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# Peroxisome proliferator-activated receptors in chronic inflammation and colorectal cancer

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## Abstract

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily and have been implicated in a variety of physiological and pathological processes, such as nutrient metabolism, energy homeostasis, inflammation and cancer. In this review, we highlight breakthroughs in our understanding of the potential roles of PPARs in inflammatory bowel disease and colorectal cancer. These PPAR receptors might hold the key to some of the questions pertinent to the pathophysiology of inflammatory diseases and colorectal cancer and could possibly serve as drug targets for new anti-inflammatory therapeutic and anti-cancer agents.

### Keywords

peroxisome proliferator-activated receptor; chronic inflammation; inflammatory bowel disease; colorectal cancer

## INTRODUCTION

The recognition of chronic inflammation caused by infections or autoimmune diseases as the seventh trait of cancer has highlighted the contribution of inflamed stroma to tumor initiation, growth and metastasis. Epidemiologic studies indicate that chronic inflammation is clearly associated with increased cancer risk in a number of instances, including esophageal, gastric, hepatic, pancreatic and colorectal cancer. For example, it has been long known that patients with persistent hepatitis B infection, *Helicobacter pylori* infection, or an immune disorder such as inflammatory bowel disease (IBD), have a higher risk for the development of liver or gastrointestinal tract cancer. It has been estimated that chronic inflammation contributes to the development of approximately 15% of malignancies worldwide (1). The best evidence for the link between inflammation and tumor progression comes from recent epidemiologic studies



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and clinical trials showing that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) reduced the relative risk of developing colorectal cancer (CRC) by 40-50% (2).

The gastrointestinal mucosa forms a complex, semi-permeable barrier between the host and the largest source of foreign antigens. The mucosal barrier consists of epithelial cell junctions and the underlying stromal elements including immune cells. An abnormal mucosal immune response to bacteria, which make up the intestinal flora, is thought to result in chronic inflammation and the development of inflammatory bowel disease (IBD). IBD, with its two clinical manifestations of Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic inflammatory disorder of the gastrointestinal tract. Chronic IBD (especially pan-colitis) significantly increases the risk of developing CRC (3). In support of this notion, the observation that 5-aminosalicylic acid (5-ASA), currently used in the treatment of UC, suppresses the development of colitis-associated cancer in an animal model (4).

A large body of evidence indicates that genetic mutations, epigenetic changes, chronic inflammation, diet and lifestyle are risk factors for cancer (5-7). Similar to other solid tumors, colorectal cancer (CRC) is a heterogeneous disease with at least three major forms: hereditary, sporadic, and colitis-associated CRC. Patients with familial adenomatous polyposis (FAP), due to a germ-line mutation in one allele of the tumor suppressor gene adenomatous polyposis coli (*APC*), have a near 100% risk of developing CRC by the age of 40, if untreated. Somatic loss of APC function occurs in about 85% of sporadic colorectal adenomas and carcinomas (8-10). Hereditary nonpolyposis colorectal cancer (HNPCC), which is due to inherited mutations in genes for DNA mismatch repair such as *MLH1*, *MSH2*, and *MSH6*, is responsible for approximately 2 to 7 percent of all diagnosed cases of CRC. The average age of patients with this syndrome develop cancer around 44 years old, as compared to 64 years old in the general population. Together with the hereditary syndromes of FAP and hereditary nonpolyposis CRC, IBD is among the top three high-risk conditions for CRC; therefore, patients with IBD face an increased lifetime risk for developing CRC. Compared with sporadic CRC, colitis-associated CRC affects individuals at a younger age than the general population.

Peroxisome proliferator-activated receptors (PPARs), which were initially identified as mediators of the peroxisome proliferators in the early 1990s (11), belong to the nuclear hormone receptor superfamily and are also ligand-dependent transcription factors. PPARs play a central role in regulating the storage and catabolism of dietary fats via complex metabolic pathways, including fatty acid oxidation and lipogenesis (12). To date, three mammalian PPARs have been identified and are referred to as PPARα (NR1C1), PPARδ/β (NR1C2) and PPARγ (NR1C3). Each PPAR isotype displays a tissue-selective expression pattern. PPARα and PPARγ are predominantly present in the liver and adipose tissue, respectively, while PPARδ is expressed in diverse tissues (13) and its expression in the gastrointestinal tract is very high compared with other tissues (14). As ligand-dependent transcription factors, transcriptional activation by PPARs depends on ligand binding and the interaction of co-regulators. PPAR ligands are chemically unrelated molecules including a variety of fatty acids, fatty acid derivatives, and steroids, as well as synthetic compounds. Polyunsaturated fatty acids activate all three PPAR isotypes with relative low affinity (15). The endogenous fatty-acid derivatives, which are mainly converted by cyclooxygenase and lipoxygenase enzymes, selectively bind and activate each PPAR isotype. For example, 15-deoxy-$\Delta^{12},\Delta^{14}PGJ_2$ ($15dPGJ_2$), a dehydration product of $PGD_2$, is a natural ligand for the PPARγ (16,17), while $PGI_2$ can transactivate PPARδ (18,19).

It is well established that modulation of PPAR activity maintains cellular and whole-body glucose and lipid homeostasis. Hence, great efforts have been made to develop drugs targeting these receptors. For example, PPARγ synthetic agonists, troglitazone, rosiglitazone and pioglitazone, are clinically used for the therapy of non-insulin-dependent diabetes mellitus.

The anti-atherosclerotic and hypolipidemic agents including fenofibrate and gemfibrozil are PPARα synthetic agonists that induce hepatic lipid uptake and catabolism. Genetic and pharmacological studies have also revealed that PPARδ agonists are potential drugs for use in the treatment of dyslipidemias, obesity and insulin resistance (20-23). Therefore, the PPARδ agonist (GW501516) is currently in phase III clinical trials to evaluate its use for treatment of patients with hyperlipidemias and obesity. In addition to modulation of lipid homeostasis and energy balance, PPARs have emerged as essential molecules in the pathogenesis of IBD and CRC.

## PPARS AND IBD

The currently available therapies for IBD include 5-aminosalicylic acid (5-ASA), corticosteroids, antibiotics, immune modulators and immunosuppressive agents such as azathioprine, 6-mercaptopurine, and cyclosporine. Corticosteroids and immunosuppressive agents are associated with significant risks of unwanted side effects and not all patients respond to these medications. For 5-ASA agents, these medications are generally safe but only induce remission in approximately 50% of patients with UC (24). It is, therefore, essential to develop newer therapeutic interventions for patients with IBD. A growing body of evidence indicates that PPARα and PPARγ have an anti-inflammatory effect on IBD and its agonists might serve as a new class of effective therapy for IBD. The role of PPARδ in IBD remains ambiguous. This deserves significant attention and future research must be directed to better understand the role of PPARs in regulating chronic inflammation in IBD.

## PPARα

PPARα is highly expressed in mouse colonic epithelial cells facing the intestinal lumen (25) and its expression induced by glucocorticoids (GC) (26). Subsequent studies further demonstrated that PPARα mediates anti-inflammatory effects of GC in a mouse model of chemically-induced colitis (27). In this study, treatment with dexamethasone, a potent synthetic member of the glucocorticoid class of steroid drugs, suppressed dinitrobenzene sulfuric acid (DNBS)-induced colitis formation in wild-type mice, but not in PPARα knockout mice. Consistent with the above results, deletion of PPARα promoted more severity of colitis in DNBS-treated mice, whereas activation of PPARα by its agonist acvtivity significantly reduced colonic inflammation in this mouse model (28). However, there is no report thus far, on of the precise role of PPARα in genetic models of IBD (transgenic and knock-out models).

## PPARγ

Although PPARγ is predominantly present in the liver and adipose tissue, it is also expressed in the intestinal epithelium, immune cells and adipocytes. However, patients with UC, but not CD, show decreased PPARγ levels in colon epithelial cells in comparison to normal controls (29). This observation raises the hypothesis that microbe-host interactions, chronic inflammation and/or genetic predisposition may lead to low PPARγ levels in colonic epithelial cells, which in turn may result in unrestrained inflammation. Several lines of evidence support the notion that PPARγ may serve as a new therapeutic target in IBD. In mouse models of chemically-induced colitis, 5-ASA treatment had a beneficial effect on colitis only in wild-type but not in heterozygous $PPAR\gamma^{+/-}$ mice, demonstrating that PPARγ mediates the anti-inflammatory effect of 5-ASA (30). Furthermore, treatment of a PPARγ ligand, thiazolidinedione, markedly reduced colonic inflammation in mouse models of chemically-induced colitis (31,32) and IL-10 deficient mice (a genetic model of colitis) (33), suggesting that activation of PPARγ suppresses inflammation in IBD.

Since PPARγ is expressed in intestinal epithelial cells, macrophage, and T and B lymphocytes, it is critical to understand the contribution of PPARγ in each cell type to this protection. The

results from two studies showed that the disruption of PPARγ in colonic epithelial cells worsened colonic inflammatory lesions in DSS-treated mice, indicating that PPARγ expression in epithelial cells is required for the prevention of experimental IBD (34,35). Similarly, mice with deficiency of PPARγ in CD4 T cells are more sensitive to trinitrobenzene sulfonic acid-induced colitis, because the deficiency of PPARγ in Treg cells impaired their ability to prevent effector CD4 T cell-induced colitis (36). Moreover, mice with a targeted disruption of PPARγ in macrophages displayed an increased susceptibility to DSS-induced colitis compared with wild-type littermates, demonstrating that PPARγ is required for macrophage-mediated protection against colitis (37). Consistent with these results, an increase in PPARγ expression by adenovirus-mediated gene transfer attenuated colonic inflammation induced by DSS in mice (38). In addition, a recent study showed that the anti-inflammatory effects of PPARγ on IBD is via maintenance of innate antimicrobial immunity in the mouse colon (39). Importantly, the studies from one randomized placebo-controlled trial and one open-label trial showed that a PPARγ agonist, rosiglitazone, has therapeutic efficacy in humans with UC (40,41). Collectively, all of these studies support a rationale to develop PPARγ agonists as potential therapeutic and prophylactic agents against IBD.

### PPARδ

Relatively little is known about the role of PPARδ in IBD and the results from two mouse models of IBD are controversial. Deletion of PPARδ significantly exacerbated colitis, whereas treatment of a PPARδ agonist didn't affect the clinical symptoms in the DSS-treated mouse model (42). This study implies that PPARδ, like PPARγ, exerts anti-inflammatory effects in IBD via a ligand independent mechanism. In contrast with this observation, administration of a PPARδ agonist caused enhanced colitis in IL-10-deficient mice (a genetic model of colitis), suggesting that PPARδ has a pro-inflammatory effect (43). Therefore, further studies are necessary to clarify the biological functions of PPARδ in the modulation of IBD.

## PPARS AND COLORECTAL CANCER

In addition to these metabolic and inflammatory properties, the roles of PPARs in CRC progression have been extensively investigated. PPARs can function as either tumor suppressors or accelerators, suggesting that these receptors are potential candidates as drug targets for cancer prevention and treatment.

### PPARα

Less is known about the role of PPARα in human cancers although long-term administration of a PPARα agonist induces the development of hepatocarcinomas in mice but not in PPARα null animals, conclusively demonstrating that PPARα mediates these effects in promoting liver cancer (44). In spite of the fact that activation of PPARα by exogenous agonists generally causes inhibition of tumor cell growth in cell lines derived from CRC, melanoma, and glial brain tumors (45-47), the physiological significance of PPARα in the regulation of CRC progression is also less well characterized than that of PPARγ and PPARδ,

### PPARγ

Due to elevated expression of PPARγ in CRC (48) and its involvement in regulating cellular differentiation, PPARγ has become a point of interest in CRC studies. However, studies of PPARγ mutation in human colon tumor samples and CRC cell lines have produced controversial results. One study showed that 8% of primary human colorectal cancers had a loss of function mutation in one allele of the PPARγ gene (49). Recent data revealed that a Pro12Ala (P12A) polymorphism in the *PPARγ* gene is associated with an increased risk of CRC (50,51). These results suggest a putative role for this receptor as a tumor suppressor. In

contrast, another study showed that the mutant PPARγ gene was not detected in human colon carcinoma samples or CRC cell lines, suggesting that PPARγ mutations in human CRC may be a rare event (52).

It is well established that activation of PPARγ results in growth arrest of colon carcinoma cells through induction of cell-cycle arrest or/and apoptosis in numerous *in vitro* studies. However, the effect of PPARγ on CRC progression *in vivo* is controversial due to conflicting results from different mouse models of colon cancer. Although PPARγ agonists inhibit colorectal carcinogenesis in xenograft models and in the azoxymethane (AOM)-induced colon cancer model (53,54), these drugs are reported to have either tumor-promoting or tumor- inhibiting effects in a mouse model of FAP, the $Apc^{Min/+}$ mouse. Multiple studies showed that administration of PPARγ agonists significantly increased the number of colon adenomas in the $Apc^{Min/+}$ mice (55-57) and even in wild-type C57BL/6 mice (58). However, other studies showed that treatment of 2 different Apc mutant models ($Apc^{Min/+}$ and $Apc^{\Delta 1309}$) with a PPARγ agonist pioglitazone resulted in a reduction of polyp number in both small and large intestines in a dose-dependent manner (59,60). These divergent effects of PPARγ might be related to drug doses and bioavailability and/or the animal models employed. These paradoxical observations appear to have been resolved by genetic studies, showing that the heterozygous disruption of PPARγ is sufficient to increase tumor number(s) in AOM-treated mice and that intestinal-specific PPARγ knockout promotes tumor growth in $Apc^{Min/+}$ mice (61,62). Thus, genetic evidence supports the hypothesis that PPARγ serves as a tumor suppressor in CRC. In addition, a combined treatment of mice with a selective COX-2 inhibitor and a PPARγ agonist significantly inhibited both the incidence and multiplicity of inflammation-associated colonic adenocarcinoma induced by AOM/DSS (63). Interestingly, a retrospective cohort study revealed that treatment of diabetic patients with a PPARγ agonist (thiazolidinediones) exhibited a mild trend toward a risk reduction of CRC, although this difference did not reach statistical significance (64). Collectively, these findings further support a rationale to develop PPARγ agonists as anti-tumor agents.

## PPARδ

The role of PPARδ in colorectal carcinogenesis is more controversial than that of PPARγ. The first evidence linking PPARδ to carcinogenesis actually emerged from studies on gastrointestinal cancer. PPARδ was identified as a direct transcriptional target of APC/b-catenin/Tcf pathway and as a repression target of NSAIDs (65,66). A large case-control study showed that the protective effect of NSAIDs against colorectal adenomas was reported to be modulated by a polymorphism in the *PPAR*™ gene (67). Moreover, COX-2-derived $PGI_2$ directly transactivates PPARδ (68) and COX-2-derived $PGE_2$ indirectly induces PPARδ activation in CRC, hepatocellular carcinoma, and cholangiocarcinoma cells (69-71). In addition, PPARδ expression and activity are also induced by oncogenic K-Ras (72). These studies indicate that PPARδ is a focal point of cross-talk between oncogenic signaling pathways.

Similar to PPARγ, investigation of PPARδ expression in human and mouse colon tumor samples and CRC cell lines generated controversial results. Some reports showed that PPARδ is elevated in most human colorectal cancers and in tumors arising in the $Apc^{Min/+}$ mice and AOM-treated rats (65,68), in agreement with the observations that activation of the b- catenin/Tcf pathway by *APC* mutation or K-Ras upregulates PPARδ expression. Importantly, the PPARδ proteins are accumulated only in human CRC cells with highly malignant morphology (73). Downregulation of PPARδ is correlated with anti-tumor effects of dietary fish oil/pectin in rats treated with radiation and AOM (74). However, other reports showed that PPARδ expression is lower in human cancer tissues and adenomas from the $Apc^{Min/+}$ mice than normal control tissues (75,76).

In a murine xenograft cancer model, the disruption of both PPARδ alleles by deletion of its exons 4-6 in human HCT-116 colon carcinoma cells decreased tumorigenicity, suggesting that activation of PPARδ promotes tumor growth (77). To further determine whether PPARδ attenuates or promotes intestinal tumor growth, three mouse models of CRC were employed, including AOM-treated mice, $Apc^{Min/+}$ mice and *Mlh*-null mice. The *Mlh* is a DNA mismatch repair gene that is involved in hereditary non-polyposis CRC. Conflicting data was obtained from studies in AOM-treated and $Apc^{Min/+}$ mice. For example, activation of PPARδ by a selective synthetic PPARδ agonist (GW501516) or a PPARδ endogenous activator ($PGE_2$) accelerated intestinal adenoma growth in $Apc^{Min/+}$ mice by promoting tumor cell survival (69,78). In contrast, another PPARδ ligand (GW0742) inhibited colon carcinogenesis in AOM-treated mice, but promoted small intestinal polyp growth in $Apc^{Min/+}$ mice (79). It is not clear whether PPARδ mediates the effects of GW0742 in this model. A genetic study showed that loss of PPARδ by deletion of its exons 4-5 attenuated both small and large intestinal adenoma growth and demonstrated that PPARδ mediated the tumor-promoting effects of the PPARδ ligand (GW501516) and $PGE_2$ in $Apc^{Min/+}$ mice (69,80). A recent study with a tissue-specific deletion of PPARδ exon 4, inhibited colonic carcinogenesis in AOM-treated mice (81), further confirmed the notion that PPARδ serves as a tumor accelerator. On the other hand, several other studies have shown different results when using PPARδ mutant mice generated by germline deletion of PPARδ exon 8. Deletion of PPARδ exon 8 enhances polyp growth in $Apc^{Min/+}$ and AOM-treated mice, in the absence of exogenous PPARδ stimulation (76,82). In *Mlh*-null mice, no significant differences are evident in the number and size of intestinal adenomas between wild-type and PPARδ mutant mice (deletion of PPARδ exon 8) (76). The conflicting results regarding the effect of PPARδ on intestinal tumorigenesis in $Apc^{Min/+}$ and AOM-treated mice may have been attributed to differences in the specific targeting strategy employed to delete PPARδ. Deletion of PPARδ exon 4 and/or 5, which encode an essential portion of the DNA binding domain, is thought to disrupt PPARδ function as a nuclear transcriptional factor and to inhibit tumorigenesis. The deletion of exon 8, the last PPARδ exon, is postulated to generate a hypomorphic allele, which retains some aporeceptor function. Indeed, the observation that the high rates of embryonic mortality, subsequent to abnormal trophoblastic giant cell differentiation and abnormal placental development occurred in deletion of PPARδ exon 4-5, but not in deletion of PPARδ exon 8 mice supports this hypothesis (83,84). Taken together, not enough evidence is available to establish whether PPARδ has pro- or anti-tumorigenic effects on CRC progression and the role of PPARδ in cancer biology remains unclear.

## SUMMARY

Emerging evidence indicates that PPARγ suppresses inflammation in IBD and tumor growth in CRC. In contrast to PPARγ, conflicting results have emerged regarding the role of PPARδ in IBD and colon carcinogenesis. Therefore, further investigation is warranted prior to considering modulation of PPARδ as an effective therapy for chemoprevention and treatment of IBD and CRC.

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