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THE ROLE OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS IN CARCINOGENESIS AND CHEMOPREVENTION

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that are involved in regulating glucose and lipid homeostasis, inflammation, proliferation and differentiation. Although all of these functions might contribute to the influence of PPARs in carcinogenesis, there is a distinct need for a balanced review of the literature and additional experimentation to determine the potential for targeting PPARs for cancer therapy and cancer chemoprevention. As PPAR agonists include drugs used for the treatment of metabolic diseases, a more complete understanding of the roles of PPARs in cancer will aid in determining any increased cancer risk for patients undergoing therapy with PPAR agonists.

At a glance

- PPARs have central roles in the regulation of glucose and lipid homeostasis through their functions as molecular sensors responsive to endogenous ligands leading to modulation of gene expression. PPARs also regulate cell proliferation, differentiation and inflammation.
- PPARα mediates hepatocarcinogenesis induced by long-term administration of PPARα agonists in rodent models, an effect not found in humans. The mechanism underlying species-specific hepatocarcinogenesis is through mouse PPARα-dependent regulation of the let-7c miRNA leading to increased expression of the oncoprotein MYC. The current interest in targeting PPARα for the prevention of certain cancers including colon and leukemia is based on studies showing that PPARα agonists inhibit proliferation of endothelial cells, increase synthesis of PPARγ agonists and potentially interfere with the Warburg effect.
- The role of PPARβ/δ in carcinogenesis is controversial. Several studies have shown that PPARβ/δ is upregulated in cancer cells by the adenomatous polyposis coli (APC)–β-catenin–TCF4 pathway and has a pro-tumorigenic effect in many cancer types. However, other studies have shown that PPARβ/δ agonists can induce terminal differentiation and inhibit innate inflammation, suggesting anti-cancer effects. In addition, a retrospective study has shown that low expression levels of PPARβ/δ are associated with decreased survival of colorectal cancer patients.

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Therefore, there remains a need to further examine the PPARβ/δ protein expression patterns quantitatively in tumor models and the putative mechanisms mediated by PPARβ/δ agonists associated with anti-apoptotic or growth stimulatory effects.

- PPARγ agonists can induce terminal differentiation, inhibit cell proliferation, promote apoptosis and inhibit innate inflammation in many cancer models. This has led to a number of clinical trials with PPARγ agonists, but these have generated mixed results. Moreover, some PPARγ agonists have been associated with pro-tumorigenic effects. Emerging evidence indicates that targeting PPARγ in combination with other chemopreventive or chemotherapeutic agents might increase the efficacy of the effects induced by monotherapies.
- Due to similarities in the abilities of the three PPARs to improve different metabolic disorders known to be associated with increased cancer risk (such as diabetes, obesity, dyslipidemias and chronic inflammation), modulating activities of the PPARs remains an attractive approach for the treatment and prevention of cancer. The challenge is to advance the discovery of molecular mechanisms of action in order to identify and characterize effective PPAR agonists with acceptable safety profiles.

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors. The three PPAR isoforms, PPARα, PPARβ/δ (also referred to as PPARβ or PPARδ) and PPARγ, are found in all mammalian species examined to date. Since the identification of the PPAR family more than twenty years ago, numerous studies have revealed that PPARs influence many important biological functions including inflammation, cell survival and differentiation. PPARs are activated by endogenous ligands derived from the metabolism of fatty acids and other compounds found in the diet, consistent with the fact that PPARs regulate the expression of many genes involved in glucose and lipid metabolism [1]. Through this mechanism, cellular homeostasis is maintained during periods of feeding and starvation. Drugs and other xenobiotics can also differentially modulate PPAR regulatory activities.

Whether PPARs function as tumor suppressors or oncogenes in cancer is still unclear. The complexity of the pathways regulated by PPARs and the propensity of these pathways to be altered in cancer offers some explanations for the disparate functions of PPARs in different tumor types. However, as targeting PPARs can improve the clinical consequences of metabolic disorders known to be associated with increased cancer risk (such as diabetes, obesity, dyslipidemias and chronic inflammation), modulating activities of the PPARs is an attractive approach for the treatment and prevention of cancer. The challenge is to elucidate the molecular mechanisms of action of PPAR agonists in different tissues and tumor types, and to identify and characterize effective PPAR agonists with acceptable safety profiles. The progress in understanding PPAR function and translating this to the clinic is discussed below. In this Review, we pay particular attention to the controversial function of PPARβ/δ in colorectal cancer.

PPAR-mediated gene expression

Substantial progress has been made in delineating the molecular mechanisms that mediate PPAR regulated gene expression and the associated cellular functions (FIG. 1). Following ligand binding, PPARs undergo a conformational change that causes the release of histone deacetylase (HDAC) co-repressors enabling PPARs to heterodimerize with retinoid X receptor (RXR). RNA polymerase II and co-activators with histone acetyl transferase (HAT) activity are then recruited to this complex, which binds to response elements in target genes leading to chromatin remodeling and ultimately increased transcription (FIG 1a). PPARβ/δ has also been shown to repress the transcription of some target genes through binding to

DNA response elements in association with co-repressors, independent of ligand binding [2, 3] (FIG. 1d). Data from reporter gene assays in cultured cells indicates that PPARβ/δ might repress PPARα and PPARγ-dependent gene expression [2]. However, follow-up studies examining this mechanism have largely been negative to date [4–7]. PPARs can also down-regulate gene expression by interfering with other proteins and transcription factors through a "trans-repression" mechanism (FIG. 1b). For example, PPARα and PPARβ/δ can sequester the p65 subunit of the nuclear factor kappa beta (NFκB) complex and prevent NFκB-dependent regulation of genes involved in pro-inflammatory responses (reviewed in [8–13]). Alternatively, trans-repression by PPARγ can involve its SUMOylation (FIG. 1c), where ligand activation leads to conjugation of PPARγ with SUMO, which binds with a nuclear co-repressor complex, causing repression of pro-inflammatory gene expression [14]. SUMOylation-dependent trans-repression might also be relevant for PPARα and PPARβ/δ because the amino acid that is SUMOylated is conserved between all three PPARs [15]. Trans-repression of pro-inflammatory signaling pathways is thought to be central to the well-documented anti-inflammatory activities associated with PPAR ligands and PPARs [8, 15]. More recently, it was shown that the beneficial effects of PPARγ activation in diabetics can be modulated by "non-agonist" PPARγ ligands that inhibit the phosphorylation of PPARγ and so are independent of the classic receptor-mediated modulation of gene transcription [16]. Thus, there are multiple levels of regulation that can be targeted to selectively alter PPAR-dependent activities.

The physiological functions of the PPARs

PPARα

PPARα, the first PPAR to be identified [17], is expressed in many tissues, particularly those that require fatty acid oxidation as a source of energy [18]. PPARα is central for maintenance of lipid homeostasis: a primary role of PPARα is to increase the cellular capacity to mobilize and catabolize fatty acids, particularly in the liver during starvation where oxidation of fatty acids is essential for energy production (FIG. 2, reviewed in [19]). Under these conditions PPARα is probably activated by endogenous fatty acids and fatty acid derivatives (reviewed in [19]). PPARα is also the molecular target of fibrates, widely used drugs that reduce serum lipids through the increased oxidation of lipids (reviewed in [19]). The number of direct PPARα target genes is large and reviewed elsewhere [20], but includes many that encode enzymes involved in glucose, lipid and amino acid metabolism [21]. PPARα can also improve insulin resistance in high fat and genetic models of diabetes through pleiotropic changes in gene expression that prevent weight gain and adiposity [22].

PPARβ/δ

PPARβ/δ also regulates glucose and lipid homeostasis (FIG. 2). PPARβ/δ is expressed in most tissues in rodents and humans [18, 23] and expression of PPARβ/δ seems to be highest in epithelia of the intestine, colon and skin [23, 24] where one study has shown that it co-localizes with RXR in the nucleus [24]. Ligands that activate PPARβ/δ increase serum high-density lipoprotein cholesterol levels in rats, non-human primates and humans [25–27]. This is probably mediated by PPARβ/δ-dependent expression of the reverse cholesterol transporter ATP-binding cassette A1 and increased apolipoprotein A1-specific cholesterol efflux [26]. Ligand activation of PPARβ/δ can also decrease serum triglycerides, prevent high fat diet-induced obesity, increase insulin sensitivity, and improve symptoms associated with metabolic syndrome [26, 28–30] through the regulation of genes encoding fatty acid metabolizing enzymes in skeletal muscle [28, 29] and genes encoding lipogenic proteins in the liver. PPARβ/δ also inhibits hepatic inflammation caused by genetic, dietary and chemical stimuli [31–35] in part by the trans-repression of NFκB-dependent signaling, resulting in reduced expression of cytokines such as tumor necrosis factor-α (TNFα), interleukin–1β

(IL1β) and IL6 (FIG. 1). Activating PPARβ/δ can also promote terminal differentiation in keratinocytes, intestinal epithelium, oligodendrocytes and osteoblasts (reviewed in [9–11, 36]) and this function might have important consequences for tumor development.

PPARγ

The physiological effects of PPARγ activation are mediated primarily by PPARγ1 and PPARγ2 derived from four different mRNA species (*PPARG1*, *PPARG2*, *PPARG3* and *PPARG4*) [37, 38]. Comprehensive, quantitative expression patterns of PPARγ at the protein level have not been determined to date in any species, but expression of PPARγ protein has been demonstrated in many cell types. Significant non-specific immunoreactivity is found with some anti-PPARγ antibodies [39, 40], which probably impacts the interpretation of results from studies examining PPARγ expression. Polyunsaturated fatty acids, fatty acid derivatives such as 15-deoxy-delta-12,14-prostaglandin J2 (15d-PGJ2), 9-hydroxyoctadecadienoic acid (9-HODE), 13-HODE and nitrated fatty acids can activate PPARγ and may be endogenous ligands (reviewed in [1]). PPARγ is critical for development, in particular the placenta and heart [41], and is also essential for adipogenesis and fat storage (FIG. 2) [42, 43]. White adipose tissue is the primary target of the PPARγ agonists, the thiazolidinediones, which decrease serum lipids by increasing adipogenesis and lipid storage, and increase the expression of various adipokines, such as adiponectin and resistin [44], which collectively increase insulin sensitivity.

PPARs and cancer development

PPARα and liver cancer

Long-term administration of PPARα agonists causes liver cancer in rodents [45], an effect that is dependent on PPARα, as *Ppar*α-null mice are resistant to the hepatocarcinogenic effects of PPARα agonists [46, 47]. The mode of action for the hepatocarcinogenic effect of PPARα agonists has been determined and interestingly, this mechanism is not evident in humans (reviewed in [48]). Recent data from studies using PPARα humanized mice (mice expressing a human *PPARA* gene on a *Ppara*-null background) offers an explanation for this difference. Although the administration of PPARα agonists causes increased expression of target genes that modulate lipid catabolism in both wild-type and PPARα humanized mice [49], hepatocarcinogenesis and the down-regulation of the let-7c micro RNA cluster is only evident in wild-type mice [50, 51]. Let7c targets the mRNA encoding MYC and in its absence, the stability of *MYC* mRNA is increased, which might contribute to increased mitogenic signaling that causes hepatocyte proliferation [51].

A controversial role of PPARβ/δ in cancer

There is no broad consensus on the role of PPARβ/δ in cancer, due to contradictory studies in the literature (reviewed in [9–12]). However, two hypotheses have emerged (FIG. 3): that PPARβ/δ is over-expressed in tumors and promotes anti-apoptotic activities and increased cell proliferation and that PPARβ/δ promotes terminal differentiation and inhibits pro-inflammatory signaling, thereby attenuating tumorigenesis.

An initial finding that expression of *PPARB/D* mRNA was higher in four colon tumors compared with non-transformed tissue was taken to indicate a role for PPARβ/δ in colon cancer progression [52]. However, in this study the expression of *PPARB/D* mRNA was essentially absent in non-transformed colon tissue [52], a finding that is not in agreement with more recent studies from our laboratory and others in both mouse and human tissue showing that PPARβ/δ is constitutively expressed at high levels in normal colonic epithelium [23, 24, 53, 54]. The increased expression of *PPARB/D* mRNA in colon tumors has been attributed to APC–β-catenin–TCF4-mediated transcription, similar to the known β-

catenin–TCF4 target gene *CCND1*, which encodes cyclin D1. This led to the provocative hypothesis that PPARβ/δ regulates genes that increase cell proliferation and promote colon carcinogenesis [52] and provided the rationale for many follow-up studies. Although some of these studies support this hypothesis others do not (reviewed in [10, 11]). One of the fundamental issues of uncertainty is whether *PPARB/D* expression is increased or decreased in tumors. Indeed, since the original report suggesting that *PPARB/D* expression is increased by an APC-dependent pathway some studies have found that *PPARB/D* expression is higher in colon tumors compared with non-transformed tissue [55–62]. Studies using other tissues also indicate that expression of *PPARB/D* is higher in tumor tissue than non-transformed tissue, including ovarian carcinomas, squamous cell carcinomas, breast tumors and endometrial carcinomas[63–67]. By contrast, studies have also found that expression of *PPARB/D* is either unchanged or lower in colorectal tumors compared with non-transformed tissue [5, 53, 54, 58, 60, 68–76], (reviewed in [11]), and in ovarian or bladder carcinomas compared with normal tissue [77, 78]. However, there are important limitations to most, but not all [54], of these studies: they typically measure only mRNA expression and not protein expression; they often lack positive and negative controls; the number of samples examined is typically small; and protein expression is analyzed by immunohistochemistry. The sole use of immunohistochemical analysis of PPARβ/δ is particularly problematic because any non-specific immunoreactivity associated with anti-PPARβ/δ antibodies can produce misleading results [79, 80], (reviewed in [10]). More extensive studies examining whether PPARβ/δ expression is increased by the APC–β-catenin–TCF4 signaling pathway, including microarray analysis and quantitative analysis of cells or tissues with activating mutations in the β-catenin pathway, have not reported increased PPARβ/δ expression [54, 68, 72, 73, 79, 81, 82]. In addition, expression of PPARβ/δ is fairly high in normal human and mouse colon [23, 24, 53, 54] where it may function to maintain differentiation in response to an endogenous ligand. Although some data showing high expression of PPARβ/δ in human colon compared with other tissues are limited to analysis from two samples from a publically available database [23], the strength of this database lies in the ability to make comparison of relative expression with many different human tissues. These data are consistent with recent studies showing robust expression of PPARβ/δ in human samples of untransformed colon [53, 54] and one study in mice showing relatively high expression of PPARβ/δ in colon and intestine as compared to ten other tissue types [24]. However, it is important to note that expression of the PPARβ/δ protein does not necessarily indicate that it is active, as the protein could be modified by endogenous ligands that may or may not be present. It also remains possible that the biological outcome (promotion or inhibition of carcinogenesis) of PPARβ/δ expression depends on the presence or absence of other gene products (oncogenes or tumor suppressors, for example).

A recent retrospective study in humans showed that higher expression of PPARβ/δ in primary tumors was associated with lower expression of Ki-67 (a surrogate marker of proliferation), increased frequency of stage I cases, a lower frequency of later stage cases and a lower rate of lymph node metastasis [60]. Interestingly, PPARβ/δ was differentially expressed, with some primary tumors exhibiting relatively high expression while other primary tumors and lymph node metastases exhibiting relatively lower expression [60]. Importantly, patients with colorectal cancer with relatively low expression of PPARβ/δ were ~4 times more likely to die of colorectal cancer than those with relatively higher expression of PPARβ/δ in primary tumors [60]. Given the more precise quantification of PPARβ/δ in this study where immunohistochemical analysis was supported by western blot analysis, a large number of patients (141), and many years of follow-up (~ 15 years), this is the best evidence to date that supports the hypothesis that PPARβ/δ has a protective role in human colorectal cancer. Interestingly, a recent study has shown that the survival of patients with colorectal cancer whose tumor samples stained positive for both PPARβ/δ and cyclooxygenase-2 (COX2) expression was reduced compared with patients with tumors that stained only for

PPARβ/δ, COX2, or were not immunoreactive for either of these proteins [62]. This suggests that increased expression of PPARβ/δ in the presence of relatively high COX2 expression could cooperatively promote colorectal cancer. However, it is important to note that this study relies on immunohistochemistry only for estimating PPARβ/δ protein expression; there is no comparison of patient survival for those with lower versus higher expression of PPARβ/δ alone (the differences in PPARβ/δ expression between tumor samples is not described); and there is no comparison of survival for patients with different stage disease whose tumors were positive for COX2 only, as patients exhibiting this phenotype with early stage I tumors should survive longer than those exhibiting this phenotype with stage II–IV tumors [83].

Much like the conflicting human data, elucidating the function of PPARβ/δ in mouse cancer models is confounded by conflicting results (reviewed in [9–12]). For example, some studies indicate that colon carcinogenesis is exacerbated in the absence of PPARβ/δ expression and/or that ligand activation of PPARβ/δ attenuates tumorigenesis [5, 70, 74, 84]. Other studies found that colon carcinogenesis is inhibited in the absence of PPARβ/δ expression and that ligand activation of PPARβ/δ promotes tumorigenesis [85–87]. Similar paradigms exist for other tumor types (reviewed in [9–12]), but not all. For example, there is good evidence that PPARβ/δ protects against, and that ligand activation of PPARβ/δ attenuates chemically-induced skin carcinogenesis [88–92]. Some studies show that activating PPARβ/δ increases proliferation and/or inhibits apoptosis in a variety of human lung, breast, liver, prostate cancer cell lines, and in some cases correlative studies in animal models support these findings (reviewed in [9, 10]). However, studies from other laboratories show that activating PPARβ/δ either inhibits or has no effect on proliferation, and has no effect or promotes apoptosis, in human lung, breast and liver cancer cell lines; correlative studies in animal models also support some of these in vitro studies (reviewed in [9, 10]). Thus, more work is needed in mouse models to try and understand the complexities of PPARβ/δ in tumorigenesis. One possible factor that might influence the role of PPARβ/δ in cancer development or suppression is its effect on angiogenesis (Box1). However, the function of PPARβ/δ and PPARγ in angiogenesis is also controversial.

Several mechanisms have been proposed to explain the pro-carcinogenic effect of PPARβ/δ. Three of these mechanisms are based in part on data from cells resembling normal mouse primary keratinocytes [93, 94]. Analyses of these cells suggested that ligand activation of PPARβ/δ increases expression of 3-phosphoinositide-dependent-protein kinase 1 (PDPK1) and integrin linked kinase (ILK), and decreases expression of phosphatase and tensin homolog deleted on chromosome ten (PTEN) causing increased phosphorylation of AKT leading to anti-apoptotic signaling and enhanced cell survival (FIG. 3) [93]. Since this initial report, some studies in cancer models have supported these findings, but others have not (reviewed in [9–12]). Issues of contention include whether true keratinocytes were studied in the models that were used to suggest this pathway was functional [93, 94]. Our studies have shown that in human N/TERT-1 and HaCaT keratinocytes and mouse primary keratinocytes that express keratin 6 and normal patterns of keratinocyte differentiation markers, PTEN is not decreased, expression of PDPK1 and ILK is not increased, and/or phosphorylation of AKT is not increased by ligand activation of PPARβ/δ, despite clear up-regulation of known PPARβ/δ target genes [95, 96]. Indeed, we have also found that ligand activation of PPARβ/δ inhibits proliferation of mouse keratinocytes, mouse neoplastic keratinocytes, human HaCaT keratinocytes and N/TERT-1 human keratinocytes and does not promote survival [88, 89, 95–97]. Microarray analyses also show that expression of *PDPK1*, *ILK* and *PTEN* mRNA is unaffected by ligand activation of PPARβ/δ [9899100101]. In our hands, ligand activation of PPARβ/δ does not promote survival of human cancer cell lines or HaCaT keratinocytes following induction of apoptosis by a variety of stimuli [4, 54, 95, 102]. Thus, we

think that there are inherent limitations in establishing the putative ILK–PDPK1–PTEN–AKT pro-survival signaling as a mechanism mediated by PPARβ/δ.

A related mechanism proposed to explain the pro-carcinogenic effects of PPARβ/δ is also based on the idea that PPARβ/δ promotes cell survival by regulation of ILK–PDPK1–PTEN–AKT. It was suggested that the high ratio of intracellular fatty acid binding protein 5 to cellular retinoic acid binding protein II found in these cells diverts all trans retinoic acid to PPARβ/δ rather than the retinoic acid receptor which is thought to cause increased expression of PDPK1 leading to anti-apoptotic activities and increased cell survival [103]. However, follow-up studies do not concur with these findings ([4], reviewed in [9]).

Another related mechanism is based on the analysis of human colon cancer cell lines and *Apc*$^{min/+}$ mice. Ligand activation of PPARβ/δ increases expression of vascular endothelial growth factor (VEGF) through a PPARβ/δ-dependent mechanism causing increased phosphorylation of AKT, which promotes cell survival by blocking apoptosis [86]. Several studies have also found evidence supporting this mechanism, primarily by showing increased expression of VEGF in colon tumors or colon cancer cell lines following treatment with a PPARβ/δ ligand [87, 104, 105]. However, we have not found altered expression of either VEGF or phosphorylation of AKT in similar models in response to activation of PPARβ/δ [102].

It has also been shown that PPARβ/δ confers resistance to PPARγ-induced apoptosis in some cancer cells based on the expression levels of both proteins in HCT116 and LS174T cells [59]. However, we and others have shown that the ratio of PPARβ/δ/PPARγ is low in HCT116 cells, that expression of PPARβ/δ is actually similar between HCT116 and LS174T cells, and that expression of PPARγ is much lower in HCT116 cells than LS174T cells [39, 52, 79]. This suggests that the observed resistance to PPARγ-induced apoptosis in HCT116 cells could reflect differences in expression of PPARγ rather than PPARβ/δ.

Two mechanisms have been proposed to explain the chemopreventive effects of PPARβ/δ (FIG. 3). The hypothesis that PPARβ/δ promotes the induction of terminal differentiation is supported by evidence from multiple models including keratinocytes, intestinal epithelium, osteoblasts, oligodendrocytes, monocytes and in a variety of cancer models including colon, breast and neuroblastoma cells (reviewed in [9–11, 36]). This mechanism involves the increased expression of gene products required for terminal differentiation, altered expression of gene products that inhibit cell proliferation, and inhibition of cell proliferation, effects that are not seen in cells lacking expression of PPARβ/δ (reviewed in [9–11, 36]). Abundant evidence also supports the idea that PPARβ/δ can inhibit pro-inflammatory signaling. For example, more than fifty studies show that PPARβ/δ can inhibit expression of pro-inflammatory signaling by decreasing the expression of TNFα, IL1β, IL6 and MCP1 (reviewed in [8–13]). Many of these changes in the expression of pro-inflammatory signaling proteins are thought to be mediated by direct inhibition of NFκB-dependent signaling (reviewed in [8–13]) (FIG. 1), but PPARβ/δ-dependent inhibition of AP1 and STAT3 phosphorylation has also been described (reviewed in [8–13]). As inflammation is associated with the development of many cancers [106] and anti-inflammatory drugs are known to effectively prevent some cancers, it is curious that no studies to date have specifically examined whether activating PPARβ/δ could prevent tumorigenesis by inhibiting inflammation. Given the strength of evidence that PPARβ/δ can mediate potent anti-inflammatory activities, this hypothesis warrants detailed examination.

PPARγ and cancer

The function of PPARγ in tumor development is also controversial. There are many published studies showing that activating PPARγ prevents cancer in tissues such as colon,

breast, prostate, lung and many others (reviewed in [107, 108]). Indeed, the majority of studies to date show that PPARγ agonists can promote terminal differentiation, inhibit cell growth and increase apoptosis of human cancer cell lines; inhibit tumorigenesis in animal models of cancer; and in some cases PPARγ agonists have shown modest efficacy for chemoprevention in clinical trials (reviewed in [107, 108]). Overall survival of patients with colorectal cancer is markedly better when PPARγ expression is detectable in primary tumors compared with the survival of patients with colorectal cancer with no detectable PPARγ expression in their primary tumors [109], similar to the retrospective study examining a relationship between survival of colorectal cancer patients and expression of PPARβ/δ [60]. This is consistent with results showing that colon tumorigenesis is exacerbated in *APC*$^{min/+}$ mice with genetic ablation of *Pparg* compared with control *APC*$^{min/+}$ mice [110].

Ligand activation of PPARγ in cancer cell lines is associated with induction of cell cycle arrest, increased expression of mRNAs and proteins required for terminal differentiation including keratins, carcinoembryonic antigen, E-cadherin, alkaline phosphatase and differentiation-related gene-1 (DRG1), as well as changes in cell morphology consistent with a differentiated phenotype [111–115]. One mechanism that may mediate PPARγ-dependent induction of terminal differentiation is through an interaction with HIC5, which may serve as a PPARγ co-activator [116]. In this model, HIC5 and PPARγ cooperatively increase expression of fatty acid binding protein, kruppel-like factor 4 (KLF4) and keratin 20; proteins known to be required for epithelial differentiation [116]. Through this mechanism, cells differentiate and in doing so, undergo obligate cell cycle arrest (FIG. 4).

PPARγ agonists modulate expression of different cell cycle regulators, including decreasing the expression of cyclin D1 [117–121], increasing expression of the cyclin dependent kinase inhibitors p21 [111, 122] and p27 [122–127], and increasing turnover of β-catenin [128, 129]. PPARγ agonists can also inhibit cell proliferation by inactivating eukaryotic initiation factor 2 leading to the inhibition of translation initiation [130]. Although it is known that these changes contribute to the mechanisms through which PPARγ agonists inhibit cell cycle progression, the precise involvement of PPARγ in causing these changes remains uncertain.

Increased apoptotic signaling is another mechanism that mediates the growth inhibitory effects of PPARγ agonists. PPARγ agonists can increase the expression of pro-apoptotic BAX and BAD [131, 132], inhibit Bcl-XL and Bcl-2 function [131, 133], increase expression of PTEN [134–138], inhibit phosphatidylinositol-3 kinase activity and AKT phosphorylation [134, 139, 140], inhibit activation of Jun N-terminal protein kinase [131] and increase turnover of the anti-apoptotic protein FLIP [141, 142]. Many of these changes increase caspase activity and apoptosis. Although there is some evidence that PPARγ may be required for regulating expression of some of these proteins such as PTEN [136, 137], many changes are independent of PPARγ and likely represent off target effects of the individual PPARγ agonists (reviewed in [143]).

Chronic inflammation associated with many cancers including colorectal, liver and lung is typically associated with increased NFκB activity and is causally linked with tumor promotion [106]. PPARγ agonists can inhibit the production of pro-inflammatory signaling proteins such as TNFα, IL6 and MCP1 and these changes are mediated through trans-repression mechanisms including directly interfering with NFκB activity and/or through receptor SUMOylation (FIG. 1). PPARγ is expressed in tumor cells and infiltrating immune cells, and there is evidence that anti-inflammatory activities are mediated by PPARγ in many cell types [15, 144]. Indeed, PPARγ expressed in intestinal epithelial cells [145] and macrophages [146] inhibits inflammation associated with experimentally-induced colitis and inflammation is known to be required for colon carcinogenesis [147].

Despite this evidence suggesting that activating PPARγ inhibits tumorigenesis, doubts persist because some studies indicate that activating PPARγ promotes tumorigenesis [148, 149150, 151]. Indeed, increased bladder cancer incidence is reported to be associated with clinical use of rosiglitazone or pioglitazone, but there is evidence that this might reflect off-target effects of these PPARγ agonists [152153]. Additionally, despite a large body of in vitro and preclinical data showing that PPARγ inhibits breast cancer [154], over-expression of a constitutively active PPARγ fusion protein caused earlier lethality compared with controls in a breast cancer model [155]. However, it is worth noting that there are substantial differences in gene expression observed between the PPARγ fusion protein and that typically found in response to ligand activation of PPARγ [156]. No definitive mechanisms have been elucidated to date that explain these pro-carcinogenic effects.

PPARs and cancer treatment and prevention

Activation of PPARs causes physiological changes that in theory should make these receptors good targets for the treatment and prevention of cancer. For example, ligand activation of both PPARβ/δ and PPARγ promotes terminal differentiation (reviewed in [10, 11, 36, 107, 108]). Agonists for all three PPARs are also known to exhibit potent anti-inflammatory activities [8, 15].

PPARα

There are studies suggesting that activating PPARα could be useful for the prevention or treatment of different cancers. Oral administration of different PPARα agonists inhibited the growth of tumors derived from melanoma, Lewis lung carcinoma, glioblastoma, and fibrosarcoma cell lines [157], and xenografts from A549 human lung cancer cells [158]. PPARα agonists also inhibited angiogenesis in these models [157, 158]. These inhibitory effects are mediated by the PPARα-dependent inhibition of endothelial cell proliferation, and PPARα-dependent down-regulation of cytochrome P450 CYP2c, an enzyme that catalyzes epoxidation of arachidonic acid to epoxyeicosatrienoic acids [158] that promote angiogenesis. As these effects are not evident in *Ppar*α-null mice [157, 158], they are PPARα-dependent and thus PPARα agonists could be used to prevent multiple tumor types (FIG. 5).

There are two other potential PPARα-dependent pathways that could inhibit tumorigenesis or tumor growth (FIG. 5). First, PPARα inhibits inflammatory signaling through repressive mechanisms mediated by interacting with the p65 subunit of NFκB (reviewed in [8–13]). Because inhibiting NFκB-dependent signals, such as TNFα, can effectively inhibit the growth of multiple tumor types [159], targeting this PPARα-dependent activity may be useful. Second, PPARα agonists also negatively influence the Warburg effect by interfering with metabolic pathways. Ligand activation of PPARα can increase mitochondrial oxidation of fatty acids [160], and inhibit expression of glutaminase [21], which decreases glutamine levels and limits cancer cell growth. As fatty acids and glutamine are enzymatically produced by the Warburg effect and are substrates required for cell proliferation[161], targeting PPARα to inhibit tumor cell proliferation by interfering with the Warburg effect should be examined (FIG. 5).

PPARβ/δ

The potential for developing chemical agonists or antagonists of PPARβ/δ for chemoprevention remains uncertain. Given the observations that ligand activation of PPARβ/δ can inhibit or prevent metabolic syndrome, obesity, dyslipidemias, glucose intolerance and chronic inflammation, and all of these diseases are associated with cancer development [106, 162, 163], it is somewhat surprising that PPARβ/δ may promote carcinogenesis. Despite significant progress made in the past ten years, it is still not possible

to unequivocally indicate whether an agonist would promote or attenuate most types of cancer (FIG. 3), with the exception of non-melanoma skin cancer where the use of PPARβ/δ agonists looks promising [88–90, 92].

Several PPARβ/δ antagonists have been developed [164–168] and the effect of two of these has been specifically examined in human cancer cell lines. The bioavailable PPARβ/δ antagonist GSK3787 inhibits PPARβ/δ-dependent activity in vivo and in vitro, despite weak PPARγ agonist activity [169]. However, antagonism of PPARβ/δ in human cancer cell lines has no effect on cell proliferation [167, 169]. While one study suggested that another PPARβ/δ antagonist inhibits proliferation of the A549 human lung cancer cell line, the concentration required to cause this effect also interfered with PPARγ [168]. Given the central role of PPARβ/δ in many important biological functions (FIG. 2) ranging from regulation of glucose and lipid homeostasis, the maintenance of terminal differentiation, modulation of innate inflammation, and possibly cancer suppression, the development and use of a compound that specifically and exclusively antagonizes PPARβ/δ for the purpose of chemoprevention, may not be feasible.

PPARγ

As studies in mouse models and cultured cells indicate that PPARγ has potential for preventing or treating cancers, clinical trials have been undertaken to determine whether PPARγ agonists can inhibit tumorigenesis and tumor progression in patients with liposarcoma, colon cancer, breast cancer or prostate cancer. Increased differentiation in liposarcoma was observed in patients treated with troglitazone [170] and another clinical trial indicated that treatment with rosiglitazone increased the mean time to progression (defined as a doubling in tumor volume) [171]. However, no effect of rosiglitazone was found in a larger cohort of patients with prostate cancer [172]. Troglitazone has been tested in patients with prostate cancer with variable results on prostate-specific antigen (PSA) levels [173, 174] and administration of LY293111 to patients with prostate cancer had no clinical effect [175]. In two phase II studies, troglitazone had no effect in either patients with breast cancer or colorectal cancer[176, 177]. Some clinical trials examining the effect of PPARγ ligands combined with other therapeutics revealed no effect for some studies [178, 179], but positive results for patients with thyroid carcinoma and glioma [180–182]. It is also worth noting that a chromosomal translocation that fuses the paired box 8 gene (*PAX8*) with the *PPARG* gene is found in some cases of thyroid cancer [183]. The function of this PAX8–PPARγ fusion protein remains unclear as some studies show that it acts as a dominant negative against PPARγ activity whereas other studies indicate it retains more classic PPARγ transcriptional activity [184, 185]. Thus, the clinical trials to date have yielded evidence suggesting that PPARγ may be suitable for targeting in pre-cancerous and cancer cells in select tumor types.

Clinical studies show that administration of PPARγ agonists is associated with increased risk of heart failure [186], bone fractures [187–190] and possibly bladder cancer [153]. Whether these negative side effects are mediated by PPARγ, and whether they represent thiazolidinedione-specific or off-target effects remains uncertain. Because PPARγ ligands can elicit different transcriptional effects due to differential recruitment of co-activators [191], it is possible that unique PPARγ ligands could be developed that retain chemopreventive activities but do not lead to negative side effects. Indeed, troglitazone was removed from the market because of idiosyncratic liver toxicity, a side effect not observed with rosiglitazone or pioglitazone. The screening and identification of natural compounds that retain PPARγ-dependent and/or PPARγ-independent anti-cancer activities could be a useful approach [143, 192]. Alternatively, development of “non-agonist” modulators of PPARγ that exhibit improved safety profiles might be a suitable strategy [16]. This suggests that PPARγ remains a viable target for the treatment and prevention of cancer.

Interestingly, chemicals that antagonize PPARγ can also inhibit the proliferation or invasiveness of human cancer cell lines [193–196]. Studies show that some of these effects are due to PPARγ-independent mechanisms [197], but in one study, knocking down the expression of PPARγ mitigated the anti-proliferative effect of a PPARγ antagonist in a human cancer cell line [195]. This paradoxically suggests that PPARγ antagonists might be useful for inhibiting tumorigenesis. However, there are several limitations with suggesting that antagonizing PPARγ will inhibit tumorigenesis including that many of the effects induced by current PPARγ antagonists do not require PPARγ, suggesting that other off-target mechanisms underlie these effects; the nature of the putative endogenous ligand that promotes tumorigenesis remains unclear; and chemicals that antagonize a nuclear receptor can also act as agonists and whether this is true for the current PPARγ antagonists has not been examined extensively to date. This last point indicates that PPARγ antagonists could function similarly to tamoxifen, which retains both agonist and antagonist activities for the estrogen receptor in a cell and tissue-specific manner [198]. Thus, whether chemicals that target PPARγ as antagonists are useful for cancer chemoprevention remains to be determined.

Pan and dual PPAR agonists

It is conceivable that agonists that target more than a single PPAR might be suitable for treating or preventing cancer. Bezafibrate is a pan PPAR agonist but some of its effects are mediated by PPARα [7]. A number of studies suggest that bezafibrate can inhibit colon tumorigenesis in both rodent [199–201] and human cancer models [202]. Support for the idea that this is mediated by PPARα comes from data showing that a specific PPARα agonist, methylclofenopate, also inhibits intestinal tumorigenesis [203]. The molecular mechanisms underlying the effects of bezafibrate and methylclofenopate on colon tumorigenesis remain elusive. Bezafibrate can also cause growth arrest, induce terminal differentiation and apoptosis in Burkitt's lymphoma cells and these effects are enhanced by co-treatment with medroxyprogesterone acetate (MPA) [204]. These changes are mediated in part by an increase in the production of 15-deoxy-$\Delta^{12,14}$ prostaglandin J2 (15-dPGJ2), a natural ligand of PPARγ [204]. Moreover, bezafibrate induces similar changes in growth, differentiation and apoptosis in B-cell chronic lymphocytic leukemia cells, and co-treatment with MPA enhances these effects through a similar mechanism mediated by increased production of 15-dPGJ2 and apparent activation of PPARγ [205]. These observations suggest that the pan PPAR agonist bezafibrate might target myeloid cancers through a mechanism that increases PPARγ activity. As bezafibrate activates PPARα, it remains a possibility that PPARα is required for these effects but this has not been determined to date (FIG. 5). The recent clinical trial demonstrating that bezafibrate is chemopreventive for colon cancer in humans [202], supports the hypothesis that development of pan PPAR agonists with relatively lower affinity for the PPARs (that is μM versus nM) could be suitable for future chemopreventive approaches. Indeed, studies suggest that high affinity dual PPAR agonists can cause tumors, including bladder cancer, liposarcomas and hemangiosarcomas, in long-term bioassays [206], indicating that the use of low affinity agents might be a more suitable approach. Identification of new dual or pan PPAR agonists could be feasible because PPAR ligands can lead to unique alterations in gene expression based in part on differential recruitment of co-activators [191]. This could lead to characterization of chemicals that do not exhibit negative side effects associated with PPAR ligands including pro-carcinogenic effects in preclinical models [206, 207]. In fact, dual and pan PPAR agonists might also help offset side effects observed with more selective PPAR agonists. For example, weight gain or bone fractures observed in response to administration of PPARγ agonists [187–190, 206] might be offset by agonist activity for PPARα or PPARβ/δ, which can increase lipid catabolism and stimulate osteoblast activity in bone [208]. As there is also good evidence that combining PPAR activation with other chemopreventive or chemotherapeutic agents can significantly

increase anti-cancer activities [92, 209–220], it remains possible that dual or pan PPAR agonists could lead to even greater improvement in efficacy.

Conclusions

Agonists for all three PPARs induce many physiological changes including increased oxidation of fatty acids that contributes to reducing serum lipids and decreasing body weight, improved insulin resistance, and inhibition of inflammatory signaling. As metabolic syndrome, obesity, dyslipidemias, glucose intolerance and chronic inflammation are associated with increased cancer risk [106, 162, 163], there is good reason to suggest that PPAR agonists should be potential candidates for treating and preventing cancer. PPARα remains a viable target for the treatment and prevention of cancer because of evidence indicating that humans are refractory to the hepatocarcinogenic effects of PPARα agonists, and because PPARα agonists can exhibit anti-inflammatory and anti-carcinogenic effects. PPARγ also remains a potential target for the treatment and prevention of cancer, in particular for PPARγ agonists with good safety profiles. By contrast, whether PPARβ/δ is suitable for targeting for the treatment and prevention of cancer is uncertain because of numerous conflicting studies. It is of interest to note that there is overlap in target genes regulated by each PPAR, but the physiological effects induced by selective PPAR agonists are unique due to the complexity of PPAR-dependent and PPAR-independent effects each agonist induces. This also illustrates the complexity of PPAR regulation and the effects resulting from receptor activation, and why considerable research and drug discovery efforts are necessary to fully delineate the potential of targeting PPARs for the treatment and prevention of cancer.

Box 1. Controversial role of PPARs in angiogenesis

The role of PPARβ/δ and PPARγ in angiogenesis remains uncertain. Angiogenesis is a complex process that provides a blood supply to growing tumors and involves production of growth factors such as vascular endothelial growth factor (VEGF) to stimulate proliferation of endothelial cells, release of proteases and expression of cell adhesion molecules to allow proliferating endothelial cells to form new blood vessels. Studies show that PPARβ/δ ligands can either increase or decrease VEGF expression in cancer cells and endothelial cells [221, 222], and increase or decrease proliferation of endothelial cells: endothelial cells from *Pparβ/δ*-null mice proliferate faster than those from wild-type mice (reviewed in [10]). Functional studies revealed that activating PPARβ/δ promotes angiogenesis in both in vitro and in vivo models [223–225], and could explain some of the pro-tumorigenic effects associated with PPARβ/δ expression. While the mechanism remains uncertain, PPARβ/δ may regulate angiogenesis by inhibiting proliferation of endothelial cells [224]. PPARγ can either promote or inhibit angiogenesis in both in vitro and in vivo models depending on the context [226–230]. PPARγ agonists can also increase expression of VEGF in cancer cells [221, 231], but decrease endothelial cell viability [227]. The anti-angiogenic effects of PPARγ activation might be mediated by down-regulation of the VEGF receptor, whereas the pro-angiogenic effects might be due to increased endothelial nitric oxide synthase activity. Because PPARβ/δ and PPARγ cause differential effects on regulatory pathways that modulate angiogenesis (such as VEGF expression and endothelial cell proliferation), and there can be differences in the outcome of functional analyses, there is currently no consensus for the role of these receptors in angiogenesis and whether they are involved in enhancing or inhibiting metastasis.

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Glossary terms

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR	This class of nuclear receptor acquired their name because the first receptor of this class identified (PPARα) mediates the phenomenon of the proliferation of peroxisomes observed in rodents given fibrates and other chemicals.
AGONIST	A compound that binds to a receptor that invokes a biological response that is most often transcriptionally mediated. The specificity of an agonist is often defined by its ability to bind with the receptor at a given concentration and whether it is able to interact with a single receptor.
ANTAGONIST	A compound that binds to a receptor and blocks all known receptor activities induced by activation by an agonist. The potency of an antagonist is often defined by the concentration required to inhibit activation by an agonist.
CHEMOPREVENTION	The inhibition or prevention of disease by use of a drug or natural compound. Many chemopreventive agents show anti-inflammatory activities.

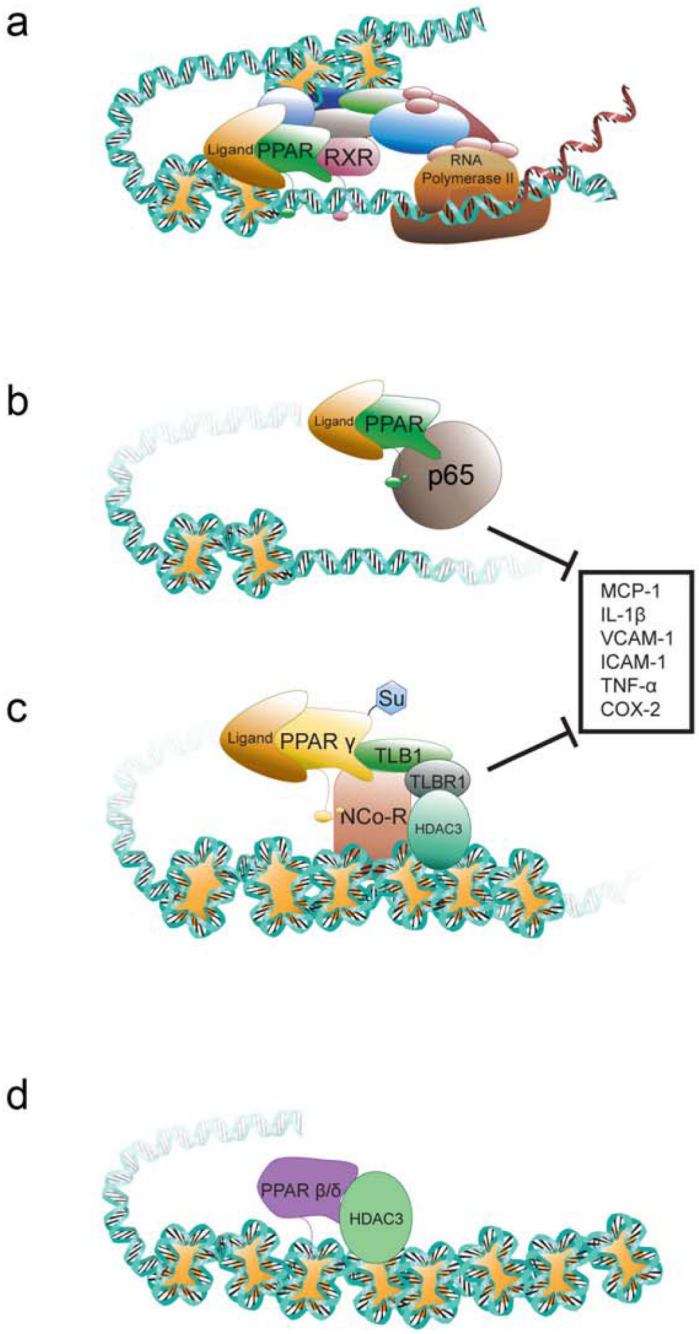

Figure 1. Molecular regulation of transcription by PPARs

a | Transcriptional up-regulation of target gene expression. Following ligand activation, PPARs heterodimerize with RXR, recruit transcriptional machinery including RNA polymerase and co-activators with histone acetyl transferase activity causing remodeling of chromatin and increased transcription. **b** | Repression of pro-inflammatory gene expression. PPARs can bind to proteins including the p65 subunit of NFκB and attenuate NFκB-dependent signaling. **c** | Repression of pro-inflammatory gene expression by PPARγ. In the presence of a toll-like receptor agonist and a PPARγ agonist, PPARγ is SUMOylated (Su) and then binds to a nuclear receptor corepressor (NCOR)-containing complex bound to a pro-inflammatory target gene (such as *TNF*, *IL6*). This prevents degradation of the NCOR

complex thereby maintaining active repression of pro-inflammatory gene expression. The lysine residue that is SUMOylated is conserved in PPARα, PPARβ/δ and PPARγ. Negative regulation of pro-inflammatory gene expression as shown in **b** and **c** underlies many of the anti-inflammatory activities associated with PPARs. **d** | Repression of gene expression by PPARβ/δ. PPARβ/δ can interact with histone deacetylases (HDAC) and maintain chromatin in a compact structure preventing gene expression. TBLX1, transducin-β-like 1, X-linked; TBLX1R1, TBLX1 receptor 1.

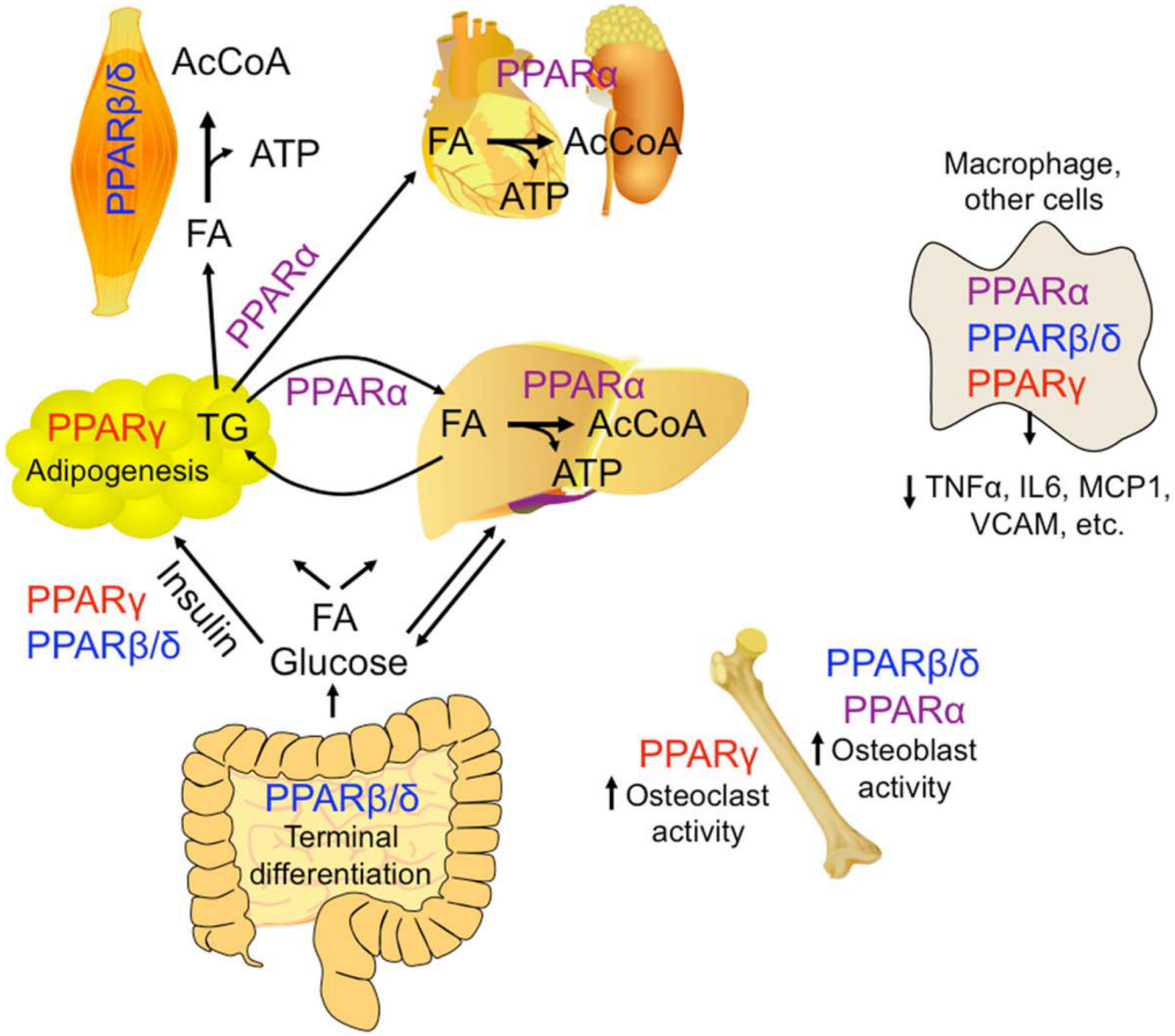

Figure 2. Physiological roles of PPARs

a | PPARα regulates expression of enzymes that lead to mobilization of stored fatty acids (FA) in adipose tissue. PPARα also regulates expression of fatty acid catabolizing enzymes in liver, heart and kidney. Released fatty acids are then oxidized in these tissues to ultimately generate ATP. PPARβ/δ is expressed at high levels in the intestine where it mediates induction of terminal differentiation of epithelium (also important for skin). Activating PPARβ/δ or PPARγ can increase insulin sensitivity causing improved glucose uptake in diabetic models. PPARβ/δ regulates expression of fatty acid catabolizing enzymes in skeletal muscle where released fatty acids are oxidized to generate ATP. PPARγ promotes differentiation of adipocytes. **b** | PPARα, PPARβ/δ and PPARγ can interfere with NFκB and AP1 in tissues including macrophages, endothelial cells, epithelial cells and others causing attenuation of pro-inflammatory signaling by decreasing expression of pro-inflammatory cytokines, chemokines and cell adhesion molecules, for example, in addition to other trans-repressive mechanisms (FIG. 1). **c** | Activation of PPARα and PPARβ/δ promote osteoblast

activity in bone whereas activation of PPARγ promotes osteoclast activity in bone. AcCoA, acetylCoA.

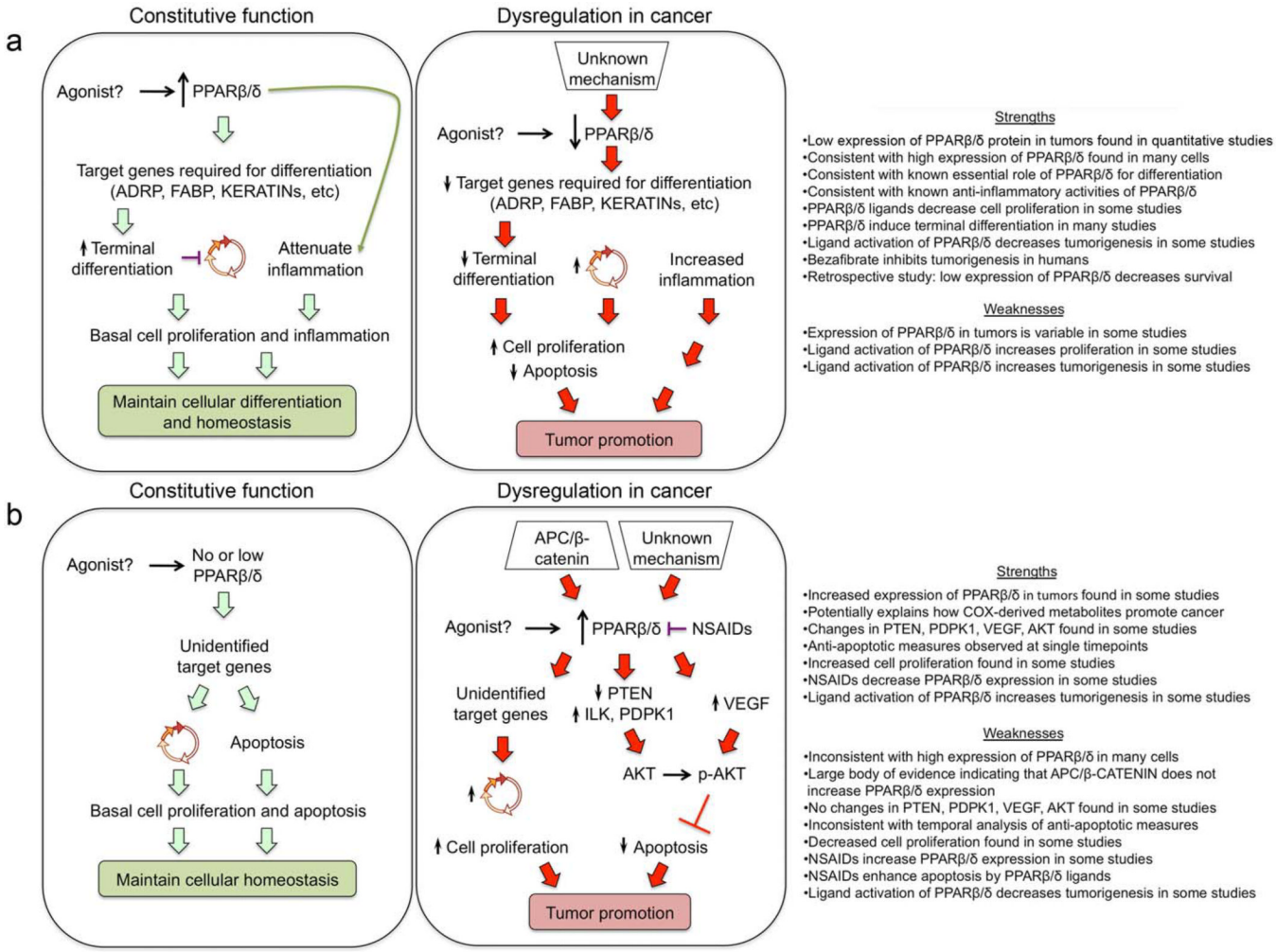

Figure 3. Contrasting mechanisms of PPARβ/δ in cancer

a | Expression of PPARβ/δ is high in epithelial cells and many other cell types. Unidentified endogenous ligands activate PPARβ/δ, increasing the expression of proteins required for promoting terminal differentiation and causing cell cycle withdrawal. Constitutive expression of PPARβ/δ also attenuates inflammation. Both of these effects explain how PPARβ/δ maintains cellular differentiation and homeostasis. Expression of PPARβ/δ in tumor cells is decreased through undefined mechanisms. This causes deregulation of terminal differentiation and inflammatory signaling that collectively causes increased cell proliferation and reduced apoptosis causing tumor promotion. In this model, ligand activation of PPARβ/δ prevents tumorigenesis and is most consistent with recent findings. The strengths of this model include that low expression of PPARβ/δ has been quantified in some tumor types and higher expression levels have been shown in normal cells and tissues. This is consistent both with data showing that PPARβ/δ is involved in cell differentiation and that some PPARβ/δ ligands inhibit cell proliferation. In addition, activation of PPARβ/δ is anti-inflammatory and this might in part explain why ligand activated PPARβ/δ decreases tumorigenesis in some studies, as does the pan PPAR agonist bezafibrate. This model is also consistent with a recent retrospective study showing reduced survival of colorectal cancer patients exhibiting relatively low expression of PPARβ/δ in primary tumors. The weaknesses of this model include that the expression of PPARβ/δ is variable in tumor types and normal tissues and that several studies have shown that ligand activation of PPARβ/δ

increases cell proliferation and tumorigenesis. **b** | A model based on the reduced expression of PPARβ/δ in normal cells. Unidentified endogenous ligands activate PPARβ/δ increasing expression of unidentified target genes that promote cell cycle progression and inhibit apoptosis. Expression of PPARβ/δ in tumor cells is increased through undefined mechanisms or by direct up-regulation mediated by APC–β-catenin-dependent signaling found in several tumor types. Unidentified endogenous ligands activate PPARβ/δ modulating expression of: PTEN, ILK and PDPDK1 or VEGF that collectively increase phosphorylation of AKT causing inhibition of apoptosis. Alternatively unidentified target genes that increase cell cycle progression could also be important. This model could explain how non-steroidal anti-inflammatory drugs (NSAIDs) inhibit tumorigenesis, although the reduced expression of PPARβ/δ is inconsistent both with the anti-inflammatory role of PPARβ/δ and data from other studies that NSAIDs increase PPARβ/δ and induce apoptosis. The strengths of this model include that increased expression of PPARβ/δ is found in some tumor types, consistent with studies that show that ligand activation of PPARβ/δ induces tumor development. In addition, this model might explain how COX-derived metabolites promote cancer. The weaknesses of this model include that other studies have shown that: PTEN, PDPK1, VEGF and AKT are not affected by PPARβ/δ, PPARβ/δ expression is not up-regulated by β-catenin and TCF4, PPARβ/δ does not promote anti-apoptotic activities, and ligand activation of PPARβ/δ decreases cell proliferation and tumorigenesis. This model is also inconsistent with studies showing relatively high constitutive expression of PPARβ/δ in epithelia.

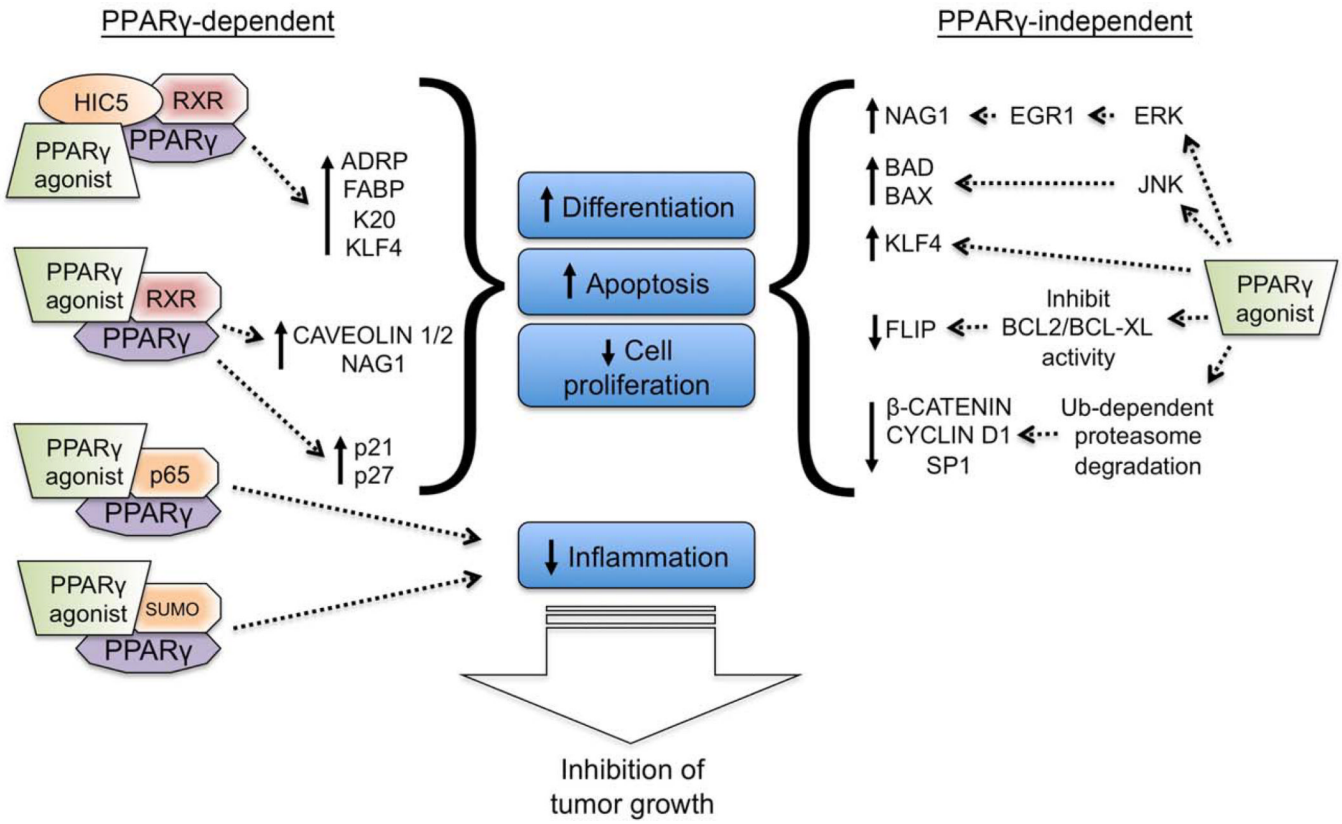

Figure 4. Targeting PPARγ for prevention and treatment of cancer

PPARγ agonists can cause both PPARγ-dependent and PPARγ-independent alterations that inhibit tumor growth. Following ligand activation, HIC5 (also known as TGFB1I1) can act as a transcriptional co-activator of the receptor complex and increase expression of genes required for induction of terminal differentiation. Ligand activation of PPARγ can also cause increased expression of caveloin, non-steroidal anti-inflammatory drug activated gene-1 (NAG1), p21 and p27 through an undefined mechanism that requires PPARγ. Ligand activation of PPARγ can attenuate inflammation by interfering with NFκB signaling and through a SUMO-dependent mechanism. In addition to these PPARγ-dependent signaling pathways, some PPARγ agonists also cause PPARγ-independent effects (off-target effects) that include induced terminal differentiation, increased apoptosis, decreased cell proliferation and inhibition of inflammation, all of which combine to inhibit tumor growth. The extent to which these changes are induced is unique for each PPARγ agonist and probably reflects differences in functional chemical groups present in the PPARγ agonists. ADRP, adipose differentiation related protein; EGFR, epidermal growth factor receptor; FABP, fatty acid binding protein; FLIP, FLICE inhibitory protein; JNK, JUN N-terminal kinase; K20, keratin 20; KLF4, Kruppel-like factor 4; RXR, retinoic X receptor; Ub, ubiquitin.

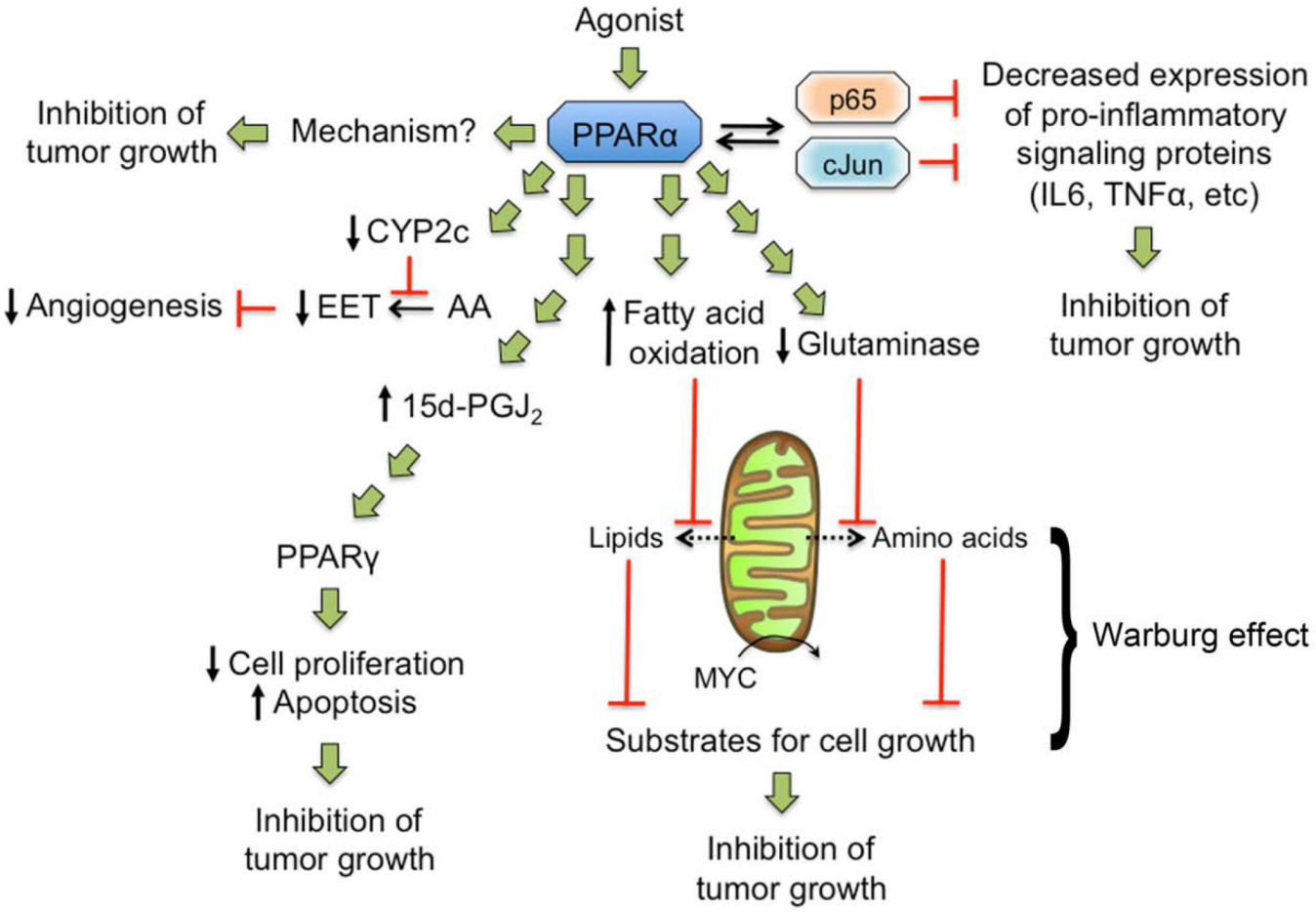

Figure 5. Potential targeting of PPARα for prevention and treatment of cancer

Activation of PPARα can inhibit cancer cell proliferation through an undetermined mechanism and interfere with pro-inflammatory signaling through trans-repression mechanism leading to reduced expression of anti-apoptotic proteins and tumor promoting molecules. PPARα ligands can increase the synthesis of the PPARγ agonist 15-Deoxy-Delta-12,14-prostaglandin J2 (15d-PGJ2), which can cause inhibition of cell proliferation and increased apoptosis in tumor cells. Activating PPARα could target tumor cells exhibiting the Warburg effect by decreasing lipids (due to increased catabolism) and inhibiting MYC-induced increases in glutaminolysis that generate amino acids (due to reduced glutaminase), substrates that are required for cell division. Ligand activation of PPARα can decrease expression of CYP2c causing reduced conversion of arachidonic acid (AA) to epoxyeicosatrienoic acids (EET), causing inhibition of endothelial cell proliferation and angiogenesis.