Minireview

Peroxisome Proliferator-activated Receptor γ and Cancers

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Abstract

The peroxisome proliferator-activated receptor γ (PPARγ) ligands have anticancer activity against a wide variety of neoplastic cells in vitro. Animal studies have chronicled their in vivo anticancer effects and chemopreventive capabilities. In addition, moderate anticancer activities of PPARγ ligands with minimal toxicities have been observed in patients with liposarcomas and prostate cancers. These compounds can slow growth and induce partial differentiation of selected cancer cells. They can decrease levels of cyclin D1 and E, inflammatory cytokines, and nuclear factor κB and increase expression of p21WAF1 and p27KIP1. Surprisingly, some or many of these effects may occur independently of PPARγ. Other data suggest that PPARγ may behave as a tumor suppressor gene, although several compelling murine models, paradoxically, suggest that under selected circumstances, PPARγ ligands may stimulate cancer formation. Nevertheless, the bulk of studies showed that PPARγ ligands do have antiproliferative activity against many transformed cells and may be helpful in the setting of adjuvant and chemopreventive treatments of several common tumors, including colon, prostate, and breast cancers.

Introduction

The PPARγ1 is a member of the NHR superfamily (1–4). It functions as a transcription factor after it heterodimerizes with the RXR and binds to specific response elements called peroxisome proliferating response elements (5). To act as a transcription factor, PPARγ requires activation by binding its ligand. Furthermore, the RXR member of this complex can also bind simultaneously with its ligand, which can result in enhanced transcriptional activity (6). The activated PPARγ/RXR heterodimer attaches to the peroxisome proliferating response element of a target gene, and coactivator proteins are recruited such as p300 (CBP), SRC-1, as well as the Drip 205 family of proteins (also known as TRAP 220) to modulate gene transcription (7). Different ligands of PPARγ appear to be able to recruit different coactivators (8, 9), which might provide specificity of biological activity of PPARγ.

Adipocyte tissue has some of the highest levels of PPARγ. However, the receptor is expressed in many other tissues and cell types throughout the body, including monocytes and macrophages (10), liver (11–13), skeletal muscle (14), breast (15), prostate (16), colon, and type 2 alveolar pneumocytes. Two PPARγ isoforms are derived by alternate promoter usage. Most tissue express the PPARγ 1 isoform, whereas the PPARγ 2 isoform is specific to adipocytes. Although a formal study has not been reported, cancer cells probably express an equivalent amount of PPARγ as their normal counterparts.

The 15-deoxy-Δ12,14-prostaglandin J2 is a naturally occurring PPARγ ligand. This eicosanoid can activate PPARγ at micromolar concentrations. Some unsaturated fatty acids also are natural ligands of the receptor. Synthetic PPARγ ligands, known as TZDs, include rosiglitazone (Avandia), pioglitazone (Actos), and troglitazone (Rezulin). The latter causes a severe idiosyncratic liver problem and thus has been discontinued. The TZDs are a breakthrough in the therapy of type II diabetes melitis because they decrease insulin resistance. TZDs enhance insulin action by increasing glucose uptake in the peripheral tissue as well as reducing the hepatic glucose output, and a strong correlation occurs between the ability of the ligand to activate PPARγ and the antidiabetic potency of the PPARγ ligand. A recently synthesized triterpinoid [2-cyano-3,12-divoalene-1,9-diene-28-oic acid] can bind to PPARγ and can induce differentiation and inhibit proliferation of a variety of cancer cells; and it has anti-inflammatory activity (17, 18).

Most of the known target genes that are transcriptionally activated by PPARγ belong to the pathway of metabolism and transport of lipids, including lipoprotein lipase, adipisin, fatty acid binding protein, Acyl-CoA synthase, and fatty acid transport protein. Furthermore, the PPARγ can mediate differentiation of the preadipocyte to adipocytes (19–21). The ligands of PPARγ can also repress transcription. For example, in monocytes and macrophages, they can lower the expression of cytokines such as IL-4 as well as proinflammatory products, including TNF, IL-1, as well as inducible nitric oxide synthetase (22–26). The proinflammatory transcription factors such as AP1, Stat, and NF-κB can also be inhibited. The mechanism by which this occurs is unclear. PPARγ can form weak interactions with the corepressors NCOR and SMRT (27). On the other hand, the repression produced by these compounds may be independent of acting as a ligand of PPARγ (discussed later). The target genes that mediate the anticancer activity of the activated PPARγ are unclear.

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3. The abbreviations used are: PPARγ, peroxisome proliferator-activated receptor γ; NHR, nuclear hormone receptor; RXR, retinoid X receptor; TZD, thiazolidinedione; TNF, tumor necrosis factor; IL, interleukin; NF-κB, nuclear factor κB; APC, adenomatous polyposis coli; TCF, T-cell factor; COX-2, cyclooxygenase 2; PSA, prostate-specific antigen.
Cancer and PPARγ

Cancer cells often obtain their proliferative advantage over their normal counterparts at least, in part, because of their inability to undergo terminal differentiation. They remain in the proliferative pool providing themselves with a growth advantage. Activation of NRs has been identified as an approach to induce differentiation and inhibit proliferation of cancer cells. The best example of this paradigm is the induction of remission of patients with acute promyelocytic leukemia using all-trans-retinoic acid (28, 29). All-trans-retinoic acid has also been used to prevent recurrence of head and neck cancers. Because normal preadipocytes can be induced to undergo terminal differentiation in the presence of ligands for PPARγ, investigators were encouraged to use TZDs to attempt to induce differentiation of human liposarcoma cells in vivo (30). Successes in vitro encouraged these same physician-scientists to give troglitazone to a series of patients with liposarcoma, which resulted in a retardation of growth and induction of differentiation of these tumor cells (31). The long-term effect of TZD on liposarcomas requires further study; nevertheless, these pioneer studies have spurred the examination of the effect of TZDs on a number of cancers both in vitro and in vivo. Table 1 provides a list of cancers in which PPARγ ligands have been shown to have an antiproliferative activity.

The genes regulated by PPARγ ligands in cancer cells that provide the antiproliferative and prodifferentiation activity are unclear. Often, the expression of the cyclin-dependent kinase inhibitors p21\(^{W vinegar}\) and p27\(^{Kip1}\) increase in the cancer cells exposed to PPARγ ligands, perhaps by inhibition of the ubiquitin-proteosome degradation pathway (32, 33). Perhaps blunting of expression or activity of a variety of inflammatory cytokines and transcription factors (i.e., TNF, IL-1, IL-4, NF-κB) may slow growth of the transformed cells. Also, the PPARγ ligand can induce apoptosis of cells with the activation of caspase-3; this is associated in some cancer cells with a decreased expression of the antiapoptotic proteins, BCL-2 and BCL-X\(_L\). DNA microarray technology was used to attempt to identify target genes of PPARγ in colon cancer cells using PPARγ agonists and antagonists. Many of the PPARγ selected targets were linked to the growth regulatory pathways (34).

Colon Cancer

Approximately 5% of individuals will develop colorectal carcinoma during their lifetime. It typically progresses from adenomatous polyps, dysplastic polyps to invasive carcinoma (35, 36). Colon cancer cells usually have a very high expression of PPARγ (13, 37, 38). Table 2 provides several key observations concerning colon cancer and PPARγ and its ligands. Several epidemiological studies suggest that PPARγ ligands have an anticolon cancer activity. Polyunsaturated fatty acids such as those present in fish oil, as well as nonsteroidal anti-inflammatory drugs, can activate PPARγ, and their consumption is associated with prevention of colon cancer (39, 40). Also, more directly, TZDs (5 × 10\(^{-6}\)–10\(^{-5}\) M) decreased the growth of colon cancer cells in vitro as well as when growing as xenografts in nude mice (41). These levels can be achieved clinically (42). A rough correlation exists between sensitivity of the colon cancer cells to their inhibition of proliferation by TZDs and their level of expression of PPARγ (13).

Mutations of PPARγ have been reported in colon cancers (36). In a large collection of 55 colon cancer samples, four somatic PPARγ mutations were found, three in exon 5 and one in exon 3. These mutations included one nonsense, two missense, and one frameshift mutation. The alterations affected the function of PPARγ and were not found in normal leukocytes of the same individuals, showing that these changes were not hereditary (36). The paradigm for most tumor suppressor genes is mutation of one allele and loss of the second allele, which is not the case for PPARγ in colon cancer. Each of the cancers with a mutant PPARγ also had a normal PPARγ allele. This suggests that the altered protein could either exert a dominant negative effect on the normal PPARγ gene product, or loss of 50% expression of PPARγ enhances the transformation to colon cancer. The approximate 50% loss of protein expression as a result of loss of an allele is known as haplo-insufficiency. Other examples of haplo-insufficiency include monoallelic germ-line RET mutations in Hirschsprung disease (43), monoallelic germline mutations of PTEN leading to Cowden Syndrome associated with a risk of development of breast and thyroid tumors (44), and monoallelic germ-line mutations of the AML1 gene associated with familial thrombocytopenia progressing to myelodysplastic syndrome and eventually to acute myeloid leukemia (45).

The frequency of PPARγ mutations in colon cancer is unclear. We examined 380 tumors and cell lines, including 55 colon cancers, and were unable to find any samples that had a PPARγ mutation (46). This suggests that PPARγ mutations may occur in cancers, but they are exceedingly rare.

A murine model does point to the protective role of PPARγ. Mice with heterozygous germ-line deletions of PPARγ (PPARγ\(^{+/−}\)) have an increased proclivity to develop carcinogen-induced colon cancer compared with wild-type mice (47). After injection of azoxymethane, all of the PPARγ\(^{+/−}\) mice, but only 50% of the wild-type mice, were dead of colon cancer by 36 weeks.

In contrast to the above investigations and observations, data from several groups draw into question the anticolonic cancer activity of PPARγ ligands. Two studies have shown that administration of a TZD to Mm mice resulted in these mice developing more frequent colon cancers than those animals.
which did not receive this PPAR ligand (48, 49). Mim mice have a germ-line mutation of the APC gene resulting in an increased frequency of small and large intestinal adenocarcinomas. In one of these studies, the Mim mice that received troglitazone had an average of three colonic cancers/mouse, whereas those that received diluent had a mean of one colonic cancer/mouse (48). The Mim mice in the second study received two different PPAR ligands; and these mice also had more colon tumors, which were also larger than the similarly treated wild-type mice. The number of small intestinal cancers was unchanged between the two groups, consistent with very little expression of PPAR in the small intestine (49).

Why do Mim mice receiving a TZD have more colon cancers and what does it mean for humans? The answers to both queries are unclear. The APC protein normally binds to β-catenin, retaining the latter in the cytoplasm and enhancing its degradation. Mutant APC loses this ability, and thus, the colons of Mim mice have high levels of β-catenin, which enters the nucleus, and binds and increases the activity of the family of transcription factors, called TCFs. This leads to the transcriptional activation of a number of cell cycle-related proteins, including c-myc and cyclin D1 (50, 51). The treatment of Mim mice with TZDs, for unclear reasons, increases the expression of β-catenin in their colons (49). In contrast, the normal colonic epithelium, as it undergoes differentiation from the crypts to the tip of the villi, decreases its expression of β-catenin, which dampens the growth promoting effects of TCFs. Thus, Mim mice appear to have a dysregulation of the normal differentiation process. This has relevance for humans because mutation of the APC gene is often the initiating event for ~80–90% of sporadic colorectal tumors (52).

Evidence has implicated PPAR in contributing to the development of colon cancer. Colon cancer cells often have high expression of PPAR (53), perhaps because inactivating mutations of APC leads to an active β-catenin/TCF4 transcription complex, which can enhance transcription of PPAR (36, 51, 53, 54). PPAR can have an antiapoptotic effect on colon cancer cells, thus providing these cells a growth advantage over their normal counterparts (54). PPAR may bind to the same target genes as PPAR, but it also binds tightly to corepressors. Therefore, PPAR may silence PPAR target genes similar to how retinoic acid receptor responsive genes are repressed by PML-retinoic acid receptor α in acute promyelocytic leukemia.

Furthermore, the COX-2 gene is highly expressed in ~70–80% of human colorectal carcinomas (55, 56). These high levels of COX-2 can result in elevated production of prostaglandin H2 that is rapidly converted to prostaglandin PGI, PGF2α, PGD2, and thromboxane A2. Prostaglandin I2 can activate PPAR (57, 58). Thus, colon cancer cells can have stimulation of PPAR from two directions, APC mutations causing hyperactivity of β-catenin/TCF4 and high levels of COX-2.

Interestingly, when COX-2 knockout mice were mated with Mim mice, the number and size of intestinal polyps markedly decreased consistent with COX-2, playing an important role in promoting the development of tumors in the APC mutant genetic background (59–61). Likewise, treatment of Mim mice with selective COX-2 inhibitors can reduce the number of polyps that develop (59). Clearly, additional studies are required to determine the role of ligands of PPAR in both the prevention and treatment of colon cancer. Also, the importance of PPAR in colon cancer requires additional investigation.

Breast Cancer

Breast cancer is one of the most frequent malignancies in females, with one woman in eight or nine developing breast cancer in her life. Breast cancer cells often express prominent levels of PPAR. Table 3 provides several salient observations concerning breast cancer and PPAR. A couple of studies have shown that ~10^-6–10^-5 m TZDs can inhibit proliferation and induce differentiation-like changes in breast cancer cell lines both in vitro and growing in nude mice (15, 62).

Additional studies have found that the combination of a retinoid with a PPAR ligand synergistically inhibited the growth and induced apoptosis of a series of breast cancer cell lines both in vitro and in xenografts growing in nude mice (62). This was associated with a decreased number of cells in S phase and an increased percentage of cells in G1. Up to 30–40% of the breast cancer cells cultured with a TZD and a retinoid became apoptotic with a fall in their levels of bcl-2. This apoptosis could be overcome by forced overexpression of bcl-2 in these cells (62).

In vivo experiments have shown that administration of a PPARγ ligand (GW7845) inhibited the development of carcinogen-induced breast cancer in rats (63). Another in vivo study showed troglitazone also prevented carcinogen (7,12-dimethylbenz(a)anthracene)-induced transformation of murine breast tissues (64). Furthermore, the addition of a retinoid to the PPARγ ligand greatly enhanced their abilities to prevent the transformation of the breasts (64). Of interest, mice who have a heterozygous germ-line deletion of PPARγ (PPARγ<sup>+/−</sup>) have a greater susceptibility to develop breast and ovarian cancers after their exposure to 7,12-dimethylbenz(a)anthracene, suggesting
that PPARγ has a protective role against development of these cancers (65).

In a series of interesting experiments with somewhat quiz-zical results, mice were genetically modified so that they con-stitutively expressed high levels of PPARγ in their breast tissue. These transgenic mice were mated with mouse mammary tumor virus polyoma middle T-expressing transgenic mice that are prone to develop breast cancer. Paradoxically, these mice had accelerated kinetics of development of breast cancer, suggesting that a ligand activated PPARγ under certain circumstances can actually enhance development of breast cancer (66). These experiments suggest that once an initiation event has occurred in breast tissue, increased PPARγ signaling might promote tumor progression in mammary gland tissue.

In summary, the overall role PPARγ plays in breast cancer is somewhat murky. In vitro and in vivo data show that PPARγ ligands can suppress breast cancer growth; and this can be enhanced by retinoids. However, two genetically modified murine models led to contradictory conclusions. Forced overexpression of PPARγ in the breasts of transgenic mice hastens their development of breast tumors; in contrast, loss of one PPARγ allele (PPARγ+/−), supposedly with reduced PPARγ expression, increased the risk of breast cancer in these mice after their exposure to a carcinogen compared with similarly treated control mice. Clearly, the role of PPARγ and its ligands in prevention and treatment of breast cancer needs clarification.

Prostate Cancer

Prostate cancer is the second leading cause of cancer-related deaths among men in the United States, with 40,000 men a year in America dying from this malignancy (67, 68). Although surgical resection and radiotherapy are both potentially curative for localized disease, advanced prostate cancer is associated with a poor prognosis. The blockade of androgen stimulation can lead to either partial or full remission, but the disease reemerges within several years in a poorly differentiated, androgen-independent form.

Prostate cancers often express fairly abundant PPARγ (69, 70). Furthermore, the PPARγ does not appear to be mutated in prostate cancers (15). In vitro studies showed that an androgen-independent prostate cancer cell line, PC-3, could be inhibited in its proliferative growth and undergo profound morphological changes when cultured with a ligand of PPARγ (Fig. 1). These cells develop prominent enlargement of the cytoplasm with numerous vacuoles. In some of the cells, the vacuoles are finely dispersed, whereas others have huge vacuoles that displace the nuclei, almost resembling adipocytes or signet ring cells. These vacuoles, however, are negative for lipids and thus do not stain with oil red 0. The cytoplasmic lumens often reveal short microvillous processes, suggesting an adenocarcinomatous differentiation. The cell surface also has short microvillous processes.

In additional investigations, TZDs, as well as prostaglandin J2, can down-regulate androgen-stimulated PSA production in the androgen responsive LNCaP prostate cancer cells (71). Reporter gene studies showed that TZDs inhibited androgen activation of an androgen response element in the regulatory region of the PSA gene. The mechanism by which TZDs inhibits the androgen signaling pathway is unclear, but it may be mod-ulating key transcriptional cofactors.

Individuals with prostate cancer have received troglita-zone as part of several clinical trials (15, 72). In the biggest study, 41 patients received 800 mg/day of troglitazone after they had radical prostatectomy with curative intent and sub-sequently developed a rising serum PSA without demonstra-ble prostate cancer. These patients, therefore, had a recurrence with a low tumor burden. They received TZD for 18–20 weeks, and the investigators believed that the speed of rise of the serum PSA for many of these individuals diminished while on treatment. However, the number of measurements of PSA before beginning troglitazone was few, complicating the calculation of the rate of rise of the serum PSA while on therapy as compared with before beginning of therapy. Furthermore, while receiving troglitazone, only 1 of 41 patients had a 50% decrease in his serum PSA, and an additional 7 of 41 patients had less than a 50% decrease in their serum PSA levels. Of those 7 individuals, 3 had androgen-dependent and 4 had androgen-independent prostate cancer. We also treated an individual who began having a rising serum PSA ~2 1/2 years after receiving a radical prostatectomy (Fig. 2). After beginning troglitazone, the PSA stabilized for 1 1/2 years; at which time, the individual discontinued the TZD because of concerns about potential liver toxicity from the TZD. Thus, although the results are not dramatic, ligands of PPARγ do appear to have moderate antiprostate cancer ac-tivity even against androgen-independent tumors, and because of the low toxicity of most TZDs, additional studies of these agents are probably warranted.

Table 3 PPARγ and breast cancer

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<tr>
<th>PPARγ: role in preventing and treating breast cancer</th>
<th>PPARγ: association with breast cancer</th>
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<td>1. TZDs decrease growth and induce differentiation and apoptosis of breast cancer cell lines in vitro and in nude mice.</td>
<td>1. Transgenic mice having a constitutively active PPARγ in their breast tissue mated with mouse mammary tumor virus transgens (breast cancer prone) result in mice with accelerated kinetics of breast cancer development.</td>
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<td>3. PPARγ ligands plus retinoids decrease mammary gland transformation in mice.</td>
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<td>4. PPARγ+/− mice are more susceptible than wild-type mice to carcinogen-induced breast cancer.</td>
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Acute Myeloid Leukemia

Macrophages and myelomonocytic leukemic cells express abundant PPARγ (73), and PPARγ ligands can induce acute myelomonocytic leukemic cells (THP1) to differentiate toward macrophages with an increased expression of the CD36 scavenger receptors, as well as other surface markers associated with differentiation including CD11b, CD14, and CD18 (73). Furthermore, other studies have shown that PPARγ ligands can inhibit the clonal proliferation of the U937 myeloid monocytic leukemic cells, and a PPARγ ligand plus 9-cis-retinoic acid was capable of synergistically inhibiting the clonal proliferation of HL-60, U937, and THP1 human myeloid leukemic cell lines. In general, however, the effect of PPARγ ligands on myeloid leukemic growth and differentiation is modest (74).

Is PPARγ a Tumor Suppressor Gene?

Conflicting data garnered in different model systems leaves open the question of whether PPARγ is a tumor suppressor gene (Table 4). Ligands of PPARγ can inhibit proliferation and induce differentiation and apoptosis of a wide-range of neoplastic cells, suggesting that PPARγ is a tumor suppressor gene. Indirect evidence is consistent with this premise. Many follicular thyroid carcinomas have the chromosomal fusion of the transcription factors PPARγ and PAX-8 (70). In vitro studies suggest that the PAX-8/PPARγ fusion protein can act in a dominant negative fashion inhibiting the activity of the normal PPARγ allele (70). Thus, this indirect evidence would suggest that inhibition of function of the wild-type PPARγ is associated with the development of thyroid cancer. Also, PPARγ heterozygous knockout mice (PPARγ+/−) have an increased susceptibility to develop colon, mammary, and ovarian tumors, as well as skin papillomas after administration of a carcinogen (65).
addition, mutations of PPARγ have been reported in primary colorectal carcinomas (75).

In contrast, other data suggest that PPARγ is not a tumor suppressor gene, including experiments with Mim mice fed a TZD, as well as transgenic mice who overexpressed PPARγ. These models suggest that PPARγ can act in a cancer-permissive fashion. Also, mice engineered to be PPARγ−/− in a variety of organ systems did not have an increased incidence of cancer in these tissues (76). In addition, an extensive study of ~400 clinical samples and cell lines from various human cancers did not detect PPARγ mutations (77). Furthermore, families having one of several different germ-line mutations of PPARγ have been identified. These individuals often have abnormalities of either fat metabolism or glucose homeostasis, but thus far, they have not been reported to have an increased proclivity to develop cancers (78–81).

In summary, the picture is unclear. Several in vitro and in vivo model systems suggest that PPARγ may behave as a tumor suppressor gene. In contrast, a couple of murine models are consistent with an activated PPARγ-enhancing tumor formation. Clearly, a better understanding of the mechanism of action of activated PPARγ is required. Adding to this complexity, a number of activities mediated by PPARγ ligands may not require PPARγ, as discussed in the next section.

Some of the Actions of PPARγ Ligands Can Occur Independent of PPARγ

Several pieces of indirect and direct evidence suggest that select anticancer activity of PPARγ ligands could occur independently of PPARγ (Table 5). Indirect evidence includes several studies that found that selective TZDs, including troglitazone but not pioglitazone or rosiglitazone, could inhibit cholesterol biosynthesis or affect cholesterol efflux from cells (82, 83). This selective response by some but not other PPARγ ligands suggests that the inhibition may not be mediated through PPARγ. Additional indirect evidence follows from the observation that pharmacological concentrations (10^{-6}–5 \times 10^{-5} \text{M}) of the PPARγ ligands are required to produce an anticancer activity or inhibit cytokines. In contrast, modulation of lipid-related genes and induction of differentiation of preadipocytes to adipocytes occurs at several logs lower concentrations, closer to the $K_d$ of PPARγ.

More direct evidence emanates from several studies. We (74) and others (84) noted that proliferation of several acute myeloid leukemia cell lines (KG-1 and KU812) was markedly inhibited by PGJ2. Several other studies used embryonic stem cells, which were made homozygously null for PPARγ (PPARγ−/−). In the first study, these cells were induced to differentiate down the macrophage pathway (85). Exposure of normal, activated macrophages to either PGJ2 or TZDs decreased their release of inflammatory cytokines such as TNF, IL-1 (IL-1β), IL-6, inducible nitric oxide synthase, and COX-2 (23, 26, 86). Surprisingly, exposure of the PPARγ−/− macrophages to either PGJ2 or TZDs also lowered their production of these anti-inflammatory molecules (85). In the second series of experiments, TZD inhibited proliferation, DNA synthesis, and caused a G1 cell cycle arrest of embryonic stem cells from both PPARγ−/− and PPARγ+/− mice (87). Likewise, TZDs inhibited both the expression of cyclin D1 and the growth of PPARγ−/− embryonic stem cell tumors growing in syngeneic mice (88).

How PPARγ ligands can act independent of PPARγ is under active study. Several hypotheses have been put forth. One group of investigators found that TZDs depleted calcium stores in PPARγ−/− ES cells leading to activation of protein kinase R that phosphorylated the α subunit of the eukaryotic initiation factor 2, causing its inactivation (87). Many cell cycle regulatory proteins as well as oncogenes contain highly structured GC rich 5’ untranslated regions, which can make them very dependent on the activity of the translation initiation factors such as
eukaryotic initiation factor 2α, and their inhibition by TZDs could explain the anticancer effects of these compounds. Several other investigations noted that the PPARγ ligand, 15-deoxy-
Δ12,14-prostaglandin J2 potently inhibited the NF-κB pathway and this could occur in the absence of PPARγ−/− in the target cells (88, 89). This PPARγ-independent inhibition may occur by covalent modifications of key cysteines in the inhibitor of nuclear factor κB kinase and the DNA binding domains of NF-κB subunits, preventing them from binding and transactivating cytokine- and growth-related genes.

In summary, PPARγ ligands do have antiproliferative, prodifferentiation, and proapoptotic effects on cancer cells. In combination with retinoids, these activities are enhanced. Although this class of nuclear hormone receptor ligands are unlikely to have a primary role in cancer therapy, their very low toxicity makes them inviting candidates for use in the adjuvant setting in combination with other drugs and for chemoprevention of selected cancers. At this time, anticancer efficacy of PPARγ ligands is being examined in liposarcomas (Dr. George Demetri, Boston, MA) and prostate cancer (Dr. Eric Small, San Francisco, CA). Prostate cancer studies are also planned at the Center for Cancer Research at the National Cancer Institute (Joseph A. Tangrea, Rockville, MD). A Phase IIa trial of the PPARγ agonist, pioglitazone, in oral leukoplakia is also being carried out at the National Cancer Institute, Division of Cancer Prevention. A breast cancer study is to be initiated shortly by Charlie (Berlin, Germany).

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References


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