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Review Article

Current Understanding of the Role of PPARγ in Gastrointestinal Cancers

Bing Zou,[1] Liang Qiao,[1,2] and Benjamin C. Y. Wong[1]

[1] *Department of Medicine; Centre Cancer Research, The University of Hong Kong, Pok Fu Lam Road, Hong Kong*
[2] *Department of Gastroenterology and Hepatology; Storr Liver Unit, Westmead Millennium Institute, University of Sydney at Westmead Hospital, Westmead, NSW 2145, Australia*

Correspondence should be addressed to Liang Qiao, qiaol@hku.hk and Benjamin C. Y. Wong, bcywong@hku.hk

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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.

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 sparkled 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-κB, 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).

TZDs 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, heteroxygous 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 suflate (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 rosigliatzone, have been reported to promote gastrointestinal tumorigenesis in C57BL/6J $APC^{Min/+}$ 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 $APC^{+/1638N}/Mlh^{+/-}$ 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].

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

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

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 were shown 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 derivertives 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 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 cellular 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-1a (HIF-1) [48]. Large-scale studies will have to be conducted to reveal the role of PPARγ ligands in angiogenesis in a particular cancer.

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 trails 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 PPARγ-dependent and a PPARγ-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.

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References

[1] I. Issemann and S. Green, "Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators," *Nature*, vol. 347, no. 6294, pp. 645–650, 1990.

[2] R. A. Graves, P. Tontonoz, and B. M. Spiegelman, "Analysis of a tissue-specific enhancer: ARF6 regulates adipogenic gene expression," *Molecular and Cellular Biology*, vol. 12, no. 3, pp. 1202–1208, 1992.

[3] Y. Zhu, K. Alvares, Q. Huang, M. S. Rao, and J. K. Reddy, "Cloning of a new member of the peroxisome proliferator-activated receptor gene family from mouse liver," *Journal of Biological Chemistry*, vol. 268, no. 36, pp. 26817–26820, 1993.

[4] T. M. Willson, P. J. Brown, D. D. Sternbach, et al., "The PPARs: fro orphan receptors to drug discovery," *Journal of Medicinal Chemistry*, vol. 43, pp. 527–550, 2000.

[5] W. R. Oliver Jr., J. L. Shenk, M. R. Snaith, et al., "Selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, pp. 5306–5311, 2001.

[6] A. Chawla, C.-H. Lee, Y. Barak, et al., "PPARδ is a very low-density lipoprotein sensor in macrophages," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 3, pp. 1268–1273, 2003.

[7] H. Lim and S. K. Dey, "PPARδ functions as a prostacyclin receptor in blastocyst implantation," *Trends in Endocrinology and Metabolism*, vol. 11, no. 4, pp. 137–142, 2000.

[8] N. S. Tan, L. Michalik, N. Noy, et al., "Critical roles of PPAR β/δ in keratinocyte response to inflammation," *Genes & Development*, vol. 15, no. 24, pp. 3263–3277, 2001.

[9] J. M. Peters, S. S. T. Lee, W. Li, et al., "Growths, adipose, brain, and skin alterations resulting from targeted disruption of the mouse peroxisome proliferator-activated receptor $\beta(\delta)$," *Molecular and Cellular Biology*, vol. 20, no. 14, pp. 5119–5128, 2000.

[10] Y.-X. Wang, C.-H. Lee, S. Tiep, et al., "Peroxisome-proliferator-activated receptor δ activates fat metabolism to prevent obesity," *Cell*, vol. 113, no. 2, pp. 159–170, 2003.

[11] A.-M. Lefebvre, B. Paulweber, L. Fajas, et al., "Peroxisome proliferator-activated receptor gamma is induced during differentiation of colon epithelium cells," *Journal of Endocrinology*, vol. 162, no. 3, pp. 331–340, 1999.

[12] W. Su, C. R. Bush, B. M. Necela, et al., "Differential expression, distribution, and function of PPAR-γ in the proximal and distal colon," *Physiological Genomics*, vol. 30, no. 3, pp. 342–353, 2007.

[13] C. G. Perry and J. R. Petrie, "Insulin-sensitising agents: beyond thiazolidinediones," *Expert Opinion on Emerging Drugs*, vol. 7, no. 1, pp. 165–174, 2002.

[14] G. I. Owen and A. Zelent, "Origins and evolutionary diversification of the nuclear receptor superfamily," *Cellular and Molecular Life Sciences*, vol. 57, no. 5, pp. 809–827, 2000.

[15] R. T. Nolte, G. B. Wisely, S. Westin, et al., "Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-γ," *Nature*, vol. 395, no. 6698, pp. 137–143, 1998.

[16] T. Shiraki, N. Kamiya, S. Shiki, T. S. Kodama, A. Kakizuka, and H. Jingami, "α/β-unsaturated ketone is a core moiety of natural ligands for covalent binding to peroxisome proliferator-activated receptor γ," *Journal of Biological Chemistry*, vol. 280, no. 14, pp. 14145–14153, 2005.

[17] H. Yki-Järvinen, "Thiazolidinediones," *The New England Journal of Medicine*, vol. 351, no. 11, pp. 1106–1118, 2004.

[18] E. A. Thompson, "PPARγ physiology and pathology in gastrointestinal epithelial cells," *Molecules and Cells*, vol. 24, no. 2, pp. 167–176, 2007.

[19] M. E. Greene, B. Blumberg, O. W. McBride, et al., "Isolation of the human peroxisome proliferator activated receptor gamma cDNA: expression in hematopoietic cells and chromosomal mapping," *Gene Expression*, vol. 4, no. 4-5, pp. 281–299, 1995.

[20] P. Tontonoz, E. Hu, R. A. Graves, A. I. Budavari, and B. M. Spiegelman, "mPPARγ2: tissue-specific regulator of an adipocyte enhancer," *Genes and Development*, vol. 8, no. 10, pp. 1224–1234, 1994.

[21] A. Werman, A. Hollenberg, G. Solanes, C. Bjørbæk, A. J. Vidal-Puig, and J. S. Flier, "Ligand-independent activation domain in the N terminus of peroxisome proliferator-activated receptor γ (PPARγ). Differential activity of PPARγ1

and -2 isoforms and influence of insulin," *Journal of Biological Chemistry*, vol. 272, no. 32, pp. 20230–20235, 1997.

[22] L. Fajas, D. Auboeuf, E. Raspé, et al., "The organization, promoter analysis, and expression of the human PPARγ gene," *Journal of Biological Chemistry*, vol. 272, no. 30, pp. 18779–18789, 1997.

[23] R. Mukherjee, L. Jow, G. E. Croston, and J. R. Paterniti Jr., "Identification, characterization, and tissue distribution of human peroxisome proliferator-activated receptor (PPAR) isoforms PPARγ2 versus PPARγ1 and activation with retinoid X receptor agonists and antagonists," *Journal of Biological Chemistry*, vol. 272, no. 12, pp. 8071–8076, 1997.

[24] A. J. Vidal-Puig, R. V. Considine, M. Jimenez-Liñan, et al., "Peroxisome proliferator-activated receptor gene expression in human tissues: effects of obesity, weight loss, and regulation by insulin and glucocorticoids," *Journal of Clinical Investigation*, vol. 99, no. 10, pp. 2416–2422, 1997.

[25] A. Zieleniak, M. Wójcik, and L. A. Woźniak, "Structure and physiological functions of the human peroxisome proliferator-activated receptor γ," *Archivum Immunologiae et Therapiae Experimentalis*, vol. 56, no. 5, pp. 331–345, 2008.

[26] D. M. Heery, E. Kalkhoven, S. Hoare, and M. G. Parker, "A signature motif in transcriptional co-activators mediates binding to nuclear receptors," *Nature*, vol. 387, no. 6634, pp. 733–736, 1997.

[27] E. M. McInerney, D. W. Rose, S. E. Flynn, et al., "Determinants of coactivator LXXLL motif specificity in nuclear receptor transcriptional activation," *Genes & Development*, vol. 12, no. 21, pp. 3357–3368, 1998.

[28] P. Puigserver, Z. Wu, C. W. Park, R. Graves, M. Wright, and B. M. Spiegelman, "A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis," *Cell*, vol. 92, no. 6, pp. 829–839, 1998.

[29] M. Adams, M. J. Reginato, D. Shao, M. A. Lazar, and V. K. Chatterjee, "Transcriptional activation by peroxisome proliferator-activated receptor γ is inhibited by phosphorylation at a consensus mitogen-activated protein kinase site," *Journal of Biological Chemistry*, vol. 272, no. 8, pp. 5128–5132, 1997.

[30] H. S. Camp and S. R. Tafuri, "Regulation of peroxisome proliferator-activated receptor γ activity by mitogen-activated protein kinase," *The Journal of Biological Chemistry*, vol. 272, pp. 10811–10816, 1997.

[31] E. Hu, J. B. Kim, P. Sarraf, and B. M. Spiegelman, "Inhibition of adipogenesis through MAP kinase-mediated phosphorylation of PPARγ," *Science*, vol. 274, no. 5295, pp. 2100–2103, 1996.

[32] J. M. Lehmann, L. B. Moore, T. A. Smith-Oliver, W. O. Wilkison, T. M. Willson, and S. A. Kliewer, "An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ)," *Journal of Biological Chemistry*, vol. 270, no. 22, pp. 12953–12956, 1995.

[33] J. M. Lehmann, J. M. Lenhard, B. B. Oliver, G. M. Ringold, and S. A. Kliewer, "Peroxisome proliferator-activated receptors α and γ are activated by indomethacin and other non-steroidal anti-inflammatory drugs," *Journal of Biological Chemistry*, vol. 272, no. 6, pp. 3406–3410, 1997.

[34] H. E. Xu, M. H. Lambert, V. G. Montana, et al., "Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 24, pp. 13919–13924, 2001.

[35] F. Chiarelli and D. Di Marzio, "Peroxisome proliferator-activated receptor-γ agonists and diabetes: current evidence and future perspectives," *Vascular Health and Risk Management*, vol. 4, no. 2, pp. 297–304, 2008.

[36] A. A. Parulkar, M. L. Pendergrass, R. Granda-Ayala, T. R. Lee, and V. A. Fonseca, "Nonhypoglycemic effects of thiazolidinediones," *Annals of Internal Medicine*, vol. 134, no. 1, pp. 61–71, 2001.

[37] S. M. Haffner, A. S. Greenbeg, W. M. Weston, et al., "Effects of rosiglitazone treatment on non-traditional markers of cardiovascular disease in patients with type 2 diabetes mellitus," *Circulation*, vol. 106, pp. 679–684, 2002.

[38] D. Romualdi, M. Guido, M. Ciampelli, et al., "Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome," *Human Reproduction*, vol. 18, no. 6, pp. 1210–1218, 2003.

[39] D. Glintborg, R. K. Støving, C. Hagen, et al., "Pioglitazone treatment increases spontaneous growth hormone (GH) secretion and stimulated GH levels in polycystic ovary syndrome," *The Journal of Clinical Endocrinology & Metabolism*, vol. 90, no. 10, pp. 5605–5612, 2005.

[40] A. Reifel-Miller, K. Otto, E. Hawkins, et al., "A peroxisome proliferator-activated receptor α/γ dual agonist with a unique in vitro profile and potent glucose and lipid effects in rodent models of type 2 diabetes and dyslipidemia," *Molecular Endocrinology*, vol. 19, no. 6, pp. 1593–1605, 2005.

[41] W.-G. Tong, X.-Z. Ding, R. Hennig, et al., "Leukotriene B4 receptor antagonist LY293111 inhibits proliferation and induces apoptosis in human pancreatic cancer cells," *Clinical Cancer Research*, vol. 8, no. 10, pp. 3232–3242, 2002.

[42] J. A. Copland, S. Kurakata, K. Fujiwara, et al., "A novel high affinity PPAR-γ agonist inhibits human anaplastic thyroid tumour growth," in *Proceedings of the AACR Annual Meeting*, Orlando, Fla, USA, 2004, LB-17.

[43] D.-C. Liu, C.-B. Zang, H.-Y. Liu, K. Possinger, S.-G. Fan, and E. Elstner, "A novel PPAR alpha/gamma dual agonist inhibits cell growth and induces apoptosis in human glioblastoma T98G cells," *Acta Pharmacologica Sinica*, vol. 25, no. 10, pp. 1312–1319, 2004.

[44] G. K. Schwartz, A. Weitzman, E. O'Reilly, et al., "Phase I and pharmacokinetic study of LY293111, an orally bioavailable LTB4 receptor antagonist, in patients with advanced solid tumors," *Journal of Clinical Oncology*, vol. 23, no. 23, pp. 5365–5373, 2005.

[45] T. Baetz, E. Eisenhauer, L. Siu, et al., "A phase I study of oral LY293111 given daily in combination with irinotecan in patients with solid tumours," *Investigational New Drugs*, vol. 25, no. 3, pp. 217–225, 2007.

[46] S. A. Kliewer, J. M. Lenhard, T. M. Willson, I. Patel, D. C. Morris, and J. M. Lehmann, "A prostaglandin J_2 metabolite binds peroxisome proliferator-activated receptor γ and promotes adipocyte differentiation," *Cell*, vol. 83, no. 5, pp. 813–819, 1995.

[47] B. M. Forman, P. Tontonoz, J. Chen, R. P. Brun, B. M. Spiegelman, and R. M. Evans, "15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 is a ligand for the adipocyte determination factor PPARγ," *Cell*, vol. 83, no. 5, pp. 803–812, 1995.

[48] E.-H. Kim and Y.-J. Surh, "The role of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, an endogenous ligand of peroxisome proliferator-activated receptor γ, in tumor angiogenesis," *Biochemical Pharmacology*, vol. 76, no. 11, pp. 1544–1553, 2008.

[49] L. Chen, C. R. Bush, B. M. Necela, et al., "RS5444, a novel PPARγ agonist, regulates aspects of the differentiated phenotype in nontransformed intestinal epithelial cells," *Molecular and Cellular Endocrinology*, vol. 251, no. 1-2, pp. 17–32, 2006.

[50] S. Drori, G. D. Girnun, L. Tou, et al., "Hic-5 regulates an epithelial program mediated by PPARγ," *Genes & Development*, vol. 19, no. 3, pp. 362–375, 2005.

[51] P. Sarraf, E. Mueller, W. M. Smith, et al., "Loss-of-function mutations in PPARγ associated with human colon cancer," *Molecular Cell*, vol. 3, no. 6, pp. 799–804, 1999.

[52] T. Ikezoe, C. W. Miller, S. Kawano, et al., "Mutational analysis of the peroxisome proliferator-activated receptor γ in human malignancies," *Cancer Research*, vol. 61, no. 13, pp. 5307–5310, 2001.

[53] J. A. Brockman, R. A. Gupta, and R. N. Dubois, "Activation of PPARγ leads to inhibition of anchorage-independent growth of human colorectal cancer cells," *Gastroenterology*, vol. 115, no. 5, pp. 1049–1055, 1998.

[54] P. Sarraf, E. Mueller, D. Jones, et al., "Differentiation and reversal of malignant changes in colon cancer through PPARγ," *Nature Medicine*, vol. 4, no. 9, pp. 1046–1052, 1998.

[55] R. A. Gupta, J. A. Brockman, P. Sarraf, T. M. Willson, and R. N. DuBois, "Target genes of peroxisome proliferator-activated receptor γ in colorectal cancer cells," *Journal of Biological Chemistry*, vol. 276, no. 32, pp. 29681–29687, 2001.

[56] G. G. Chen, J. F. Lee, S. H. Wang, U. P. F. Chan, P. C. Ip, and W. Y. Lau, "Apoptosis induced by activation of peroxisome-proliferator activated receptor-gamma is associated with Bcl-2 and NF-κB in human colon cancer," *Life Sciences*, vol. 70, no. 22, pp. 2631–2646, 2002.

[57] T. Shimada, K. Kojima, K. Yoshiura, H. Hiraishi, and A. Terano, "Characteristics of the peroxisome proliferator activated receptor γ (PPARγ) ligand induced apoptosis in colon cancer cells," *Gut*, vol. 50, no. 5, pp. 658–664, 2002.

[58] R. A. Gupta, P. Sarraf, E. Mueller, et al., "Peroxisome proliferator-activated receptor γ-mediated differentiation: a mutation in colon cancer cells reveals divergent and cell type-specific mechanisms," *Journal of Biological Chemistry*, vol. 278, no. 25, pp. 22669–22677, 2003.

[59] T. Yoshizumi, T. Ohta, I. Ninomiya, et al., "Thiazolidinedione, a peroxisome proliferator-activated receptor-gamma ligand, inhibits growth and metastasis of HT-29 human colon cancer cells through differentiation-promoting effects," *International Journal of Oncology*, vol. 25, no. 3, pp. 631–639, 2004.

[60] L. Qiao, Y. Dai, Q. Gu, et al., "Down-regulation of X-linked inhibitor of apoptosis synergistically enhanced peroxisome proliferator-activated receptor γ ligand-induced growth inhibition in colon cancer," *Molecular Cancer Therapeutics*, vol. 7, no. 7, pp. 2203–2211, 2008.

[61] G. D. Girnun, W. M. Smith, S. Drori, et al., "APC-dependent suppression of colon carcinogenesis by PPARγ," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 21, pp. 13771–13776, 2002.

[62] J. Lu, K. Imamura, S. Nomura, et al., "Chemopreventive effect of peroxisome proliferator-activated receptor γ on gastric carcinogenesis in mice," *Cancer Research*, vol. 65, no. 11, pp. 4769–4774, 2005.

[63] Y. Dai, L. Qiao, W. C. Kwok, et al., "Peroxisome proliferator-activated receptor-γ contributes to the inhibitory effects of embelin on colon carcinogenesis," *Cancer Research*, vol. 69, no. 11, pp. 4776–4783, 2009.

[64] C. A. McAlpine, Y. Barak, I. Matise, and R. T. Cormier, "Intestinal-specific PPARγ deficiency enhances tumorigenesis in $Apc^{Min/+}$ mice," *International Journal of Cancer*, vol. 119, no. 10, pp. 2339–2346, 2006.

[65] N. Niho, M. Takahashi, T. Kitamura, et al., "Concomitant suppression of hyperlipidemia and intestinal polyp formation in Apc-deficient mice by peroxisome proliferator-activated receptor ligands," *Cancer Research*, vol. 63, no. 18, pp. 6090–6095, 2003.

[66] N. Niho, M. Takahashi, Y. Shoji, et al., "Dose-dependent suppression of hyperlipidemia and intestinal polyp formation in Min mice by pioglitazone, a PPARγ ligand," *Cancer Science*, vol. 94, no. 11, pp. 960–964, 2003.

[67] E. Osawa, A. Nakajima, K. Wada, et al., "Peroxisome proliferator-activated receptor γ ligands suppress colon carcinogenesis induced by azoxymethane in mice," *Gastroenterology*, vol. 124, no. 2, pp. 361–367, 2003.

[68] H. Kohno, S. Yoshitani, S. Takashima, et al., "Troglitazone, a ligand for peroxisome proliferator-activated receptor γ, inhibits chemically-induced aberrant crypt foci in rats," *Japanese Journal of Cancer Research*, vol. 92, no. 4, pp. 396–403, 2001.

[69] T. Tanaka, H. Kohno, S.-I. Yoshitani, et al., "Ligands for peroxisome proliferator-activated receptors α and γ inhibit chemically induced colitis and formation of aberrant crypt foci in rats," *Cancer Research*, vol. 61, no. 6, pp. 2424–2428, 2001.

[70] L. Fajas, V. Egler, R. Reiter, S. Miard, A.-M. Lefebvre, and J. Auwerx, "PPARγ controls cell proliferation and apoptosis in an RB-dependent manner," *Oncogene*, vol. 22, no. 27, pp. 4186–4193, 2003.

[71] J.-W. Huang, C.-W. Shiau, Y.-T. Yang, et al., "Peroxisome proliferator-activated receptor γ-independent ablation of cyclin D1 by thiazolidinediones and their derivatives in breast cancer cells," *Molecular Pharmacology*, vol. 67, no. 4, pp. 1342–1348, 2005.

[72] C.-W. Shiau, C.-C. Yang, S. K. Kulp, et al., "Thiazolidenediones mediate apoptosis in prostate cancer cells in part through inhibition of Bcl-xL/Bcl-2 functions independently of PPARγ," *Cancer Research*, vol. 65, no. 4, pp. 1561–1569, 2005.

[73] A. Elnemr, T. Ohta, K. Iwata, et al., "PPARgamma ligand (thiazolidinedione) induces growth arrest and differentiation markers of human pancreatic cancer cells," *International Journal of Oncology*, vol. 17, no. 6, pp. 1157–1164, 2000.

[74] H. Koga, S. Sakisaka, M. Harada, et al., "Involvement of p21WAF1/Cip1, p27Kip1, and p18INK4c in troglitazone-induced cell-cycle arrest in human hepatoma cell lines," *Hepatology*, vol. 33, no. 5, pp. 1087–1097, 2001.

[75] F. Chen and L. E. Harrison, "Ciglitazone-induced cellular anti-proliferation increases p27 kip1 protein levels through both increased transcriptional activity and inhibition of proteasome degradation," *Cellular Signalling*, vol. 17, no. 7, pp. 809–816, 2005.

[76] L. Qiao, Y. Dai, Q. Gu, et al., "Loss of XIAP sensitizes colon cancer cells to PPARγ independent antitumor effects of troglitazone and 15-PGJ_2," *Cancer Letters*, vol. 268, no. 2, pp. 260–271, 2008.

[77] Y. Dai, L. Qiao, W. C. Kwok, et al., "Loss of XIAP sensitizes rosiglitazone-induced growth inhibition of colon cancer in vivo," *International Journal of Cancer*, vol. 122, no. 12, pp. 2858–2863, 2008.

[78] Y. Kim, N. Suh, M. Sporn, and J. C. Reed, "An inducible pathway for degradation of FLIP protein sensitizes tumor cells to TRAIL-induced apoptosis," *Journal of Biological Chemistry*, vol. 277, no. 25, pp. 22320–22329, 2002.

[79] E. Saez, P. Tontonoz, M. C. Nelson, et al., "Activators of the nuclear receptor PPARγ enhance colon polyp formation," *Nature Medicine*, vol. 4, no. 9, pp. 1058–1061, 1998.

[80] K. Yang, K.-H. Fan, S. A. Lamprecht, et al., "Peroxisome proliferator-activated receptor γ agonist troglitazone induces colon tumors in normal C57BL/6J mice and enhances colonic carcinogenesis in $Apc^{1638N/+}Mlh1^{+/-}$ double mutant mice," *International Journal of Cancer*, vol. 116, no. 4, pp. 495–499, 2005.

[81] S. S. Palakurthi, H. Aktas, L. M. Grubissich, R. M. Mortensen, and J. A. Halperin, "Anticancer effects of thiazolidinediones are independent of peroxisome proliferator-activated receptor γ and mediated by inhibition of translation initiation," *Cancer Research*, vol. 61, no. 16, pp. 6213–6218, 2001.

[82] S. J. Baek, L. C. Wilson, L. C. Hsi, and T. E. Eling, "Troglitazone, a peroxisome proliferator-activated receptor γ (PPARγ) ligand, selectively induces the early growth response-1 gene independently of PPARγ: a novel mechanism for its anti-tumorigenic activity," *Journal of Biological Chemistry*, vol. 278, no. 8, pp. 5845–5853, 2003.

[83] Y. Akasaki, G. Liu, H. H. Matundan, et al., "A peroxisome proliferator-activated receptor-γ agonist, troglitazone, facilitates caspase-8 and -9 activities by increasing the enzymatic activity of protein-tyrosine phosphatase-1B on human glioma cells," *Journal of Biological Chemistry*, vol. 281, no. 10, pp. 6165–6174, 2006.

[84] X. Li, X. Yang, Y. Xu, et al., "Troglitazone inhibits cell proliferation by attenuation of epidermal growth factor receptor signaling independent of peroxisome proliferator-activated receptor γ," *Cell Research*, vol. 19, no. 6, pp. 720–732, 2009.

[85] J. Bassaganya-Riera, A. B. Carter, S. A. Misyak, and R. Hontecillas, "Dietary modulation of inflammation-induced colorectal cancer through PPARγ," *PPAR Research*, vol. 2009, Article ID 498352, 9 pages, 2009.

[86] S. H. Mir-Madjlessi, R. G. Farmer, K. A. Easley, and G. J. Beck, "Colorectal and extracolonic malignancy in ulcerative colitis," *Cancer*, vol. 58, no. 7, pp. 1569–1574, 1986.

[87] A. Ekbom, C. Helmick, M. Zack, and H.-O. Adami, "Increased risk of large-bowel cancer in Crohn's disease with colonic involvement," *The Lancet*, vol. 336, no. 8711, pp. 357–359, 1990.

[88] L. Dubuquoy, C. Rousseaux, X. Thuru, et al., "PPARγ as a new therapeutic target in inflammatory bowel diseases," *Gut*, vol. 55, no. 9, pp. 1341–1349, 2006.

[89] M. Ricote, A. C. Li, T. M. Willson, C. J. Kelly, and C. K. Glass, "The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation," *Nature*, vol. 391, no. 6662, pp. 79–82, 1998.

[90] Y. M. Shah, K. Morimura, and F. J. Gonzalez, "Expression of peroxisome proliferator-activated receptor-γ in macrophage suppresses experimentally induced colitis," *American Journal of Physiology*, vol. 292, no. 2, pp. G657–G666, 2007.

[91] N. Watanabe, K. Ikuta, K. Okazaki, et al., "Elimination of local macrophages in intestine prevents chronic colitis in interleukin-10-deficient mice," *Digestive Diseases and Sciences*, vol. 48, no. 2, pp. 408–414, 2003.

[92] C. Rousseaux, B. Lefebvre, L. Dubuquoy, et al., "Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-γ," *Journal of Experimental Medicine*, vol. 201, no. 8, pp. 1205–1215, 2005.

[93] J. D. Ramakers, M. I. Verstege, G. Thuijls, A. A. Te Velde, R. P. Mensink, and J. Plat, "The PPARγ agonist rosiglitazone impairs colonic inflammation in mice with experimental colitis," *Journal of Clinical Immunology*, vol. 27, no. 3, pp. 275–283, 2007.

[94] C. Lytle, T. J. Tod, K. T. Vo, J. W. Lee, R. D. Atkinson, and D. S. Straus, "The peroxisome proliferator-activated receptor γ ligand rosiglitazone delays the onset of inflammatory bowel disease in mice with interleukin 10 deficiency," *Inflammatory Bowel Diseases*, vol. 11, no. 3, pp. 231–243, 2005.

[95] J. D. Lewis, G. R. Lichtenstein, R. B. Stein, et al., "An open-label trial of the PPARγ ligand rosiglitazone for active ulcerative colitis," *American Journal of Gastroenterology*, vol. 96, no. 12, pp. 3323–3328, 2001.

[96] R. G. Kurumbail, A. M. Stevens, J. K. Gierse, et al., "Structural basis for selective inhibition of cyciooxygenase-2 by anti-inflammatory agents," *Nature*, vol. 384, no. 6610, pp. 644–648, 1996.

[97] J. A. Baron, B. F. Cole, R. S. Sandler, et al., "A randomized trial of aspirin to prevent colorectal adenomas," *The New England Journal of Medicine*, vol. 348, no. 10, pp. 891–899, 2003.

[98] X. M. Fan, X. H. Jiang, Q. Gu, et al., "Inhibition of Akt/PKB by a COX-2 inhibitor induces apoptosis in gastric cancer cells," *Digestion*, vol. 73, no. 2-3, pp. 75–83, 2006.

[99] M. Zhang, C. Deng, J. Zheng, J. Xia, and D. Sheng, "Curcumin inhibits trinitrobenzene sulphonic acid-induced colitis in rats by activation of peroxisome proliferator-activated receptor gamma," *International Immunopharmacology*, vol. 6, no. 8, pp. 1233–1242, 2006.

[100] A. S. Felts, C. Ji, J. B. Stafford, et al., "Desmethyl derivatives of indomethacin and sulindac as probes for cyclooxygenase-dependent biology," *ACS Chemical Biology*, vol. 2, no. 7, pp. 479–483, 2007.

[101] W.-H. Sun, G.-S. Chen, X.-L. Ou, et al., "Inhibition of COX-2 and activation of peroxisome proliferator-activated receptor γ synergistically inhibits proliferation and induces apoptosis of human pancreatic carcinoma cells," *Cancer Letters*, vol. 275, no. 2, pp. 247–255, 2009.

[102] O. Schröder, Y. Yudina, A. Sabirsh, N. Zahn, J. Z. Haeggström, and J. Stein, "15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 inhibits the expression of microsomal prostaglandin E synthase type 2 in colon cancer cells," *Journal of Lipid Research*, vol. 47, no. 5, pp. 1071–1080, 2006.

[103] G. P. Vandoros, P. A. Konstantinopoulos, G. Sotiropoulou-Bonikou, et al., "PPAR-gamma is expressed and NF-κB pathway is activated and correlates positively with COX-2 expression in stromal myofibroblasts surrounding colon adenocarcinomas," *Journal of Cancer Research and Clinical Oncology*, vol. 132, no. 2, pp. 76–84, 2006.

[104] M. Guarino, "Epithelial-mesenchymal transition and tumour invasion," *International Journal of Biochemistry and Cell Biology*, vol. 39, no. 12, pp. 2153–2160, 2007.

[105] L. Chen, B. M. Necela, W. Su, et al., "Peroxisome proliferator-activated receptor γ promotes epithelial to mesenchymal transformation by Rho GTPase-dependent activation of ERK1/2," *Journal of Biological Chemistry*, vol. 281, no. 34, pp. 24575–24587, 2006.

[106] A. Margeli, G. Kouraklis, and S. Theocharis, "Peroxisome proliferator activated receptor-γ (PPAR-γ) ligands and angiogenesis," *Angiogenesis*, vol. 6, no. 3, pp. 165–169, 2003.