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Review Article

Peroxisome Proliferator-Activated Receptors and Progression of Colorectal Cancer

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The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily. These receptors are also ligand-dependent transcription factors responsible for the regulation of cellular events that range from glucose and lipid homeostases to cell differentiation and apoptosis. The importance of these receptors in lipid homeostasis and energy balance is well established. In addition to these metabolic and anti-inflammatory properties, emerging evidence indicates that PPARs can function as either tumor suppressors or accelerators, suggesting that these receptors are potential candidates as drug targets for cancer prevention and treatment. However, conflicting results have emerged regarding the role of PPARs on colon carcinogenesis. Therefore, further investigation is warranted prior to considering modulation of PPARs as an efficacious therapy for colorectal cancer chemoprevention and treatment.

1. INTRODUCTION

Understanding the biology of intestinal epithelial cells may reveal the molecular pathogenesis of a number of digestive diseases. One such disease, colorectal cancer (CRC), leads to significant cancer-related morbidity and mortality in most industrialized countries. Initiation and progression of CRC are a complex process that results from the loss of the normal regulatory pathways that govern a balance between epithelial cell proliferation and death. For example, alterations in multiple pathways such as Wnt/APC, COX-2, and Ras are known to play major roles in CRC progression. The standard treatment for advanced malignancies has improved greatly over the past decade but is still not satisfactory. Therefore, significant effort has been exerted to identify novel drug targets for both the prevention and treatment of this disease. One group of compounds found to decrease the risk of colorectal cancer includes nonsteroidal anti-inflammatory drugs (NSAIDs), which target the cyclooxygenase enzymes (COX-1 and COX-2). However, prolonged use of high doses of these inhibitors (except for aspirin) is associated with unacceptable cardiovascular side effects [1–3]. Thus, it is now crucial to develop more effective chemopreventive agents with minimal toxicity and maximum benefit.

Dietary fat intake is an environmental factor that is associated with some human diseases such as diabetes, obesity, and dyslipidemias. Some nuclear hormone receptors play a central role in regulating nutrient metabolism and energy homeostasis. These nuclear receptors are activated by natural ligands, including fatty acids and cholesterol metabolites. Among these receptors, special attention has been focused on the members of the peroxisome proliferator-activated receptors (PPARs) family, which were initially identified as mediators of the peroxisome proliferators in the early 1990s [4]. PPARs play a central role in regulating the storage and catabolism of dietary fats via complex metabolic pathways, including fatty acid oxidation and lipogenesis [5]. 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 expresses in diverse tissues [6]. In common with other members of the type II

steroid hormone receptor superfamily, PPARs are ligand-dependent transcription factors and form heterodimers with another obligate nuclear receptors, such as retinoid X receptors (RXRs) [4, 7, 8]. Each PPAR-RXR heterodimer binds to the peroxisome proliferator responsive element (PPRE) located in the promoter region of responsive genes.

It is well established that modulation of PPAR activity maintains cellular and whole-body glucose and lipid homeostases. Hence, great efforts have been made to develop drugs targeting these receptors. For example, PPARγ synthetic agonists, rosiglitazone and pioglitazone, are antidiabetic agents which suppress insulin resistance in adipose tissue. The antiatherosclerotic 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 important roles of PPARδ in regulating lipid metabolism and energy homeostasis. Genetic studies indicate that overexpression of constitutively active PPARδ in mouse adipose tissue reduced hyperlipidemia, steatosis, and obesity induced by either genetics or a high-fat diet. In contrast, PPARδ null mice treated in similar fashion exhibited an obese phenotype [9]. Pharmacologic studies demonstrate that the PPARδ selective-agonist (GW501516) attenuated weight gain and insulin resistance in mice fed with high-fat diets [10] and increased HDL-C while lowering tryglyceride levels and insulin in obese rhesus monkeys [11]. Furthermore, preclinical studies revealed that PPARδ agonists diminished metabolic derangements and obesity through increasing lipid combustion in skeletal muscle [12]. These results suggest that PPARδ agonists are potential drugs for use in the treatment of dyslipidemias, obesity, and insulin resistance. Therefore, the PPARδ agonist (GW501516) is currently in phase III clinical trials to evaluate its use for treatment of patients with hyperlipidemias and obesity. However, recent studies showing that some agonists of PPARs promote carcinogenesis in animal models have raised concerns about using these agonists for the treatment of metabolic diseases. For example, 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 [13]. Furthermore, the PPARδ agonist (GW501516) accelerates intestinal polyp growth in $Apc^{Min/+}$ mice [14, 15]. These results raise concerns for developing this class of agents for human use and support the rationale for developing PPARδ antagonists as chemopreventive agents.

2. PPARs AND COLORECTAL CANCER

Significant effort has been concentrated on deducing the role of PPARs in CRC and other cancers. A large body of evidence indicates that PPARγ serves as a tumor suppressor. Contradictory evidences suggest that PPARδ can act as either a tumor suppressor or tumor promoter. A few evidences support a role of PPARα in CRC.

2.1. PPARα

Although the tumor-promoting effects of PPARα in hepatocarcinomas are clear, less is known about the role of PPARα in human tumors. Generally, activation of PPARα by exogenous agonists causes inhibition of tumor cell growth in cell lines derived from CRC, melanoma, and glial brain tumors [16–18]. There is no evidence showing that PPARα expression is elevated in human cancers.

2.2. PPARγ

The prominent role of PPARγ in regulating cellular differentiation prompted a great effort to investigate the function of PPARγ in cancer field. While PPARγ is elevated in CRC [19], suggesting that this receptor may contribute to tumor biology, studies of PPARγ mutation in CRC from humans, animals, and cultured cells produced controversial results. One study showed that 8% of primary human colorectal tumors had a loss of function mutation in one allele of the PPARγ gene [20]. Recent data revealed that a Pro12Ala (P12A) polymorphism in the PPARγ gene is associated with increased risk of CRC [21, 22]. These results suggest a putative role for this receptor as a tumor suppressor. In contrast, another study showed that mutant PPARγ gene has not been detected in human colon tumor samples and CRC cell lines, suggesting that PPARγ mutations in human CRC is a rare event [23].

In vitro studies show that activation of PPARγ results in growth arrest of colon carcinoma cells through induction of cell-cycle arrest or/and apoptosis. Several potential downstream targets of PPARγ for mediating antitumor effects of PPARγ have been identified in various cancer cell types. Activation of PPARγ negatively regulatescell cycle progression by modulating a number of cell cycle regulators: (1) inhibiting E2F activity in transformed adipogenic cells [24], (2) Rb hyperphosphorylation in vascular smooth muscle cells and pituitary adenoma cells [25, 26], (3) cyclin D1 expression in Ras-transformed intestinal epithelial cells, pancreatic, or breast cancer cells [27–29], and (4) inducing CDK inhibitor expression such as p18, p21, and p27 in hepatoma cells [30]. Activation of PPARγ has also been reported to inhibit tumor cell growth by upregulation of the transcriptional repressor TSC22 in colon cancer cells [31] and GADD153 in nonsmall-cell lung carcinoma cells [32]. PPARγ agonists induce apoptosis by induction of PTEN expression in pancreatic, breast, and colon cancer cells [33] and inhibition of NFκB and Bcl-2 expression in colon cancer cells [34]. Moreover, PPARγ exhibits antiangiogenic effects by inhibiting VEGF expression in tumor cells and VEGF receptors in endothelial cells [35, 36]. It has also been reported that PPARγ agonists suppress tumor cell invasion in colon and breast cancer cells by downregulation of matrix metalloproteinase-7 (MMP-7) and induction of MMP inhibitors [37, 38]. In addition, the ability of PPARγ to suppress tumor growth is also through inhibiting APC/β-catenin and COX-2/PGE_2 signaling pathways, which are pivotally involved in colon carcinogenesis [39–42].

However, the role of PPARγ in colorectal cancer progression is controversial because there are conflicting results in mouse models of colon cancer. Although PPARγ agonists inhibit colorectal carcinogenesis in xenograft models and in the azoxymethane (AOM)-induced colon cancer model [43, 44], these drugs are reported to have both tumor-promoting and tumor-inhibiting effects in a mouse model for familial adenomatous polyposis, the $Apc^{Min/+}$ mouse. It has been reported that administration of PPARγ agonists significantly increases the number of colon adenomas in the $Apc^{Min/+}$ mice [45–47] and even in wild-type C57BL/6 mice [48]. However, other studies show that treatment of 2 different Apc-mutant models ($Apc^{Min/+}$ and $Apc^{\Delta 1309}$) with the PPARγ agonist pioglitazone resulted in reduction in the number of both small and large intestinal polyps in a dose-dependent manner [49, 50]. These paradoxical observations appear to have been resolved by genetic studies showing that the heterozygous disruption of PPARγ is sufficient to increase tumor number in AOM-treated mice and that intestinal-specific PPARγ knockout promotes tumor growth in $Apc^{Min/+}$ mice [39, 51]. These genetic evidences support the hypothesis that PPARγ serves as tumor suppressor in colorectal cancer. One possible explanation for the differences in phenotype caused by pharmaceutical versus genetic manipulation of PPARγ in mouse models may be due to the PPARγ-independent effect of the agonist drugs, drug doses used, and animal models employed. This controversial extends beyond CRC. For example, data are conflicting from different animal models of breast cancer as well. PPARγ agonist suppresses NMU-induced mammary carcinomas [52]. However, overexpression of a constitutively active form of PPARγ accelerates mammary gland tumor development in MMTV-PyV transgenic mice [53].

2.3. PPARδ

PPARδ has been shown to play an important role in embryo implantation [54], atherogenic inflammation [55], regulating cell survival in the kidney following hypertonic stress [56], and skin following wound injury [57, 58]. The role of PPARδ in colorectal carcinogenesis is more controversial than that of PPARγ. The first evidence linking the PPARδ to carcinogenesis actually emerged from studies on gastrointestinal cancer. PPARδ is elevated in most human colorectal cancers and in tumors arising in the $Apc^{Min/+}$ mice, and AOM-treated rats [59, 60]. Importantly, the PPARδ proteins are accumulated only in human CRC cells with highly malignant morphology [61]. Downregulation of PPARδ is correlated with antitumor effects of dietary fish oil/pectin in rats treated with radiation and AOM [62]. PPARδ was identified as a direct transcriptional target of APC/β-catenin/Tcf pathway and as a repression target of NSAIDs [59, 63]. A case-control study in a large population showed that the protective effect of NSAIDs against colorectal adenomas was reported to be modulated by a polymorphism in the PPARδ gene [64]. PPARδ expression and activity are also induced by oncogenic K-ras [65]. In addition, COX-2-derived PGI_2 directly transactivates PPARδ [60], and COX-2-derived PGE_2 indirectly induces PPARδ activation in CRC, hepatocellular carcinoma, and cholangiocarcinoma cells [66–68]. These studies indicate that PPARδ is a focal point of cross-talk between these signaling pathways.

In a murine xenograft cancer model, the disruption of both PPARδ alleles in human HCT-116 colon carcinoma cells decreased tumorigenicity, suggesting that activation of PPARδ promotes tumor growth [69]. However, PPARδ has been reported to have both tumor-promoting and tumor-inhibiting effects based on conflicting data obtained from mouse models of colon cancer. For example, activation of PPARδ by a selective synthetic PPARδ agonist (GW501516) or a PPARδ endogenous activator (PGE_2) accelerates intestinal adenoma growth in $Apc^{Min/+}$ mice by promoting tumor cell survival [14, 66]. A subsequent genetic study showed that deletion of PPARδ attenuates both small and large intestinal adenoma growth, and PPARδ is required for the tumor-promoting effects of PPARδ ligand (GW501516) and PGE_2 in $Apc^{Min/+}$ mice [15, 66]. Another study showed that loss of PPARδ in $Apc^{Min/+}$ mice significantly reduced growth of tumors larger than a diameter of 2 mm, even though PPARδ deficiency did not affect overall tumor incidence [70]. In contrast to these reports suggesting that PPARδ serves as tumor accelerator, recent conflicting reports show that PPARδ deficiency enhances polyp growth in $Apc^{Min/+}$ and AOM-treated mice in the absence of exogenous PPARδ stimulation [71, 72]. Moreover, a PPARδ ligand (GW0742) inhibits colon carcinogenesis in AOM-treated mice but promotes small intestinal polyp growth in $Apc^{Min/+}$ mice [73].

One explanation for these disparate results may be due to differences in the genetic background of $Apc^{Min/+}$ mice, animal breeding, or possibly to differences in the specific targeting strategy employed to delete PPARδ. For example, the average number of polyps in 13-week old $Apc^{Min/+}$ mice on a C57BL/6 genetic background is about 50, while the polyp number in $Apc^{Min/+}$ mice on a mixed-genetic-background (C57BL/6 $\times$ 129/SV) is about 120. Our results also show that the breeding strategy affects the number and size of polyps in mice even on the same genetic background. Mice generated by breeding female $PPAR\delta^{-/-}/Apc^{Min/+}$ with male $PPAR\delta^{-/-}/Apc^{+/+}$ exhibit increased adenoma number with a larger average size than those obtained by breeding female $PPAR\delta^{-/-}/Apc^{+/+}$ with male $PPAR\delta^{-/-}/Apc^{Min/+}$. Finally, the PPAR$\delta$ null mice we studied were obtained from Beatrice Desvergne in Switzerland. These mice were generated by deleting exons 4 and 5 encoding the DNA binding domain [74], while Peters group generated the PPARδ knockout mice by inserting a neomycin resistance cassette into the last exon (exon 8) [75]. It has been suggested that the strategy employed to disrupt PPARδ by the Peters group might have led to a hypomorphic allele, which retains some aporeceptor function, thus making it difficult to correctly interpret their results. Indeed, conflicting results in the context of embryonic lethality have also been observed from these two PPARδ mutant mouse strains [74, 75]. To further clarify the role of PPARδ in colorectal tumorigenesis, it is important to investigate the role of PPARδ in animal models that are dependent on activation of other oncogenes

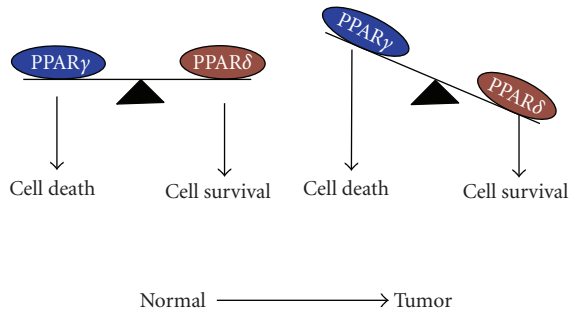

Figure 1: A potential model for PPARs regulating colorectal tumor growth.

or disruption of other tumor suppressors to verify our conclusions that activation of PPARδ is proneoplastic.

Studies in other types of cancer also support the hypothesis that PPARδ serves as a tumor accelerator. A selective PPARδ agonist (GW501516) has been shown to stimulate proliferation of human breast, prostate, and hepatocellular carcinoma cells [68, 76, 77]. In a xenograft model, blocking PPARδ activation reduced ovarian tumor growth [78]. PPARδ knockout mice exhibited significant impaired angiogenesis and tumor growth after these mice were injected s.c. with mouse Lewis lung carcinoma and melanoma cells [79]. In a mouse mammary tumor model, treatment with the PPARδ agonist (GW501516) accelerated tumor formation, while a PPARγ agonist (GW7845) delayed tumor growth [80]. Taken together, the role of PPARδ in cancer biology remains unclear.

3. SUMMARY

Despite extensive research on both PPARγ and PPARδ in CRC, the role of these receptors remains highly controversial in this disease. Emerging evidence demonstrates that cooperative interactions between Wnt, COX-2, and PPARs signaling pathways can initiate cellular transformation and promote progression of colorectal cancer. These studies provide support for evaluating the efficacy of PPARδ antagonists for cancer prevention and/or treatment. We propose a potential working model as a useful starting point for future studies (see Figure 1).

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