

Peroxisome proliferator-activated receptors: roles in tumorigenesis and chemoprevention in human cancer

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Peroxisome proliferator-activated receptors are nuclear receptors that were isolated for their ability to modulate lipid metabolism. Similar to other members of the nuclear receptor family, peroxisome proliferator-activated receptors bind ligand as heterodimers and exert their effects via transcriptional regulation through their DNA binding domains. During the past decade, it has become clear that peroxisome proliferator-activated receptors also contribute to a variety of different biologic processes, including atherosclerosis, insulin resistance, and more recently, cancer. In this review, we discuss the evidence for the different peroxisome proliferator-activated receptors' roles in tumorigenesis and also their potential application for the treatment and prevention of neoplastic diseases. *Curr Opin Oncol* 2001, 13:78–83 © 2001 Lippincott Williams & Wilkins, Inc.

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Current Opinion in Oncology 2001, 13:78–83

Abbreviations

APC	adenomatous polyposis coli
DBD	DNA-binding domain
min	multiple intestinal neoplasia
NSAIDs	nonsteroidal antiinflammatory drugs
PPAR	peroxisome proliferator-activated receptor
RXR	9- <i>cis</i> retinoic acid receptor
TCF	T-cell factor

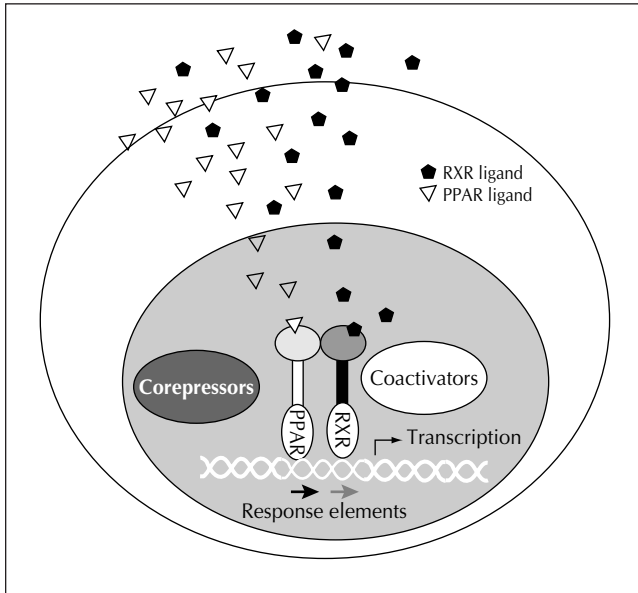
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Peroxisome proliferator-activated receptors (PPARs) are part of the nuclear receptor superfamily, whose members include the retinoic acid receptors, thyroid hormone receptors, steroid receptors, and receptors that do not have clearly defined natural ligands, the so-called orphan receptors [1–3]. PPARs were originally identified as nuclear receptors that mediate the biologic effects of a group of synthetic compounds called peroxisome proliferators. Three subtypes of PPARs have been identified in mammalian cells, termed PPAR α , PPAR γ , and PPAR δ (also known as PPAR β or NUC1) [2,4–6]. PPAR α is highly expressed in liver and brown fat and is also found in kidney, heart, and skeletal muscle. PPAR γ is mainly expressed in adipose tissue, and to a lesser extent in colon and other tissues. PPAR δ is ubiquitously expressed, with the highest level found in the gut, kidney, brain, and heart [7]. The molecular and genetic organization of the three different PPAR genes is complex and beyond the scope of this review.

Similar to other nuclear receptors, PPARs are ligand-activated transcription factors, in which transcriptional activation of target genes depends on the binding of ligand to the receptor. PPARs are fully functional only when they heterodimerize with the 9-*cis* retinoic acid receptor, RXR. The transcriptional activity of the PPAR:RXR complex is further modulated by nuclear receptor coactivators or corepressors (Fig. 1) [8]. The identified ligands for PPARs include peroxisome proliferators, antidiabetic compounds such as the thiazolidinediones, fibrates, fatty acids, and eicosanoids [9–13]. Although some ligands are shared by all three isotypes of PPARs, PPAR α binds with relative high affinity to long-chain polyunsaturated fatty acids (*eg*, linoleic acid) and eicosanoids (*eg*, 8S-HETE and leukotriene B₄), whereas the prostaglandin 15-deoxy- $\delta^{12,14}$ -prostaglandin J₂ is the most potent natural occurring ligand for PPAR γ . Similarly, the thiazolidinedione class of drugs is thought to be PPAR γ specific. Highly PPAR δ -specific ligands have yet to be identified.

Recent studies have demonstrated that PPARs participate in many important physiologic responses. The PPARs' role in human diseases, such as diabetes, obesity, atherosclerosis, and the inflammatory response, has been recently reviewed elsewhere [14]. In this review we discuss the evidence for the PPARs' involvement in human cancers, with a particular focus on PPAR δ and PPAR γ and their contribution toward colorectal carcinogenesis.

Figure 1. Peroxisome proliferator-activated receptors (PPARs) bind 9-*cis* retinoic acid (RXR) to form heterodimeric transcription factors



The PPARs form heterodimers with RXR and bind PPAR response elements via their DNA-binding domain. Upon ligand activation, transcriptional activity is upregulated by the nuclear receptors in part through their interactions with nuclear corepressors and coactivators.

Three isotypes with distinct and overlapping functions

The PPARs contain four major regions that are highly conserved among the nuclear receptor superfamily: the A/B domain, the C domain, the D domain, and the E/F domain. The C domain is the DNA-binding domain (DBD) and is highly conserved among different receptors. The ligand-binding domain comprises the E/F domain. Although the structural arrangement and functional domains are similar among the three PPAR isotypes, they each appear to carry out distinct physiologic functions [15]. For example, PPAR α regulates the transcriptional activity of genes that are involved in lipid metabolism such as fatty acid uptake through plasma membranes, fatty acid binding in the cytoplasm, fatty acid oxidation, and lipoprotein assembly and transport. Animal knockout studies have recently demonstrated that PPAR α is the critical mediator of the peroxisome proliferation phenotype in rodents [16–18]. PPAR γ , conversely, primarily regulates the storage of fatty acids in adipose tissue by inducing terminal differentiation of preadipocytes [19]. Most of the known PPAR γ target genes in fatty tissue are primarily implicated in the lipogenic pathway. In addition, PPAR γ is thought to modulate the body's response to insulin, based on the thiazolidinedione class of drugs' ability to lower serum glucose levels. The exact mechanism involved with this remains elusive, as heterozygous PPAR γ knockout mice are not prone to insulin resis-

tance when given a high-fat diet, though this phenotype is abrogated when the mice are given a thiazolidinedione class drug [20–22]. Interestingly, PPAR γ homozygous null mice are not viable, though placental rescue experiments convincingly demonstrate PPAR γ 's role in adipogenesis. The physiologic role of PPAR δ had until recently not been elucidated. The creation of the PPAR β (PPAR δ) knockout mouse has demonstrated that this receptor is also involved with lipid metabolism and the inflammatory response [23•].

Nuclear receptors and tumorigenesis

The dysfunction of certain nuclear receptors has long been associated with tumorigenesis in humans and animals. For example, although the molecular mechanisms are not clearly understood, the sex hormone receptors have been implicated in the development of human breast and prostate cancers. This is evidenced by effective antiestrogen and antiandrogen receptor therapies directed against certain subtypes of these malignancies [24–26]. Similarly, some leukemias are characterized by chromosomal translocations resulting in the generation of chimeric genes leading to nuclear receptor dysfunction [27]. A classic example of this is acute promyelocytic leukemia, in which the translocation of chromosomes 15 and 17 leads to the fusion of the *pml* gene and the gene for retinoic acid receptor α . The resulting promyelocytic leukemia–retinoic acid receptor α chimeric transcription factor blocks differentiation by aberrantly recruiting transcriptional coactivators [28]. Historically, it has been well documented that PPAR α is a critical mediator of the hepatocarcinogenic effects of certain peroxisome proliferators in rodents [29]. This was shown conclusively by the failure of PPAR α null mice to develop liver cancer upon peroxisome proliferator stimulation. However, no carcinogenic effects of peroxisome proliferators have been found in primates, including humans. The molecular basis of this species-specific response remains undefined. More intriguingly, the PPAR γ ligand troglitazone has been shown to increase formation of intestinal polyps in the mouse model of familial adenomatous polyposis, the multiple intestinal neoplasia (*min*) mouse [30,31]. However, this thiazolidinedione class of drug has also been demonstrated to induce terminal differentiation or apoptosis in a variety of human cancers. Taken together, there is compelling evidence that deregulation of certain nuclear receptors is involved in a variety of neoplastic processes.

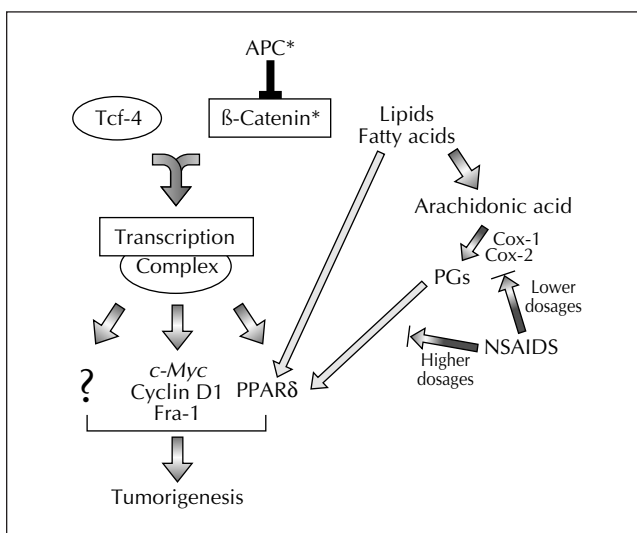
Peroxisome proliferator-activated receptor δ as a mutual target of the adenomatous polyposis coli tumor suppressor pathway and nonsteroidal antiinflammatory drugs

The development of colon cancer requires the accumulation of multiple genetic alterations [32]. The majority

of colon cancers are initiated by inactivating mutations in the adenomatous polyposis coli (APC) tumor suppressor gene, which encodes a large protein with multiple functional domains. One of the most important functions of the APC gene product is to target the protein β -catenin for degradation [33]. Originally identified as a cell adhesion molecule, β -catenin has been shown to form a transcription complex with members of the T-cell factor (TCF)/lymphocyte enhance factor (LEF) transcription factor family [34,35]. More than 90% of human colon cancers are initiated by an elevation in β -catenin/TCF activity caused by either inactivating mutations of *APC* or oncogenic mutations of β -catenin [36,37]. Thus, it is conceivable that identification of the downstream target genes of the β -catenin/TCF pathway may elucidate the mechanisms through which the APC tumor suppressor regulates cell growth. Several prominent target genes of this pathway have been recently identified (Fig. 2) [38–41].

Through a quantitative analysis of the differentially expressed genes affected by reintroduction of the APC tumor suppressor in human colon cancer cells, PPAR δ was identified as a downstream target gene of the APC/ β -catenin/TCF pathway [42••]. In this study, expression of PPAR δ was repressed by wild-type *APC* or a dominant-negative mutant form of *TCF4*. Further analysis revealed that the genomic sequence of the PPAR δ promoter contained two canonical *TCF4*-binding sites. *In vitro* selection of a random oligonucleotide duplex pool with a PPAR δ DBD yielded a novel

Figure 2. Peroxisome proliferator-activated receptors (PPAR δ) as a mediator of the APC tumor suppressor pathway and nonsteroidal antiinflammatory (NSAID)-induced toxicity



PPAR δ is a downstream effector of the adenomatous polyposis (APC) pathway, such that its upregulation induces cellular growth and proliferation. PPAR δ may also be a target of NSAIDs, either directly or indirectly, as a downstream effector of cyclooxygenase (COX).

PPAR δ -responsive element. The PPAR δ -responsive element was highly specific for PPAR δ , as opposed to the previously published peroxisome proliferator responsive element, which appears to be equally capable of binding all three isotypes of PPARs. More interestingly, a PPAR δ -responsive element-driven luciferase reporter was markedly inhibited by the nonsteroidal antiinflammatory drugs (NSAIDs) sulindac sulfide and indomethacin, which have been demonstrated to be effective chemopreventive drugs for colon cancer in humans and animal models. This inhibition of PPAR δ activity seemed to be highly specific, as NSAID-induced apoptosis in colon cancer cells could be partially rescued by overexpression of PPAR δ . Furthermore, NSAIDs, especially sulindac sulfide, have been shown to directly disrupt the ability of PPAR δ to bind to its responsive elements in *in vitro* DNA-binding assays. These findings suggest a molecular link between the genetic pathways of colorectal tumorigenesis and the mechanism by which NSAIDs can prevent colon cancer. Furthermore, this line of investigation may also provide a molecular basis for the epidemiologic association between dietary fat consumption and the relative risk of colon cancer, as products of fatty acid metabolism may serve as natural ligands for PPAR δ [43]. Thus, as summarized in Figure 2, *APC* or β -catenin mutations can result in increased PPAR δ activity, whereas NSAIDs can potentially compensate for this defect by suppressing PPAR δ activity and promoting apoptosis.

The identification of PPAR δ as a target for the NSAID-induced chemoprevention of colon cancer also helps to reconcile several points of controversy regarding their mechanisms of action. Previously, the striking chemopreventive effects of NSAIDs seen in familial adenomatous polyposis patients and the min mouse model were attributed to the inhibition of cyclooxygenases [44]. It was believed that this inhibition resulted in a decreased production of prostaglandins and other eicosanoids, which in turn decreased cellular proliferation via undefined mechanisms. This notion is supported by the fact that expression of cyclooxygenase-2 is elevated in some human colorectal tumors [45]. The most compelling evidence comes from animal studies in which inactivation of the *COX-2* gene in min mice is associated with a marked decrease in intestinal polyps [46].

However, it remains unclear whether NSAIDs exert their chemopreventive effect solely through the cyclooxygenase pathway. For instance, NSAID derivatives that lack the ability to inhibit cyclooxygenase have been shown to inhibit colonic tumor growth [47,48]. Conversely, colon cancer cells completely devoid of cyclooxygenase activity are inhibited as effectively as cyclooxygenase-producing cells [49,50]. In addition, *COX-1* and *COX-2* null mouse embryo fibroblasts remain

sensitive to the antineoplastic effect of NSAIDs [51]. Finally, the concentration of NSAIDs that inhibit cell growth is 10 to 100 times higher than that required to inhibit cyclooxygenase activity [50]. These observations have suggested that the chemopreventive and apoptosis-inducing activities of some NSAIDs are not entirely related to the inhibition of cyclooxygenase and that other cellular targets may exist. The discovery of PPAR δ as a mutual target of APC and NSAIDs may resolve these issues. Normally, some of the eicosanoids produced by cyclooxygenase may serve as naturally occurring ligands for PPAR δ and thereby promote cell proliferation. To exert their antiproliferative effects, NSAIDs could inhibit cyclooxygenase activity at low dosages and directly target PPAR δ at higher concentrations (Fig. 2). Several lines of evidence support this model. First, certain forms of prostaglandins and other eicosanoids have been identified as PPAR ligands [11,13]. Second, a product of cyclooxygenase-2 metabolism, cPGI, has been shown to bind PPAR δ . This cyclooxygenase-2-derived ligand can rescue the infertility found in *COX-2* null mice, demonstrating that PPAR δ is a downstream effector of cyclooxygenase-2 [52•]. Finally, it has been recently shown that PPAR δ knockout mice are insensitive to the antiinflammatory effects of sulindac [23•]. Thus the role of NSAID-induced chemoprotection may be more complex than previously believed, with PPAR δ potentially serving as a nodal point for multiple different pathways.

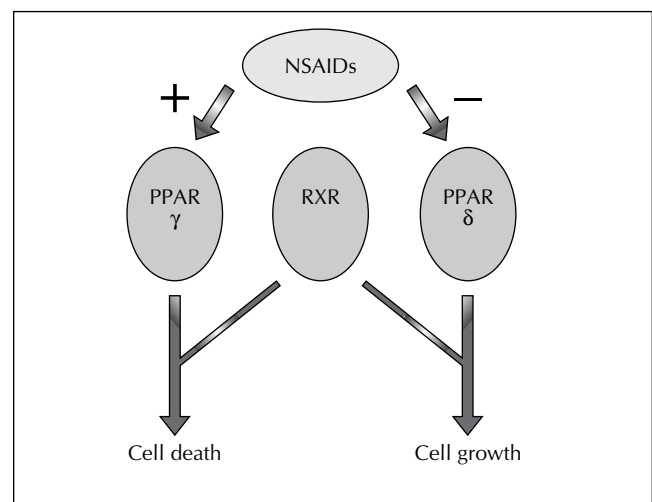
Peroxisome proliferator-activated receptors δ versus γ in tumorigenesis and chemoprevention

Several studies have suggested that PPAR γ may also play a role in colon cancer development. In 1998, two separate groups reported that PPAR γ agonists could promote intestinal tumorigenesis in the min mouse, thus implicating PPAR γ in the oncogenesis of colorectal tumors [30,31]. However, Sarraf *et al.* [53] reported that nude mice injected with human tumors displayed differentiation and inhibition of their cancers when given the same PPAR γ agonists. Although there is no satisfactory explanation for these contradictory actions of PPAR γ agonists, they are highly reminiscent of the species-specific response to PPAR α ligands (*eg*, peroxisome proliferators) in rodents versus humans. A role for PPAR γ in intestinal tumorigenesis has been further implicated by the recent identification of loss-of-function mutations in human colon cancers. In this study, one allele of the PPAR γ gene in four of 55 sporadic colorectal cancers was mutated, suggesting that PPAR γ may function as a tumor suppressor for colon cancer [54••]. However, it remains unclear whether these heterozygous mutations of PPAR γ play a key role in colorectal tumorigenesis. The role of PPAR γ in colon cancer is further complicated by the findings that some

NSAIDs can serve as weak ligands for PPARs [55]. Additionally, a growing body of evidence has shown that PPAR γ agonists exhibit antitumor and apoptosis-inducing activities in a broad range of human malignancies, including breast cancer, prostate cancer, and liposarcomas [56–67]. It is conceivable that the function of PPAR γ agonists in nonadipocytes, including a variety of human cancer cells, is to promote terminal differentiation in a nonspecific fashion.

Because RXRs are required to form functional heterodimers for both PPAR δ and PPAR γ , it is possible that there is normally a balanced regulation between PPAR δ and PPAR γ through their competition for RXRs. In fact, it has been reported that PPARs and the thyroid hormone receptor can compete with each other for the availability of RXR [6,68–71]. The studies mentioned here suggest that PPAR δ could promote cellular proliferation, whereas PPAR γ may inhibit cell growth and induce apoptosis. Therefore, colorectal tumorigenesis may be the result of a tipped balance towards PPAR δ ligand binding and activation, as summarized in Figure 3. If this model proves to be correct, it would further aid efforts to address colorectal cancer chemoprevention, as either PPAR δ antagonists or PPAR γ agonists (or both) could be utilized as chemopreventive agents for colon cancer. Identification of the downstream effectors of these PPARs may even allow for more specific therapies directed toward the prevention and treatment of many different human malignancies.

Figure 3. A model for peroxisome proliferator-activated receptors (PPAR)-induced tumorigenesis



PPAR γ heterodimerizes with 9-*cis* retinoic acid (RXR) and in the presence of an agonist ligand induces cellular differentiation and death. PPAR δ also forms heterodimers with RXR, but upon ligand activation causes cellular growth and proliferation. A decrease in PPAR γ activity or an increase in PPAR δ activity may result in tumorigenesis. Nonsteroidal antiinflammatory drugs (NSAIDs) may reverse this balance by binding as an agonist to the PPAR γ :RXR complex or inhibiting the activity of the PPAR δ :RXR complex.

Conclusions

The identification of PPAR δ as a mutual target for the APC tumor suppressor and NSAIDs has provided new insights into the tumorigenesis and chemoprevention of colon cancer. However, many critical questions remain. Further genetic evidence is needed to confirm the involvement of PPAR δ in colorectal tumorigenesis. One such study would be to cross the min mouse with PPAR δ null animals. If the model is correct, the min/PPAR δ null mice would be expected to have fewer tumors. In addition, the creation of a PPAR δ null human colorectal cancer cell line would also aid in elucidating the biologic function of this receptor in human cancers. This may be especially relevant as previous examples have clearly demonstrated differences between human and rodents in their response to various PPAR ligands. Moreover, it is of critical importance to identify PPAR δ -specific agonists as well as antagonists. Lack of PPAR δ -specific ligands has significantly hampered the investigations of its biologic functions. Likewise, PPAR δ -specific antagonists may serve as the most effective and least toxic chemopreventive agents for human cancers. Finally, identification of the important downstream target genes will certainly aid in fully understanding the biologic functions of PPAR δ , which will ultimately lead to the development of better and more efficacious chemopreventive agents.

Acknowledgments

We thank Ken Kinzler, Bert Vogelstein, and members of the Molecular Genetics Laboratory of The Johns Hopkins Oncology Center for their helpful insights and discussions. BHP is a recipient of the Howard Hughes Medical Institute Postdoctoral Fellowship for Physicians. The work was supported in part by grants from the American Cancer Society Illinois Division, Otho S.A. Sprague Memorial Institute, and the Concern Foundation (TCH). BHP wishes to thank Dr. Rachel Damico for her enthusiasm and support. TCH wishes to thank Drs. Michael A. Simon and Terrance Peabody of The University of Chicago Medical Center for their enthusiastic support. We apologize to the researchers whose original contributions could not be cited due to space limitations.

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