Minireview

Peroxisome Proliferator-activated Receptor Modulators As Potential Chemopreventive Agents

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Abstract

Peroxisome proliferator-activated receptors (PPARs), members of the superfamily of nuclear steroid hormone receptors, have traditionally been studied for their role in lipid, glucose, and energy homeostasis. Recent evidence suggests that pharmacological activation of PPARγ and PPARα, and inhibition of PPARδ, may prevent cancer. PPARγ agonists induce differentiation, inhibit the growth of established tumor cells *in vitro* and *in vivo,* and have chemopreventive effects in animal models. PPARα has anti-inflammatory and differentiating activity and protects against the oxidative damage associated with aging. In contrast, PPARδ expression may be a factor in colorectal carcinogenesis. PPARδ is normally repressed by the adenomatous polyposis coli tumor suppressor gene, and impaired adenomatous polyposis coli is strongly associated with human colorectal cancer risk. This review presents a rationale for using PPAR modulators as cancer chemopreventive drugs.

Introduction

PPARs[2] are ligand-activated transcription factors that heterodimerize with the RXRs and bind to peroxisomal proliferator response elements in the promoter region of target genes. Three PPAR isoforms have been cloned (α, γ, and δ), each exhibiting distinct patterns of tissue distribution and ligand specificity. PPARα regulates numerous aspects of fatty acid catabolism, whereas PPARγ controls adipocyte differentiation, systemic glucose levels, and lipid homeostasis (reviewed in Refs. 1 and 2). PPARδ is involved in development, embryo implantation, myelination of the corpus callosum, lipid metabolism, and epidermal cell proliferation (3, 4). Significant species differences in response to PPARα, but not PPARγ, have been noted. Specifically relevant to cancer, PPARα agonists increase peroxisomes and induce hepatomegaly and liver cancer in rodents. However, humans are refractory to the hepatotoxic actions of these drugs (reviewed in Ref. 5). In the following sections, evidence is presented for each PPAR class and the specific PPAR agonists that may play a role in cancer chemoprevention.

PPARγ and Cancer

The observation that PPARγ stimulates adipose differentiation in cultured mouse fibroblasts generated interest in the receptor's potential anticancer effects (6). Subsequent studies showed that activation of the receptor inhibits proliferation, and in some cases induces differentiation and/or apoptosis, in a variety of tumor cell lines (Table 1). Some of the most extensive work has been conducted in the colon, where PPARγ is expressed at high levels in normal tissue (7), and in both well- and poorly differentiated colon cancers (8). PPARγ-selective ligands inhibit proliferation and induce differentiation in colon cancer cell lines (8, 9) and diminish growth of human colon tumor xenografts (Ref. 8; Table 2). Importantly, for the purposes of chemoprevention, these ligands prevent the development of carcinogen-induced preneoplastic aberrant crypt foci in rats (10). Loss-of-function somatic mutations in the PPARγ gene are found in sporadic human colon cancers, suggesting that PPARγ may function directly as a tumor suppressor (11). PPARγ agonists also suppress macrophage activation and inflammatory cytokine production *in vitro* (12, 13) and reduce inflammation (10, 14) and neoplastic lesion development (10) in rodent models of inflammatory bowel disease. The latter finding is particularly relevant to chemoprevention, because the risk of colorectal cancer is increased in patients with this disease (reviewed in Ref. 15).

In contrast, other studies indicate that PPARγ activation promotes colon cancer in mice carrying a nonsense mutation in the APC tumor suppressor gene; defective APC is highly associated with human colorectal cancer risk (16). The TZDs troglitazone and rosiglitazone enhance colon tumorigenicity in these genetically predisposed mice; the more potent PPARγ agonist rosiglitazone induces more malignant tumors. However, pharmacological doses of troglitazone are not tumorigenic in wild-type mice, suggesting that increased risk is limited to animals harboring a mutant APC gene (17, 18).

Data available from other target sites suggest that PPARγ activation has chemopreventive potential. The receptor is expressed in human breast cancer cell lines and breast adenocarcinomas, and TZDs inhibit growth of breast cancer cells *in vitro* and *in vivo,* inducing differentiation in some cases (19, 20). However, cell lines expressing the highest levels of PPARγ are relatively unresponsive to TZD treat-

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[2] The abbreviations used are: PPAR, peroxisome proliferator-activated receptor; AOM, azoxymethane; APC, adenomatous polyposis coli; COX, cyclooxygenase; RXR, retinoic X receptor; TZD, thiazolidinedione.

Table 1 Antiproliferative effects of PPARγ ligands *in vitro*[a]

Ligand	Cell Line
Troglitazone	Bladder [39], breast [19, 20], colon [8, 9], lung [78], hematopoetic system [79], pancreas [36], prostate [24, 25], stomach [80]
Rosiglitazone	Colon [8, 9], prostate [24, 25, 81]
Pioglitazone	Breast [19], colon [8], liposarcoma [82], hematopoetic system [79], stomach [80]
Ciglitazone	Lung [31], prostate [26]
GW 1929	Neuroblastoma [83]
15d-PGJ_2[b]	Breast [84], colon [8], lung [31, 78], prostate [24, 25, 26], neuroblastoma [83]

[a] Growth inhibitory effects of PPARγ ligands in cancer cell lines, sometimes accompanied by induction of differentiation, apoptosis, and/or cell cycle arrest.
[b] 15d-PGJ_2, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2.

Table 2 Anticancer effects of PPARγ ligands in animal studies[a]

Target organ	Ligand	Results	Comments	Reference
Mammary gland	GW 7845	Prevented MNU-induced tumor development in rats	Additive effects with tamoxifen; no increase in body weight noted	[21]
	Troglitazone	Prevented DMBA-induced preneoplastic lesions in mouse mammary organ culture	Significant synergistic effects with RXR ligand	[22]
	Troglitazone	Inhibited growth of human breast cancer cells in immunodeficient mice		[20]
Colon	Troglitazone	Inhibited growth of human colon carcinoma cells in immunodeficient mice		[8]
	Troglitazone	Prevented development of AOM- and AOM/DSS-induced aberrant crypt foci in rats		[10]
	Pioglitazone	Prevented development of AOM/DSS-induced aberrant crypt foci in rats		[10]
Prostate	Troglitazone	Inhibited growth of human prostate cancer cells in immunodeficient mice	No additive effects with ATRA; necrotic and apoptotic changes noted. Similar changes, associated with troglitazone treatment of primary prostate tumors cultured *in vitro*	[24]

[a] MNU, *N*-methyl-*N*-nitrosourea; DMBA, 7,12-dimethylbenz(*a*)anthracene; AOM, azoxymethane; DSS, dextran sodium sulfate; ATRA, all-*trans*-retinoic acid.

ment. Adding a mitogen-activated protein kinase inhibitor overcomes this insensitivity, suggesting that phosphorylation prevents PPARγ activation (19).

The relevance of PPARγ activation for chemoprevention has been demonstrated in rodent mammary cancer models. The highly potent and specific PPARγ ligand GW 7845 significantly reduces tumor incidence, number, and weight in estrogen receptor-positive mammary tumors when fed to rats after carcinogen administration. Additive effects are observed on coadministration with suboptimal doses of the antiestrogen tamoxifen (21). Likewise, troglitazone prevents development of carcinogen-induced early neoplastic lesions in mouse mammary gland organ culture when administered during initiation or promotion stages. Synergism was noted with RXR-selective ligands (22), although similar effects were not observed in human breast cancer cell lines induced to differentiate in response to PPARγ activation (19). PPARγ ligands also diminish expression of aromatase (23), the rate-limiting enzyme in estrogen biosynthesis, which may contribute to chemopreventive effects in estrogen-responsive tissues.

In the prostate, PPARγ is expressed in primary cancers and cell lines, and receptor agonists display antiproliferative effects *in vitro* (24–26) and in xenografts in nude mice (24); effects *in vivo* are associated with necrotic, as well as apoptotic changes (24). Additionally, a subset of human prostate tumors carry hemizygous deletions of the PPARγ gene (25). In preliminary clinical studies, 20% (8 of 41) of prostate cancer patients treated with troglitazone showed decreased serum prostate-specific antigen levels, and 39% showed prolonged stabilization (25). Consistent with these findings, troglitazone decreases prostate-specific antigen levels in prostate cancer cell lines (24, 25). The actions of PPARγ ligands in the prostate may be associated with decreased activation of the androgen receptor (27) or a reduction in circulating estrogens (reviewed in Ref. 28), secondary to reduced aromatase expression (23).

PPARγ ligands also inhibit proliferation of human lung, urinary bladder, pancreatic, neuroblastoma, gastric, and liposarcoma cell lines (Table 1) and induce differentiation and inhibit growth of liposarcomas in patients (29). The activated form of matrix metalloproteinase-2, strongly associated with tumor growth, metastasis, and angiogenesis (30), markedly decreases in lung cancer cells treated with PPARγ agonists (31). Furthermore, PPARγ activators are direct inhibitors of angiogenesis both *in vitro* and *in vivo* (32, 33). A role for PPARγ in thyroid follicular carcinoma is suggested by the presence in these tumors of a PAX8-PPARγ1 fusion oncoprotein, which functions as a dominant negative suppressor of wild-type PPARγ (34).

Recent investigations have provided clues about the signaling pathways used by PPARγ agonists to suppress neoplasia. Inhibition of tumor cell growth has been associated with G_1 cell cycle arrest (9, 35, 36), which in some cases is linked to loss of DNA binding activity of the transcriptional regulator E2F/DP (37). Other mechanisms that may be involved include up-

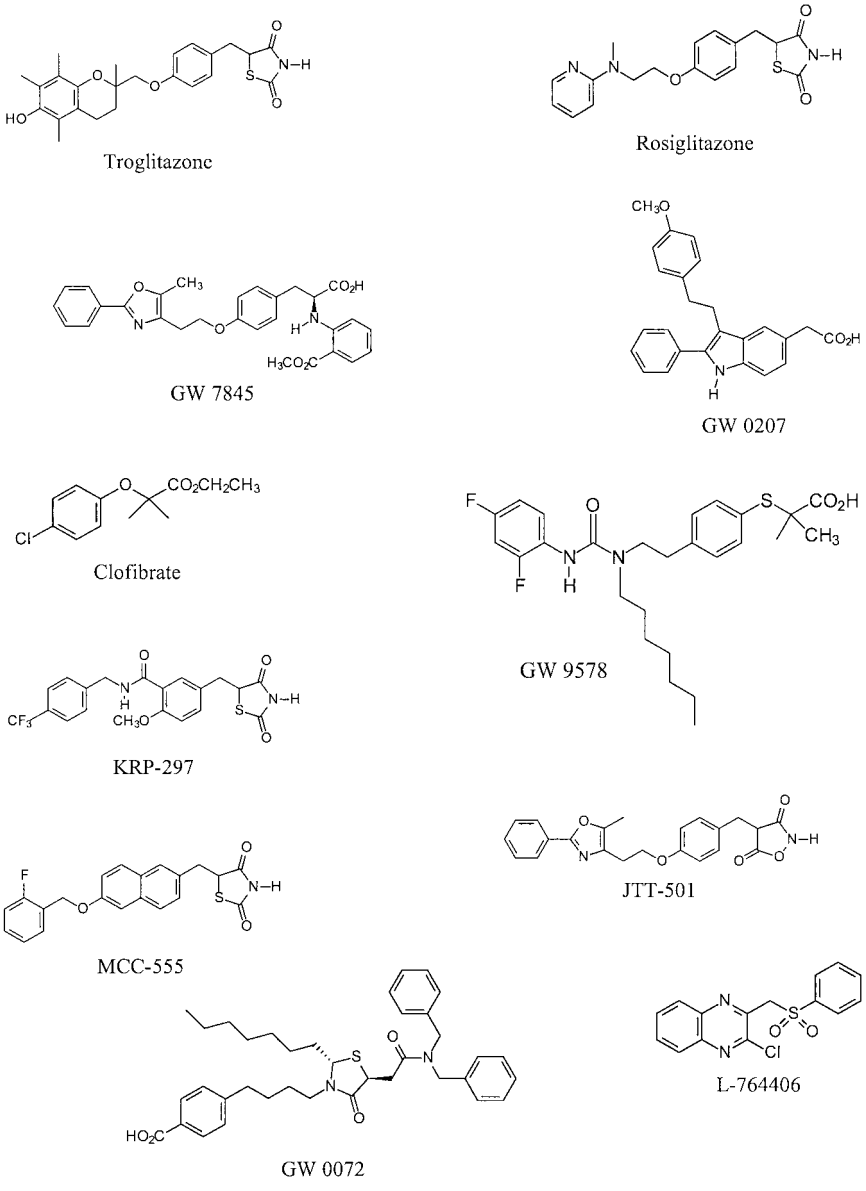

Fig. 1. Chemical structures of PPAR modulators.

regulation of the cyclin-dependent kinase inhibitors p18 ^{INK4c} and p21 $^{Waf1/Cip1}$ and reduced expression of cyclin D1 (31, 38–40). Recent studies showed that the antiproliferative and anti-inflammatory activities of PPARγ ligands are mechanistically distinct. PPARγ-dependent antiproliferative effects involve repression of cyclin D1 via sequestration of p300 and interference with c-*fos*-directed transcription. Anti-inflammatory effects, independent of this receptor, are mediated via inhibition of the intracellular kinase intracellular κB kinase, involved in nuclear factor κ B activation (40). Additionally, PPARγ agonists up-regulate the phosphatase and tension homologue (PTEN) tumor suppressor, suggesting that phosphoinositide signaling pathways are also associated with PPARγ-mediated growth suppression (41).

PPARα and Cancer

Several studies have established a link between PPARα activation and epidermal differentiation. Fibrates, which are PPARα ligands, induce differentiation and inhibit proliferation of human keratinocytes *in vitro* (42), and in normal (43) and hyperproliferating (44) mouse skin *in vivo,* but are inactive in PPARα-deficient mice (43). Farnesol also stimulates PPARα-dependent differentiation in epidermal keratinocytes (45). Topical PPARα agonists have weak preventive effects on tumor promotion in mouse skin, despite up-regulation of PPARα in untreated tumors compared with normal epidermis (46). In this regard, PPARα expression is also up-regulated in human prostate adenocarcinomas (47). The significance of this observation is as of yet unknown.

Some anticancer actions of phenylacetate may be mediated by PPARα activation. The relative potencies of phenylacetate and its analogues as PPARα activators correlate strongly to their growth inhibitory effects in human cancer cell lines (48). Phenylacetate also activates PPARγ (49), making it difficult to ascribe growth-inhibitory effects specifically to activation of the α isoform. It is important to note that PPARα ligands are inactive in tumor cell lines in which PPARγ ligands are effective antiproliferative agents (8, 9, 25); however, the status of PPARα expression in these tumor cell lines is unknown.

In rodents, PPARα activation has been associated with both anti- (50, 51) and proinflammatory (52) actions. Opposing effects have also been described in humans. PPARα agonists diminish expression of inflammatory markers in human cells and patients treated with fibrates (53, 54). In contrast, expression of the inflammatory mediator COX-2 in human breast and colon cancer cells is up-regulated by PPARα agonists (55). The latter finding is particularly troublesome, given that increased COX-2 expression has been specifically linked to enhanced colon cancer risk (reviewed in Ref. 28).

Other possible connections between PPARα and cancer prevention come from the inverse association of PPARα activation with decreased oxidative stress and aging, both linked with tumorigenesis (reviewed in Ref. 56). PPARα agonists administered to aged PPARα-replete, but not aged PPARα-null mice, decreased tissue levels of lipid peroxides and the oxidant-stress-activated transcription factor nuclear factor κ B (51). Additionally, reduced expression of PPARα and peroxisome-associated genes is observed in aged mice; PPARα agonists restore expression to levels seen in young animals (57).

PPARδ and Cancer

In contrast to the γ and α isoforms, activation of PPARδ is associated positively with tumorigenesis. PPARδ transcription is normally suppressed by wild-type APC but is up-regulated in colorectal cancer cells, which have an inactivating APC mutation through enhanced β-catenin/Tcf-4 binding to TCF-4-responsive elements in the PPARδ promoter (58). Xenografts of PPARδ-null colon cancer cell lines display decreased tumorigenicity in nude mice (59). Consistent with these findings, PPARδ is overexpressed in human and rodent colorectal tumors, as well as preneoplastic colonic mucosa (58, 60, 61). Although initial experiments suggested that nonsteroidal anti-inflammatory drug-induced apoptosis is mediated in part by PPARδ inhibition (58), this was not confirmed in additional studies (59). However, additional experiments in PPARδ-null mice indicate that nonsteroidal anti-inflammatory drug-mediated anti-inflammatory response, which may also be chemopreventive, is at least partially dependent on PPARδ (3).

PPAR Modulators

As suggested by the data presented above (Fig. 1), agonists of PPARγ and PPARα, and antagonists of PPARδ, may find utility as chemopreventive agents. Although no selective PPARδ inhibitors have been identified, a number of agonists for these isoforms has been described. Selective PPARγ agonists include classic TZDs (troglitazone, rosiglitazone, pioglitazone, and ciglitizone; Refs. 62 and 63) and non-TZD-type agonists. Representatives of the latter include *N*-(2-benzoylphenyl)-*L*-tyrosine derivatives, such as GW 1929, GI 262570, and GW 7845, which are among the most potent and selective PPARγ agonists identified to date (64, 65). GW 0207, a 2,3-disubstituted indole-5-carboxylic acid, is also a potent and selective PPARγ agonist (66).

Fibrates are weak PPARα agonists used to treat hyperlipidemia (2). Newer PPARα agonists, such as the ureidofibrate GW 9578, are significantly more potent (67) and can be used to study the effects of PPARα in neoplasia. If both PPARα and PPARγ are involved in tumorigenesis, dual receptor agonists, such as the TZD KRP-297 (68) and the related isoxazolidinedione derivative JTT-501 (69), may also find utility as chemopreventive agents.

The following compounds can act as partial PPARγ agonists/antagonists. Although TZD MCC-555 is a low-affinity PPARγ ligand, it is an effective PPARγ activator in animals (70). L-764406, a sulfonyl quinoxaline derivative, is a potent and specific PPARγ ligand and partial agonist that covalently modifies the receptor (71). The thiazolidine acetamide GW 0072 is a high-affinity PPARγ ligand and weak partial transcriptional activator of the receptor; it is also a potent inhibitor of rosiglitazone-induced adipocyte differentiation (72).

These partial agonists/antagonists display unique biological properties that may translate to distinct therapeutic and/or toxicological profiles, similar to selective estrogen receptor modulators (partial estrogen receptor agonists/antagonists; reviewed in Ref. 28). This is significant, because the selective PPARγ agonist troglitazone can have rare but serious hepatotoxic consequences (73). Moreover, it is possible that the cancer-promoting effects of PPARγ ligands, as observed in animals predisposed to colon cancer, can be mitigated using partial agonists.

Conclusions

The PPAR system's relevance to carcinogenesis is just beginning to be unraveled. Additional research is needed to characterize expression patterns of the various PPAR isoforms in cancerous and precancerous tissue and to determine their precise roles in the carcinogenic process. Numerous fatty acids and their metabolites activate PPAR receptors (74, 75). Thus, PPARs may also provide the missing molecular link between high-fat diets and nutritionally sensitive cancers (76). Although the physiological function of the PPAR was once thought to be restricted to lipid metabolism, it is now clear that these receptors are involved in numerous biological processes. Confirming a crucial role for PPARs in tumorigenesis will foster development of a novel class of cancer preventive drugs (77).

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Erratum

In the article by Kopelovich *et al*., entitled "Peroxisome proliferator-activated receptor modulators as potential chemopreventive agents," which appeared in the March 2002 issue of *MCT* (pp. 357–363), Dr. Judith R. Fay's affiliation was listed incorrectly as National Cancer Institute, Division of Cancer Prevention, Bethesda, MD 20892-7322. Dr. Fay's correct affiliation is **CCS Associates, Mountain View, California 94043.**

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