson, "Peroxisome proliferator-activated receptor β expression in human breast epithelial cell lines of tumorigenic and non-tumorigenic origin," *The International Journal of Biochemistry & Cell Biology*, vol. 34, no. 9, pp. 1051–1058, 2002.

[62] T. Tanaka, H. Kohno, S.-I. Yoshitani, et al., "Ligands for peroxisome proliferator-activated receptors α and γ inhibit chemically induced colitis and formation of aberrant crypt foci in rats," *Cancer Research*, vol. 61, no. 6, pp. 2424–2428, 2001.

[63] G. Muzio, M. Maggiora, M. Oraldi, A. Trombetta, and R. A. Canuto, "PPARα and PP2A are involved in the proapoptotic effect of conjugated linoleic acid on human hepatoma cell line SK-HEP-1," *International Journal of Cancer*, vol. 121, no. 11, pp. 2395–2401, 2007.

[64] M. Maggiora, M. Bologna, M. P. Cerù, et al., "An overview of the effect of linoleic and conjugated-linoleic acids on

the growth of several human tumor cell lines," *International Journal of Cancer*, vol. 112, no. 6, pp. 909–919, 2004.

[65] S. A. Saidi, C. M. Holland, D. S. Charnock-Jones, and S. K. Smith, "In vitro and in vivo effects of the PPAR-alpha agonists fenofibrate and retinoic acid in endometrial cancer," *Molecular Cancer*, vol. 5, article 13, 2006.

[66] P. Thuillier, G. J. Anchiraico, K. P. Nickel, et al., "Activators of peroxisome proliferator-activated receptor-α partially inhibit mouse skin tumor promotion," *Molecular Carcinogenesis*, vol. 29, no. 3, pp. 134–142, 2000.

[67] M. Grabacka, P. M. Plonka, K. Urbanska, and K. Reiss, "Peroxisome proliferator-activated receptor α activation decreases metastatic potential of melanoma cells in vitro via down-regulation of Akt," *Clinical Cancer Research*, vol. 12, no. 10, pp. 3028–3036, 2006.

[68] M. Grabacka, W. Placha, P. M. Plonka, et al., "Inhibition of melanoma metastases by fenofibrate," *Archives of Dermatological Research*, vol. 296, no. 2, pp. 54–58, 2004.

[69] T. Hays, I. Rusyn, A. M. Burns, et al., "Role of peroxisome proliferator-activated receptor-α (PPARα) in bezafibrate-induced hepatocarcinogenesis and cholestasis," *Carcinogenesis*, vol. 26, no. 1, pp. 219–227, 2005.

[70] F. J. Gonzalez, "The peroxisome proliferator-activated receptor α (PPARα): role in hepatocarcinogenesis," *Molecular and Cellular Endocrinology*, vol. 193, no. 1-2, pp. 71–79, 2002.

[71] K. Takashima, Y. Ito, F. J. Gonzalez, and T. Nakajima, "Different mechanisms of DEHP-induced hepatocellular adenoma tumorigenesis in wild-type and *Pparα*-null mice," *Journal of Occupational Health*, vol. 50, no. 2, pp. 169–180, 2008.

[72] H. B. Rubins, S. J. Robins, D. Collins, et al., "Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol," *The New England Journal of Medicine*, vol. 341, no. 6, pp. 410–418, 1999.

[73] M. H. Frick, O. Elo, K. Haapa, et al., "Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease," *The New England Journal of Medicine*, vol. 317, no. 20, pp. 1237–1245, 1987.