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<td>Author(s)</td>
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<tr>
<td>Citation</td>
<td>Ppar Research, 2009</td>
</tr>
<tr>
<td>Issued Date</td>
<td>2009</td>
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<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10722/124952">http://hdl.handle.net/10722/124952</a></td>
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Review Article

Current Understanding of the Role of PPARγ in Gastrointestinal Cancers

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Received 16 July 2009; Accepted 28 August 2009

Recommended by Howard Glauert

Numerous studies have indicated that PPARγ plays multiple roles such as in inflammation, cell cycle control, cell proliferation, apoptosis, and carcinogenesis, thus PPARγ contributes to the homeostasis. Many in vitro studies have showed that ligand-induced activation of PPARγ possess antitumor effect in many cancers including CRC. However, the role of PPARγ in gastrointestinal cancers, especially in colorectal cancer, is rather controversial. Nevertheless, some recent studies with the positive results on the possible application of PPARγ ligands, such as Bezafibrate or Rosiglitazone in gastrointestinal cancers, have suggested a potential usefulness of PPARγ agonists in cancer prevention and therapy. In this review, the authors discuss the recent developments in the role of PPARγ in gastrointestinal cancers.

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1. An Overview of PPAR Family

Peroxisome proliferator-activated receptor (PPAR) is a member of a family of nuclear hormone receptors that consists of three isoforms: PPARα, PPARγ, and PPARδ (also known as PPARβ). Within this family are also retinoid X receptor (RXR), vitamin D receptor, and the thyroid hormone receptor. PPARs act as a ligand-activated transcription factor and are involved in many different biological functions. Extensive study of PPARs was probably sparked by the identification of PPARα in 1990 [1], which was soon followed by the identification of two other members PPARγ and PPARδ [2, 3]. Each isoform of PPARs is encoded by a separate gene and exhibits different tissue distribution patterns. For example, PPARα is principally expressed in tissues that exhibit a high rate of fatty acid metabolism (e.g., brown adipose tissue, liver, kidney, and heart) and is the primary target for the fibrate class of drugs [4]. PPARδ is ubiquitously expressed in many tissues, and its physiological roles are multiple, including but may not be limited to lipid trafficking [5, 6], blastocyst implantation [7], wound healing [8], and the regulation of fatty acid catabolism and energy homeostasis [9, 10]. PPARγ is richly expressed in adipose tissue, intestinal epithelial cells [11, 12], and macrophages. Low level of PPARγ has also been found in skeletal muscle [13].

Like other nuclear receptors (NRs), all PPARs share a similar modular structure with functionally distinct domains called A/B (ligand-independent activation domain), C (DNA binding domain), D (hinge domain), and E/F (ligand-binding domain, LBD) (Owen et al. [14]). The N-terminal domain A/B has been relatively well conserved through evolution, whereas the C domain is the most conserved of all the functional domains. The less conserved domain D functions as a flexible hinge between the C and E/F domains and contains a sequence recognized by transporting proteins. Some of the amino acids are involved in the activities of nearby domains, leading to the dimerization and recognition of the target DNA sequences (Owen et al. [14]). The largest domain is the LBD located at the C-terminus [15], which is responsible for the binding of a specific ligand to PAR receptors, and subsequent activation of PPAR through binding to peroxisome proliferators response elements (PPREs) on the promoter region of the target genes. Thus, LBD is the major functionally related domain of the PPARs.
PPARs seem to regulate gene transcription by two mechanisms: transactivation and protein-protein interaction with other transcription factors. Transactivation of PPARs is a DNA-dependent mechanism, which involves binding of the PPAR ligands and heterodimerization between PPARs and RXR (Retinoid X receptor) [16]. The heterodimer between PPARs and RXR then binds to PPRE, resulting in stimulation of transcription. In contrast, the protein-protein interaction mechanism involves the activation of target genes through other transcription factors, such as AP1, NF-kB, Smads, STATs, and NFATs. It is suggested that most of inhibitory effects of PPARs are mediated by this mechanism [17, 18].

In this review, we only focus on the controversial role of PPARγ human gastrointestinal cancers.

2. PPARγ

In human, the PPARγ gene is located on chromosome 3 at position 3p25.2 [19]. Two isoforms of PPARγ have been identified: PPARγ1 and PPARγ2. These two isoforms only differ in their N termini sequences: PPARγ2 protein contains an additional 30 N-terminal amino acids, but is otherwise identical to PPARγ1. Both PPARγ1 and PPARγ2 N termini function as translational initiators, but the activity of PPARγ2 is higher than that of PPARγ1, suggesting that PPARγ1 and PPARγ2 N termini have distinct activation capacities, and perhaps may have different functions. PPARγ2 is predominantly expressed in adipose tissue, and it has been demonstrated that PPARγ2 N termini is more important in the process of adipocyte differentiation and metabolism [20, 21]. In contrast, PPARγ1 is relatively stable and expressed at very high levels in the gastrointestinal epithelium [12, 22, 23], and low levels were observed in many other tissues [24].

The function of PPARγ relies on its interactions with a coactivator or corepressor. Binding of PPARγ to a coactivator affects the chromatin structure through acetylation of histones, whereas binding of PPARγ to a corepressor alters the chromatin structure through deacetylation of histones. Both coactivators and corepressors are highly versatile and are not specific for particular PPAR subtypes [25]. Binding of PPARγ with coactivators may be either ligand-dependent or ligand-independent. Most coactivators interact with the LBD of NRs utilizing the LXXLL helical motifs in a ligand-dependent manner [26, 27]. In contrast, PPARγ coactivator-1α (PGC-1α) binds to the hinge domain of PPARγ in a ligand-independent manner [28]. In addition to the ligand-dependent and ligand-independent activation of PPARγ, the activity of this transcription factor may also be modulated by posttranscriptional modification, such as phosphorylation [29–31].

3. PPARγ Ligands

Over the past several years, various natural and synthetic PPARγ ligands have been identified, and new ligands are under fast development.

In the broad sense, these ligands include specific PPARγ agonists [32], PPARγ partial agonists [33], and PPARα/γ dual agonists [34]. Synthetic PPARγ agonists are able to modulate the adipocyte differentiation, and thus have been used as potential antidiabetic drugs [20, 32, 33]. The most commonly used PPARγ agonists are Thiazolidinediones (TZDs), which include Troglitazone (Rezulin), Pioglitazone (Actos), and Rosiglitazone (Avandia).

Toxins are widely used in animal studies and clinical trials to investigate the role of PPARγ. The roles of PPARγ ligands are multiple. Some TZDs have been licensed for use in patients with Type 2 diabetes mellitus (T2DM) [35], some may benefit cardiovascular parameters, such as lipids, blood pressure, inflammatory biomarkers, endothelial function, and fibrinolytic state [36, 37]. Moreover, they have been successfully used in nondiabetic insulin-resistant conditions such as polycystic ovary syndrome [38, 39]. The synthetic PPARγ ligands, however, are associated with various side effects, such as increased adiposity, edema, hepatotoxicity, and cardiac hypertrophy. Therefore, partial PPARγ ligands with weaker side effects such as LSN862 have been developed [33, 40], and newer PPARγ ligands that do not fall into the category of TZDs are under active development and their biological activities have been tested in various cancer cells. For example, the roles of LY293111 (Eli Lilly), CS-7017 (Sankyo), Spirolaxine (Sigma-Tau), and TZD-18 (Merck) have been investigated in various in vitro systems, and some are under clinical trials [41–45].

In addition to synthetic ligands, some endogenous (or natural) compounds are potent activators for PPARγ. Among the natural PPARγ ligands is cyclopentone 15-deoxy-E12,14-prostaglandin J2 (15d-PGJ2). This agent is probably the most potent endogenous PPARγ ligand [46, 47] and has been widely used to study the role of PPARγ activation in cancer cells [48].

4. Role of PPARγ in Tumorigenesis of Gastrointestinal Cancers

As discussed earlier, PPARγ is richly expressed in the normal gastrointestinal epithelium. Significantly high level of PPARγ has been observed in the highly differentiated epithelial cells of the proximal colon [11, 12] and small intestine [12, 49]. In small intestine, PPARγ is particularly expressed at the crypt/villus junction where small intestine epithelial cells cease to proliferate and undergo differentiation to mature to functional villus epithelial cells. These observations indicate that PPARγ might play an important role in the regulation of differentiation of gastrointestinal epithelial cells. The fact that PPARγ is expressed at a much higher level in the proximal colon than in distal colon implies that PPARγ may play a complex role in the colon. The mechanisms by which PPARγ regulates the differentiation of human gastrointestinal epithelial cells are not yet clear, but may involve a collaboration of PPARγ with the transcription factor Hic5 as the transactivation of Hic5 by PPARγ was shown to promote differentiation of intestinal epithelial cells during embryonic development [50].
The expression pattern of PPARγ in colon cancer has been previously reported. Loss-of-function mutations to PPARγ have been reported to be associated with increased propensity of human colon cancers [51] although the mutation of PPARγ is very rare [52]. Many in vitro studies have revealed that activation of PPARγ inhibits proliferation and induces apoptosis of some colon cancer cell lines [53–60]. Compatible with these findings, heterozygous loss of PPARγ increases the susceptibility of colon and stomach into carcinogen-induced colon cancer and gastric cancer, respectively, [61–63]. Biallelic knockout of PPARγ in colonic epithelial cells resulted in increased tumor incidence and tumor size in APC+/Min mice [64], and Pioglitazone suppressed colon tumor growth in APC+/Min mice in a dose-dependent manner [65–67]. Similar results were reported in studies conducted in other animal models. Troglitazone inhibited the formation of preneoplastic colonic aberrant crypt foci (ACF) in rats treated with either AOM or the combination of AOM with dextran sulfate (DSS) [68, 69]. Several PPARγ ligands including pioglitazone, rosiglitazone, and RS5444 have been reported to inhibit ACF formation in AOM-mediated colon cancer models [12, 67]. All these studies have suggested that PPARγ functions as a tumor-suppressor gene and it might be involved in cancer suppression under the physiological conditions.

Carcinogenesis usually results from an imbalanced cell proliferation and apoptosis. The inhibitory effect of PPARγ activation on colon cancer could be attributed to several mechanisms. For example, ligands-induced activation of PPARγ was found to inhibit phosphatidylinositol 3-kinase (PI3K)/Akt signaling and retinoblastoma protein (Rb) dephosphorylation [70], induce expression of cyclin D1 [71] and Bcl-xl/Bcl-2 [72], upregulate p21 and p27 [73–75], interact with XIAP [76], upregulate PTEN [77], and enhance the sensitivity of tumor cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induced cell death [78]. Inhibition of hyperlipidemia, a well-established oncogenic factor for colon cancer, has also been proposed as one of the mechanisms responsible for the inhibitory effect of PPARγ ligand on colon cancer [65, 66].

Although induction of apoptosis by PPARγ agonists has been frequently suggested as one of the mechanisms responsible for their anticancer effects, it is less clear and perhaps controversial whether PPARγ-induced apoptosis is actually receptor-mediated, or apoptosis simply occurs as an off target effect of PPARγ agonists.

To complicate the issues even further is the fact that the inhibitory effect of PPARγ activation on colon cancer formation does not have a universal support. For example, two PPARγ agonists, troglitazone and rosiglitazone, have been reported to promote gastrointestinal tumorigenesis in C57BL/6J APCMin/+ mice [11, 79], raising the serious concerns about the possibility that individuals who are on TZDs for T2DM might be at risk for colon cancer. These results were not able to be reproduced by other studies [65, 66]. On the contrary, long-term treatment with high concentrations of TZDs was found to increase the frequency of caecal tumors in wild-type C57BL/6J and C57BL/6J APC+/1638N/Mlh1/− double mutant mice [80]. Part of the explanation is that in these mouse model studies, the doses of TZDs used were far greater than the doses that can be tolerated in human. Also, to add to the complexity of the role of PPARγ in colon carcinogenesis, it has been reported that many TZDs may activate PPARγ independent of PPARγ receptor [72, 76, 81–84] but may require the presence of APC gene [61].

The contradictory results reported in these studies have clearly reflected the complexity of the role of PPARγ in colon carcinogenesis. Large-scale in vivo studies using not only PPARγ activators or inhibitors but also in knockout mice, especially colon specific knockout of PPARγ, would generate more valuable data.

5. Role of PPARγ during Anti-Inflammatory Process

In recent years, the causative link between inflammation and cancer has attracted considerable attention. The mechanism and molecular pathways of chronic inflammation leading to CRC development have been discussed in much detail in a recent review [85]. It has been commonly agreed that in the development of CRC, inflammatory bowel diseases (IBD, which includes ulcerative colitis and Crohn’s disease) are among the major risk factors. These risk factors are particularly important in children and young adults of less than 30 years of age [86, 87].

There is an ample amount of evidence suggesting a role of PPARγ in inflammatory processes. PPARγ expression is reduced in ulcerative colitis [88]. PPARγ has been identified as anti-inflammatory molecules in IBD [89]. Mice with a targeted disruption or elimination of the PPARγ gene in intestinal epithelial cells showed an increased susceptibility to dextran sulfate sodium- (DSS-) induced IBD [90].

As macrophages play important role in the anti-inflammatory effect in the colon, its correlation with PPARγ has been actively studied. It has been shown that mice with a targeted disruption of the PPARγ gene in the macrophages of the intestinal epithelia also showed an increased susceptibility to DSS-induced IBD [90, 91], suggesting an important anti-inflammatory role of PPARγ.

However, 5-aminosalicylic acid (5-ASA) is an anti-inflammatory drug widely used in the treatment of IBD. It has been reported that 5-ASA could bind to and activate PPARγ [92]. Binding of 5-ASA to PPARγ receptor was found to be similar to the crystal orientation of the TZD head group of rosiglitazone. These observations indicated that 5-ASA exerted its anti-inflammatory effect through activating PPARγ pathway. Based on these observations, PPARγ ligands have been considered a group of potentially useful therapeutic agents for CRC and IBD [93, 94]. In a clinical trial, rosiglitazone was found to produce clinical and endoscopic remission of patients with ulcerative colitis in the majority of patients although this study was limited by its low number of patients [95].
COX-2, was found to activate the PPAR γ cancer [99]. Other COX-2 inhibitors such as indomethacin, a dietary agent with a strong ability to inhibit NF-κB, were shown to activate PPAR γ pathways [100]. In addition, inhibition of Cox-2 and activation of inflammatory, and anticancer effects of most, if not all, Cox inhibitors. For example, Curcumin, a widely recognized kinase receptors. The important ligands that may activate the tyrosine kinase receptors include epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (ILGF), and hepatocyte growth factor (HGF). Binding of these ligands to receptors alters the functions of some of the down-stream target genes: downregulation of the E-cadherin gene via the transcription factor Snail pathway; or directly affects cell adhesion and/or the cytoskeletal dynamics. Notch, Hedgehog, and NF-κB signaling pathways have also been found to be involved in EMT.

It has been reported that PPARγ promotes EMT by Rho GTPase-dependent activation of ERK1/2 in intestinal epithelial cells [105]. RS5444 (a novel third-generation thiazolidinedione derivative) caused dramatic changes in cell morphology, which were associated with increased motility and diminished cellular adherence in nontransformed rat intestinal epithelial cells (RIEs). These data suggest novel effects of PPARγ on cell-cell and cell-matrix interactions [49]. However, the precise role and mechanism by which PPARγ regulates EMT and cancer metastasis are not yet well defined.

7. Role of PPARγ in Angiogenesis
Angiogenesis plays an important role in the development and metastasis of all solid cancers. The regulatory role of PPARγ in angiogenesis has been demonstrated in vitro and in vivo, as reviewed in details elsewhere [48, 106]. The effect of PPARγ ligands on angiogenesis is bidirectional, possibly depends on cell types and specific pathways involved. Most of the studies showed that PPARγ ligands inhibit angiogenesis, but opposite results have been reported. For example, 15d-PGJ2 inhibits angiogenesis via upregulation of HGF, VEGF, Flt-1 (VEGF receptor-1), and Flk/KDR (VEGF receptor-2). The same agent may also stimulate angiogenesis via the induction of heme oxygenase-1 (HO-1), endothelial nitric-oxide synthase, and hypoxia-inducible factor-1α (HIF-1α) [48]. Large-scale studies will have to be conducted to reveal the role of PPARγ ligands in angiogenesis in a particular cancer.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are also a group of PPARγ activators. These agents are a widely used as anti-inflammatory drugs and pain killers. These agents can inhibit cyclooxygenase (COX) enzymes [96], and have a chemopreventive effect in various cancers, including CRC and gastric cancer [97, 98]. It has been reported that the chemopreventive effect of NSAIDs in gastrointestinal cancers was mechanistically attributable to their ability to activate PPARγ.

It is now widely accepted that activation of PPARγ may be an important mechanism responsible for the anti-inflammatory, and anticancer effects of most, if not all Cox inhibitors. For example, Curcumin, a widely recognized dietary agent with a strong ability to inhibit NF-κB and COX-2, was found to activate the PPARγ pathway in colon cancer [99]. Other COX-2 inhibitors such as indomethacin and sulindac sulphide also showed to activate PPARγ pathways [100]. In addition, inhibition of Cox-2 and activation of PPARγ may have synergistic effect in inhibiting the growth of certain cancers such as pancreatic cancer [101].

The mechanisms by which COX inhibition leads to PPARγ activation are not clearly defined, but may be possibly due to antagonizing NF-κB activity, suppressing IL-8 and iNOS expressions, or increased production of prostaglandins derivatives such as 15d-PGJ2 [102, 103].

Overall, those data suggested that activation of PPARγ exerts an anticancer effect partially through anti-inflammatory function.

6. Role of PPARγ in Epithelial Mesenchymal Transition (EMT) and Tumor Invasion
Metastasis is a subsequent behavior of all malignant tumors, and often the cause of cancer mortality. EMT plays an important role during tumor metastasis. Some of the proteins involved in EMT could be utilized as potential prognostic markers or therapeutic targets.

EMT is regulated by multiple signaling pathways [104]. The process starts from ligand-induced activation of tyrosine kinases. The important ligands that may activate the tyrosine kinase receptors include epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (ILGF), and hepatocyte growth factor (HGF). Binding of these ligands to receptors alters the functions of some of the down-stream target genes: downregulation of the E-cadherin gene via the transcription factor Snail pathway; or directly affects cell adhesion and/or the cytoskeletal dynamics. Notch, Hedgehog, and NF-κB signaling pathways have also been found to be involved in EMT.

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### Table 1: Some of the clinical trials on the role of PPARγ ligands on CRC.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Drug used</th>
<th>Number of patients</th>
<th>Combined treatment</th>
<th>Tumors</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Tepmongkol et al.</td>
<td>Rosiglitazone</td>
<td>23</td>
<td>Radioiodine</td>
<td>Thyroid carcinoma</td>
<td>Responded</td>
</tr>
<tr>
<td>Hau et al.</td>
<td>Pioglitazone</td>
<td>14</td>
<td>Capecitabine/Temozolomide and Rofecoxib</td>
<td>Glioma</td>
<td>Partial response</td>
</tr>
<tr>
<td>Kebebew et al.</td>
<td>Rosiglitazone</td>
<td>10</td>
<td>Radioiodine</td>
<td>Thyroid carcinoma</td>
<td>Responded</td>
</tr>
<tr>
<td>Schwartz et al.</td>
<td>LY293111</td>
<td>38</td>
<td>No</td>
<td>Solid tumors</td>
<td>No response</td>
</tr>
<tr>
<td>Baetz et al.</td>
<td>Ly293111</td>
<td>28</td>
<td>Irinotecan</td>
<td>Solid tumors</td>
<td>No response</td>
</tr>
<tr>
<td>Demetri et al.</td>
<td>Troglitazone</td>
<td>3</td>
<td>No</td>
<td>Liposarcoma</td>
<td>Responded</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>Rosiglitazone</td>
<td>106</td>
<td>No</td>
<td>Prostate carcinoma</td>
<td>No response</td>
</tr>
<tr>
<td>Tenenbaum et al.</td>
<td>Bezafibrate</td>
<td>3011</td>
<td>No</td>
<td>Colon cancer</td>
<td>Responded</td>
</tr>
<tr>
<td>Read et al.</td>
<td>Rosiglitazone</td>
<td>23</td>
<td>Bexarotene</td>
<td>Solid tumor</td>
<td>No response</td>
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<tr>
<td>Debrock et al.</td>
<td>Rosiglitazone</td>
<td>12</td>
<td>Pretreatment</td>
<td>Liposarcoma</td>
<td>Negative</td>
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<tr>
<td>Burstein et al.</td>
<td>Troglitazone</td>
<td>22</td>
<td>Prechemotherapy or Prehormonal</td>
<td>Breast cancer</td>
<td>No response</td>
</tr>
<tr>
<td>Kulke et al.</td>
<td>Troglitazone</td>
<td>25</td>
<td>No</td>
<td>Colon cancer</td>
<td>No response</td>
</tr>
<tr>
<td>Mueller et al.</td>
<td>Troglitazone</td>
<td>41</td>
<td>Preandrogen deprivation</td>
<td>Prostate cancer</td>
<td>No response</td>
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</table>
8. Current Clinical Trials

Although many in vitro and in vivo data have demonstrated a potential therapeutic role of PPARγ ligands in many cancers, the results from clinical trials are limited and the efficacy of PPARγ ligands in most cancers was less satisfactory. The poor outcome may be partially related to the fact that most of these clinical trials that turned out to be negative on therapeutic effect were conducted in patients with refractory and advanced solid tumors, which are notoriously refractory to most of the available therapeutic approaches.

Table 1 lists some of the clinical trials on treatment of different human cancers by PPARγ ligands. From these data, it is probably more plausible to designate PPARγ ligands as a group of biological modifier in human cancers rather than therapeutic agents.

PPARγ agonists are generally well tolerated. The major adverse effects are gastrointestinal toxicity, include diarrhea, vomiting, and abdominal pain [44, 45]. Certain TZDs, such as troglitazone, has been removed from clinical use because of the severe side effects. Overall, it is still inconclusive to state a definite therapeutic role of PPARγ agonists in gastrointestinal cancers.

9. Conclusions

In summary, role of PPARγ in CRC is rather controversial. PPARγ ligands may exert therapeutic effects on colon cancer through a PPAR-γ-dependent and a PPAR-γ-independent pathway. The therapeutic effects of the current PPARγ ligands in colon cancer are less optimal. Thus, new PPARγ ligands are currently under development. Exploration of combinational therapy using PPARγ ligands and other therapeutic drugs should be encouraged.

Acknowledgment

The studies reported in this review article were partially supported by the University of Hong Kong Seed Funding programs (Grant code: 10208191.49710.20600.301.01).

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