

Review Article

PPAR γ : The Portrait of a Target Ally to Cancer Chemopreventive Agents

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Peroxisome proliferator-activated receptor-gamma (PPAR γ), one of three ligand-activated transcription factors named PPAR, has been identified as a molecular target for cancer chemopreventive agents. PPAR γ was initially understood as a regulator of adipocyte differentiation and glucose homeostasis while later on, it became evident that it is also involved in cell differentiation, apoptosis, and angiogenesis, biological processes which are deregulated in cancer. It is now established that PPAR γ ligands can induce cell differentiation and yield early antineoplastic effects in several tumor types. Moreover, several bioactive natural products with cancer protecting potential are shown to operate through activation of PPAR γ . Overall, PPAR γ appears to be a prevalent target ally to cancer chemopreventive agents and therefore pursuing research in this area is of great relevance.

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1. INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear receptors that function as transcription factors regulating the expression of genes involved in lipid biosynthesis, glucose metabolism, as well as cell proliferation, differentiation, and survival [1–4]. Their discovery was driven by search of a molecular target for peroxisome proliferators, a group of agents named after their property to increase peroxisomes in rodent liver [5, 6]. Later on, activity studies helped elucidate the versatile role of these molecules in modulating diverse biological functions such as metabolism, tissue remodeling, inflammation, angiogenesis, and carcinogenesis [7–11]. Three PPAR gene types have been identified: α , β/δ , and γ [12, 13]. Between them, PPAR γ is the most intensively investigated [14, 15].

2. THE HUMAN PPAR γ GENE

The human PPAR γ gene consists of six coding exons located at chromosome 3p25.2 and extends approximately over 100 kb of genomic DNA [16]. Three major transcriptional start sites have identified where three mature mRNAs originate from, differing in their 5' untranslated regions

[17, 18]. Notably PPAR γ 1 and PPAR γ 3 mRNAs code for the same protein of 475 amino acids, while PPAR γ 2 transcript codes for a different protein which contains an additional 28 N-terminal amino acids [19].

2.1. Tissue distribution of different PPAR γ isoforms

The PPAR γ 1 is found in virtually all tissues, such as liver, skeletal muscle, prostate, kidney, breast, intestine, and the gonads. The PPAR γ 2 is the major PPAR γ isoform expressed mainly in adipose tissue where it normally operates as an adipocyte-specific transcription factor in preadipocytes and regulates adipose tissue differentiation, and the PPAR γ 3 isoform is restricted to adipose tissue and large intestine [18, 20].

2.2. PPAR γ protein structure and function

Similar to other members of the nuclear hormone receptors superfamily, PPAR γ protein has three functional domains: the N-terminal domain, the DNA-binding domain, and a carboxy-terminal ligand-binding pocket (Figure 1).

PPAR γ protein receptor is activated by a number of endogenous and exogenous ligands of various

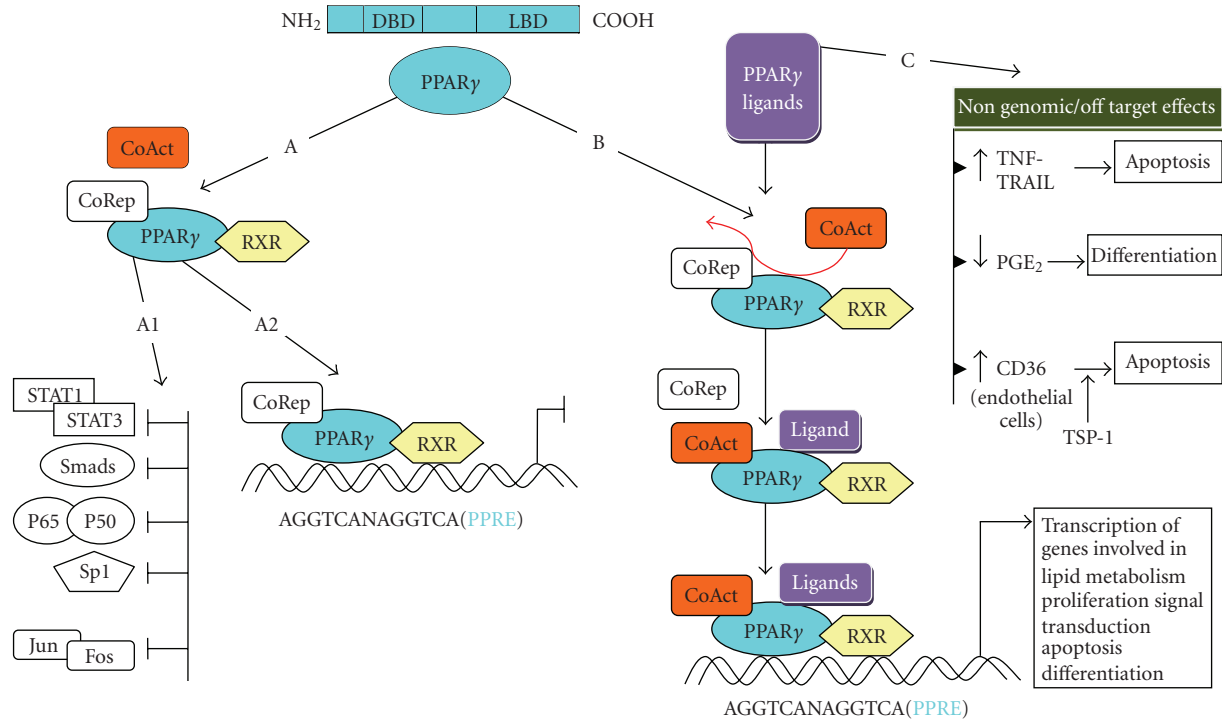


FIGURE 1: *Peroxisome proliferator-activated receptor- γ and ligands: pathways and functions.* PPAR γ protein exhibits a structural organization consisting of three functional domains: an N-terminal domain, a DNA-binding domain (DBD) and a carboxy-terminal ligand binding domain (LBD). PPAR γ forms heterodimers with a second member of the nuclear receptor family, the retinoic X receptor (RXR). Unliganded PPAR γ suppresses transcription (pathway A) either by interfering with key transcription factors (pathway A1) or through recruitment of corepressors (CoRep) on a PPRE element (pathway A2). Ligand binding to PPAR γ (pathway B) triggers conformational changes that lead to dissociation of corepressors (CoRep) and subsequent association of coactivators (CoAct). The complex is binding to PPREs and triggers transcription (pathway B). PPARs ligands can also exert their action through PPAR γ -independent mechanisms also (pathway C). For instance in NSCLC cell lines activation of TNF-TRAIL induce apoptosis, while PGE₂ degradation, through 15-hydroxyprostaglandin dehydrogenase induction, results in enhanced epithelial differentiation. In endothelial cells PPAR γ ligands can markedly boost expression of CD36 which functions as the receptor of endogenous antiangiogenic molecule thrombospondin-1, thereby potentiating the apoptotic response. (PFAs: polyunsaturated fatty acids, TZDs: thiazolidinediones, PPRE: peroxisome proliferator response element, TNF: tumor necrosis factor, TRAIL: TNF-related apoptosis-inducing ligand, NSCLC: non-small cell lung carcinoma).

potencies. Among pharmaceutical compounds, thiazolidinedione (TZD) class of insulin-sensitizing drugs (also called glitazones) are best known to operate as ligands to PPAR γ [21, 22] while long-chain polyunsaturated fatty acids are the most well-characterized endogenous ligands [23].

The activated PPAR γ protein becomes operational following its heterodimerization with retinoid X receptors (RXR) [24]. The PPAR γ /RXR complex translocates to the nucleus where it binds to target genes which contain a peroxisome proliferator response element (PPRE). A PPRE consist of a direct repetition of the consensus sequence AGGTCA separated by a single nucleotide (Direct repetition; DR1) [17]. To initiate transcriptional regulation of PPRE-bearing genes, the PPAR γ /RXR complex requires accessory proteins to bind on. These proteins can either trigger (coactivators) or represses gene transcription (corepressors) (Figure 1). It must be noted though that besides their PPAR γ -dependent genomic effects, PPAR γ ligands can also influence cellular biology via nongenomic, PPAR γ -independent events [25] (Figure 1).

As a rule, the transcriptional activity of PPAR γ is negatively modulated through phosphorylation by MAPK [26–28]. Phosphorylation of human PPAR γ 1 protein at Ser-84 site restrains its function [27], and phosphorylation of PPAR γ 2 modifies the A/B domain and reduces its ligand binding affinity [29]. However, not all phosphorylation events are inhibitory. For example, it has been found that missense mutation which results in the conversion of proline to glutamine at position 115 can render PPAR γ 2 constitutively active through modulation of the MAPK-dependent phosphorylation status of serine 114 [30] while phosphorylation by protein kinase A (PKA) was shown to enhance its activity [31].

Until now, three molecular processes have been proposed for the termination and downregulation of PPAR γ signaling: the phosphorylation of Ser-84/112 of PPAR γ 1/2 by ERKs [27], the proteasomal degradation of ligand-activated PPAR γ [32], and the interaction with MEKs, which promotes its expulsion from the nucleus [33].

3. PPAR γ IN CANCER

Early studies portrayed PPAR γ as an important regulator of preadipocyte differentiation and glucose homeostasis. Later on, it was identified that PPAR γ regulates biological processes which are considered hallmarks of cancer such as cell differentiation, apoptosis, and angiogenesis. This knowledge, coupled with data showing that PPAR γ ligands could yield anticancer effects in several cell types, led researchers postulate a role for PPAR γ in carcinogenesis [11, 34, 35].

Apoptosis is believed to be a fundamental molecular mechanism through which PPAR γ activators exert their action against cells which undergo malignant transformation [36–38]. Moreover, apart from their direct inhibitory effects on cancerous transformed cells, PPAR γ can also inhibit angiogenesis which is a prerequisite for tumor formation and growth [39–41]. It is suggested that the antiangiogenic activity of PPAR γ can be accomplished either by blocking the production the angiogenic ELR+CXC chemokines by cancer transformed cells or by inducing expression of the thrombospondin-1 receptor CD36 in endothelial cells [42–44]. In addition, latest exciting data, which showed that PPAR γ agonists were able to inhibit the canonical WNT signaling in human colonic epithelium, raises hopes that such agents can possibly block cancer initiation at a stem cell level [45].

It must be underlined herein that despite demonstration of cancer-preventive effects of PPAR γ ligands in vitro, clinical trials and animal models failed so far to show significant benefits [46]. The fact that PPAR γ ligands have been used in clinic trials at concentrations above those needed to elicit receptor agonistic activity poses questions for receptor-independent off-target effects [47].

3.1. PPAR γ and gastrointestinal cancer

PPAR γ are heterogeneously expressed throughout the gastrointestinal epithelium, showing significant differences in abundance, distribution, and functions. This protein is principally expressed in differentiated epithelial colonic cells, preferably in the proximal colon [48]. Sarraf et al. showed that PPAR γ activation could stimulate a program that is characteristic of colonic cell differentiation [49].

A functional genomics analysis conducted for the identification of PPAR γ gene targets revealed that the majority of these genes were transcribed throughout the colon, but their expression varied in cells purified from the proximal colon and in those from the distal colon. Metabolic functions of PPAR γ were elicited primarily in the proximal colon, whereas signaling functions were recognized in the distal colon. Interestingly, TZDs transactivated the PPAR γ gene targets at the proximal colon but repressed them in the distal colon. TSC22, a TGF β target gene known to inhibit colon cell proliferation, was also identified as a PPAR γ target gene [50]. It is worth mentioning that both TGF β and PPAR γ pathways attenuate during transition from adenoma to carcinoma [51]. From a pharmacological point of view, Yamazaki et al. showed that activation of the RXR/PPAR γ

heterodimer by their respective ligands could be considered a useful chemopreventive strategy for colorectal cancer. They found that a combination of the RXR alpha ligand 9-cis-retinoic acid with ciglitazone synergistically inhibited the cell growth and induced apoptosis in Caco2 human colon cancer cells that expressed high levels of p-RXR alpha protein [52].

In the most widely used preclinical model of sporadic colon carcinogenesis, the azoxymethane-treated mice, activation of PPAR γ suppressed carcinogenesis but only before damage to the APC/beta-catenin pathway [53]. However, two papers published ten years ago reported that troglitazone and rosiglitazone increased occurrence of colon tumors in mice-caring mutations in the APC gene [48, 54]. Moreover, although pioglitazone was later reported to suppresses colon tumor growth in Apc+/- mice [55], biallelic knockdown of PPAR γ in colonic epithelial cells was associated with an increase of tumor incidence [56]. It should be reminded, however, that although TZDs are considered pure PPAR agonists, they also wield off-target effects not mediated through linkage to PPAR receptors. An in-depth analysis of the role of TZDs against colon cancer can be facilitated through development of tissue-specific PPAR γ knockout mice [57]. Interestingly, a small phase II clinical trial using troglitazone failed to document tumor responses in patients with advance stage metastatic colon cancer [58].

Overall, existing evidence indicates that PPAR γ agonists have a potential to inhibit cancer formation in the distal colon, but they are practically inactive in advanced stages of colon cancer.

3.2. PPAR γ and lung cancer

Lung cancer is a major global health problem because of its incidence and mortality. It remains the top cancer killer worldwide to which early-detection strategies and development of new therapies failed so far to improve its lethal outcome [59]. This tobacco-related cancer epidemic persists despite public implementation of tobacco control measures because the majority of tobacco-smoke users declare powerlessness to quit. Therefore, the search for potent chemopreventive agents and the development of effective chemoprevention strategies for lung cancer is a viable pursuit highly justified [60, 61].

Several studies have shown that PPAR γ agonists can inhibit growth and induce changes associated with differentiation and apoptosis in lung cancer [62–64]. TZDs induced upregulation of PTEN and p21, downregulation of cyclins D and E, and reduced expression of fibronectin and its receptor integrin $\alpha 5\beta 1$ in human lung carcinoma cell lines [65–68].

A first evidence of clinical efficacy of PPAR γ agonists as cancer chemopreventives in lung cancer was recently published. A retrospective analysis of a database from ten Veteran Affairs medical centers revealed a significant reduction (33%) in lung cancer risk in diabetic patients who were treated with TZDs compared with nonusers of TZDs [69]. However, other studies damped early this enthusiasm by showing that diabetic patients treated with TZDs were at increased risk for cardiovascular complications [70].

It is critical to understand that cancer-protecting effects of PPAR γ agonists in lung cancer can be PPAR γ dependent but also PPAR γ independent [71]. Characteristically, TZDs suppressed the expression of antiapoptotic mediator prostaglandin E(2) in NCLC cells through induction of 15-hydroxyprostaglandin dehydrogenase [72] and enhanced TRAIL-induced apoptosis through upregulation of death receptor 5 DR5 and downregulation of c-FLIP in human lung cancer cells [73].

The combination of PPAR γ agonists with other chemopreventive agents emerges as a challenging issue in lung cancer chemoprophylaxis. Notably, an amazing synergy of clinically achievable concentrations of lovastatin (an HMG-CoA reductase inhibitor) and troglitazone was recently shown against lung cancer cells [74]. This effect was accompanied by synergistic modulation of E2F-1, p27 \wedge Kip1, CDK2, cyclin A and RB. In another study, a combination of low-doses of MK886 (5-lipoxygenase activating protein-directed inhibitor), ciglitazone and 13-cis-retinoic acid, also demonstrated synergistic inhibitory activity against lung cancer cells [75]. These studies provide a framework for the development of rationally designed drug combinations aimed to target simultaneously the PPAR γ and other cofactors.

3.3. PPAR γ and other malignancies

Epidemiological studies suggested that high consumption of carotenoids (known PPAR γ activators) could protect women from the development of breast cancer [76, 77]. These findings are also supported by experiments which show that activation of PPAR γ can induce terminal differentiation, cell cycle arrest, or apoptosis of preneoplastic and cancerous mammary epithelial cells [78–80]. Unfortunately, this is not the case for advanced breast cancer: a phase II trial of troglitazone in patients with breast cancer metastases failed recently to prove clinical benefits [81].

Prostate cancer appears to be an attractive tumor target for PPAR γ agonists because cancerous prostate cells express higher levels of PPAR γ compared with their normal counterparts [82]. Moreover, it has been shown that PPAR γ 1/2 activation suppressed the high level of endogenous COX-2 in normal prostate epithelial cells [83] while TZDs mediated apoptosis in prostate cancer cells through inhibition of Bcl-xL/Bcl-2 functions [84]. In the clinical setting, reduction and prolonged stabilization of prostate-specific antigen levels were demonstrated in patients treated with troglitazone [82, 85]. The above data provide a rationale to consider investigating PPAR γ ligands for their role in preventive and possibly therapeutic management of prostate cancer.

In gynecological cancer, Wu et al. reported that rosiglitazone could block or delay the development of hyperplasia and subsequent endometrial cancer. This PPAR γ agonist induced apoptosis in both PTEN intact and PTEN null cancer cell lines and decreased proliferation of the endometrial hyperplastic lesions in a PTEN(+/-) murine model [86].

In human pancreatic cancer cell lines, treatment with TZDs was found to induce cell cycle arrest and increase expression of pancreatic differentiation markers [87, 88].

Moreover, activation of PPAR γ together with RXR resulted in suppression of pancreatic cancer cell growth through suppression of cyclin D1 [89].

Among sarcoma tumors, it is liposarcomas which are considered targets for PPAR γ agonists because they show a high expression of this nuclear receptor [90]. However, although pioglitazone was found capable to terminally differentiate human liposarcoma cells in vitro, it failed an early phase II trial despite induced changes in relevant target genes [91].

In thyroid cancer, a functional chromosomal translocation of part of PAX8 gene which encodes the DNA-binding domain to the activation domain of the PPAR γ gene has been detected in patients with follicular type carcinoma [92]. This chimeric fusion protein is resistant to PPAR γ ligands, invalidating any anticancer effects of PPAR γ ligands in this setting. However, it has been suggested that PPAR γ ligands could have activity in combination with retinoids and/or histone deacetylase inhibitors in thyroid tumors which express both PPAR γ and also RXR γ [93, 94].

4. PPAR γ AS A MEDIATOR TO CANCER PROTECTING NATURAL PRODUCTS

Evidence has accumulated which affirms that bioactive natural compounds can play an important role in cancer chemoprevention through modulation of PPAR γ . Preclinical studies and epidemiological data support that tumor growth and metastasis can be restrained or delayed by several herbal products [95–98]. Moreover, it is believed that novel agents derived from bioactive phytochemicals can be used as adjuncts to enhance therapeutic efficacy of standard treatments [99, 100]. Among natural products, triterpenoids, flavonoids, carotenoids, and linoleic acid are the most extensively studied as cancer chemopreventives and have invariably been found to operate as PPAR γ activators.

Terpenoids of plant origin have shown antitumor activity which indicates a potential role for these compounds as cancer chemopreventives [100–102]. Specifically, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), a synthetic triterpenoid, which was shown to activate PPAR γ and induce growth arrest and apoptosis in treated breast cancer cells [103]; also, glycyrrhizin the major triterpene glycoside phytochemical in licorice root and the triterpenoid acid betulinic acid which is found in the bark of several species of plants, both have shown pro-PPAR γ activities in cancer cells. These phytochemicals were found to induce expression of proapoptotic protein caveolin-1 and the tumor-suppressor gene Kruppel-like factor-4 (KLF-4) in colon and pancreatic cancer cells [104, 105]. It should though be noted that although caveolin-1 is generally considered a proapoptotic molecule, it has also been associated with drug resistance and possibly metastasis [106]. It is believed that some PPAR γ agonists induce whilst others repress caveolin-1 [107].

Isoflavones are well known to function as phytoestrogens. They bind to the estrogen-related receptors but also to PPAR α and PPAR γ [108]. As a result, their biological effects are determined by the balance between activated ERs and PPAR γ [109]. Liang et al. investigated apigenin, chrysin,

and kaempferol in mouse macrophages and found that these flavonoids stimulated PPAR γ transcriptional activities as allosteric effectors rather than pure agonists [110]. In the clinical setting, purified isoflavones have only been investigated for safety, bioavailability, and pharmacokinetics in men with early-stage prostate cancer [111–114].

Carotenoids are another class of phytochemicals found to activate PPAR γ in cancer cells. Hosokawa et al. reported that the edible carotenoid fucoxanthin, when combined with troglitazone, induced apoptosis of Caco-2 cells [115]. Moreover, in epidemiological studies, consumption of carotenoids was shown to protect against breast cancer [76, 77]. Interestingly, Cui et al. unveiled recently the molecular mechanisms which underlie the chemopreventive activity of β -carotene against breast cancer. They found that β -carotene significantly increased PPAR γ mRNA and protein levels in a time-dependent fashion, while 2-chloro-5-nitro-N-phenylbenzamide (GW9662), an irreversible PPAR γ antagonist, attenuated apoptosis caused by β -carotene in cancer-transformed cells [36].

Linoleic acid, a naturally occurring omega-6 fatty acid which is abundant in many vegetable oils, has been studied comprehensively for its prophylactic effects against cancer formation [116]. Conjugated linoleic acid, which is found especially in eggs and in the meat and dairy products of grass-fed ruminants, was shown to modulate cell-cell adhesion and invasiveness of MCF-7 cells through regulation of PPAR γ expression [117]. Moreover α -eleostearic acid (ESA), a linolenic acid isomer, induced apoptosis in endothelial cells and inhibited angiogenesis, also through activation of PPAR γ [118]. More recent studies brought up additional evidence and provided insights into molecular mechanisms of the protective effects of linoleic acid against colon cancer. Yasui et al. reported that 9trans-11trans-conjugated linoleic acid inhibited the development of azoxymethane-induced colonic aberrant crypt foci in rats at preinitiation and postinitiation level through activation of PPAR γ and downregulation of cyclooxygenase-2 and cyclin D1 [119]. In addition, Sasaki et al. showed that linoleic acid was capable to inhibit azoxymethane-induced transformation of intestinal cells and tumor formation [120]. In most studies, the differentiation-promoting and carcinogenesis-blocking effects were mostly attributed to activation of PPAR γ by linoleic acid products [121]. Finally, apart from its direct action as a PPAR γ activator, linoleic acid was found to modulate interactions between PPAR β/δ and PPAR γ isoforms [122].

Finally, in the class of capsaicinoids, capsaicin, the spicy component of hot peppers, was shown to induce apoptosis of melanoma as well as colon and prostate cancer cells, and was associated with activation of the PPAR γ in the case of colon cancer [123–125]. However, controversy exists regarding cancer-preventing and cancer-promoting effects of capsaicin [126, 127].

It must be noted that besides their PPAR γ -mediated effects, natural products can also induce transcription of detoxification enzymes glutathione S-transferases (GST) which are known to protect cells from chemical-induced carcinogenesis [128, 129]. Recently, Park et al. examined GSTA2 gene induction by thiazolidinedione and 9-

cis-retinoic acid and investigated the molecular basis of PPAR γ /RXR-mediated GSTA2 induction in the H4IIE hepatocytes. They found that both PPAR γ and RXR agonists could increase the expression of GSTA2 but treatment of cells with a combination of PPAR γ and RXR agonists produced synergistic increase [130]. This data suggest that cancer-preventive functions of PPAR γ activators may be related to some extent to a parallel induction of GSTA2.

5. CONCLUSION

Existing data suggest that peroxisome proliferator-activated receptor-gamma (PPAR γ) is a potential target ally to cancer chemopreventive agents. Although PPAR γ was first understood as a key regulator of adipocyte differentiation and glucose homeostasis, it is now recognized that it is also involved in cell proliferation, differentiation, apoptosis, and angiogenesis. Meticulous research for PPAR γ agonists with potency to function as cancer chemopreventive agents is highly warranted.

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