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PPAR gamma, bioactive lipids, and cancer progression

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1. ABSTRACT

In this article we review the evolution of cancer research involving PPARgamma, including mechanisms, target genes, and clinical applications. For the last thirteen years, the effects of PPARgamma activity on tumor biology have been studied intensely. Most of this research has focused upon the potential for employing agonists of this nuclear receptor in cancer treatment. As a monotherapy such agonists have shown little success in clinical trials, while they have shown promise as components of combination treatments both in culture and in animal models. Other investigations have explored a possible role for PPARgamma as a tumor suppressor, and as an inducer of differentiation of cancer stem cells. Whereas early studies have yielded variable conclusions regarding the prevalence of PPARgamma mutations in cancer, the protein level of this receptor has been more recently identified as a significant prognostic marker. We predict that indicators of PPARgamma activity may also serve as predictive markers for tailoring treatments.

2. INTRODUCTION

PPARgamma is a member of the peroxisome proliferator activated receptor (PPAR) family, a subfamily of the nuclear receptor superfamily. The name derives from the fact that the first identified member, mPPAR, was observed to respond to a group of hepatocarcinogens that up-regulate the proliferation of peroxisomes (1). The gamma variant was first cloned from a Xenopus cDNA library, along with the alpha and beta variants (2). In the same study, all three receptors were observed to increase the activity of the acyl coenzyme A oxidase promoter, evidencing a role in the regulation of beta-oxidation. The same year, a sequence identified on the acyl coenzyme A oxidase promoter that bound to one of the PPARs was found to be indispensible for this induction and was, thus, termed a "peroxisome proliferator response element" (PPRE) (3). A number of additional genes containing active PPREs in their promoters have since been characterized, and most of these are similarly involved in lipid metabolism (4). Not long after the discovery of the three PPAR variants, a murine version of the gamma variant (mPPARgamma1) was cloned (5). This was followed by a second murine form (mPPARgamma2) which, through a screening of several genes, was discovered to be part of an mRXR heterodimer known to be necessary for the transcription of aP2, a lipoprotein expressed only in adipocytes (6). Accordingly, the same study found mPPARgamma2 mRNA expression to be at least 20 fold higher in murine adipose tissue than in several other organs. mPPARgamma2 was, thus, believed to be involved in adipocyte differentiation. Indeed, it was later shown that murine fibroblasts could be differentiated into adipocytes *in vitro* through retroviral expression of mPPARgamma2 (7).

PPARgamma1 and PPARgamma2, which arise from separate promoters on the same gene, are also present in humans (8). The PPARgamma2 form contains 28 extra N-terminal amino acids that increase the ligand independence of its activity (9). At least two dominant-negative isoforms of PPARgamma have also been identified, emerging through the inclusion of introns with stop codons. Among these are gammaORF4, which ends in the fourth intron (10), and PPARgamma1_{tr}, which ends in the third intron (11). Both of these lose their activity through exclusion of the C-terminal ligand-binding domain, a common alternative splicing strategy for deactivating members of the nuclear receptor superfamily (12). Other transcripts also arise from distinct promoters, but it is currently understood that the proteins they encode are not unique. A third promoter, for example, results in mRNA transcript PPARgamma3, which yields PPARgamma1 after translation (13). Two additional promoters are known to produce mRNA transcripts PPARgamma4 and PPARgamma6 (14, 15), which both also presumably yield PPARgamma1 after translation (15), although any data verifying this have not been published.

Tissue localization experiments on the active forms of PPARgamma have found that the PPARgamma1 form is expressed ubiquitously at the mRNA level, whereas PPARgamma2 is expressed primarily in adipocytes like its murine homologue (16). The same experiments have also found that the mRNA level of PPARgamma2 in adipose tissue is positively associated with obesity and can be down-regulated through caloric restriction. Shortly after PPARgamma's role in adipocyte differentiation was characterized, the thiazolidinedione (TZD) drug troglitazone was discovered to be a potent ligand (17). Currently, PPARgamma is understood to be the primary mediator of TZDs' ability to reverse insulin resistance in patients with type II diabetes (18). PPARgamma is also believed to play a role in suppressing the development of atherosclerosis (19). More recently, PPARgamma has been characterized *in vitro* as an antagonist of the differentiation of mesenchymal stem cells into osteoblasts, while PPARgamma antagonists have been proposed for use as therapeutic enhancers of osteogenesis in patients with osteoporosis (20).

Shortly after PPARgamma's role in adipocyte differentiation was characterized, differentiation and growth inhibition effects were demonstrated in cell lines from several types of cancer, both *in vitro* and in xenografts (21-24). For the last decade much research has, therefore, focused upon characterizing the role of this receptor in cancer biology, as well as the potential for exploiting its agonists as clinical treatments. Early studies, however, collectively failed to establish either mutations of PPARgamma or changes in PPARgamma mRNA level as prevalent events in tumorigenesis (25-27). Additionally, speculation emerged that the anticarcinogenic effects elicited by synthetic agonists are independent of this receptor's activity (28, 29). Clinical trials also failed to demonstrate the effectiveness of such agonists as a monotherapy for cancer treatment, a fact which fueled a search for combination treatments to enhance their effects (30). Other researchers directed their focus toward developing optimized compounds derived from thiazolidinediones, with or without PPARgamma activation activity (31). Within the last 2-3 years, a significant shift in the understanding of PPARgamma's role in tumor biology has occurred; studies employing immunohistochemistry staining have shown that the alteration of PPARgamma protein level is, in fact, significantly correlated with both tumor progression and patient prognosis in several types of carcinomas. An understanding of PPARgamma's activity, as well as the post-genomic regulation of this activity, therefore, holds much promise for both the development of future treatments and the classification of tumors.

3. HISTORY OF CANCER RESEARCH INVOLVING PPARgamma

3.1. Characterization of the anti-carcinogenic effects of PPARgamma agonists

3.1.1. Early experiments with troglitazone

PPARgamma's potential tumor suppressive role was first explored when the same research group that characterized its role in adipocyte differentiation demonstrated that a human liposarcoma cell line could be re-differentiated through treatment with the PPARgamma agonist troglitazone (22). The following year, the same

research group confirmed similar effects in carcinoma cell lines from colon cancer and breast cancer (23, 24), while another group repeated them in prostate cancer (21). Differentiation was observed in each of these studies; however, the type of differentiation and the methods of measurement varied. The colon cancer group observed re-differentiation into normal colon mucosa through both an increase in carcinoembryonic antigen staining (immunohistochemistry) and changes in the expression profile of several mRNAs associated with malignancy (northern blot). The breast cancer study observed suppression of both K19 and Muc-1, while changes in gene expression usually observed during adipocyte differentiation were absent. The prostate cancer group observed differentiation through several markers including a decrease in PSA. This group then carried out a morphological analysis of TEM images from the treated cells. Interestingly, the cytoplasmic volume increased, along with the number and volume of vacuoles. Many of these cells contained vacuoles large enough to displace the nuclei as in adipocytes; however, unlike the storage vacuoles of such cells, they did not stain positively for lipids. Growth inhibition was also observed in each of these studies, and the timescale for this effect was much longer than for a cytotoxic agent. The colon cancer study measured growth after 7 days of continuous culturing, while the prostate cancer study examined colony formation on soft agar. In xenografts of highly malignant PC-3 (prostate cancer) cells in immuno-compromised mice, continuous treatment with troglitazone similarly halted the growth of tumors for about a week before they resumed the growth curve characteristic of the control group (21). It is worth noting that troglitazone, the PPARgamma agonist used in all of these experiments, is no longer used clinically in the United States on account of liver toxicity (32).

3.1.2. A growing repertoire of qualitative effects on tumors

As more studies have been performed with other agonists, such as rosiglitazone, ciglitazone, pioglitazone, and edogenous ligants, an increasing number of qualitative effects on tumor biology have since been documented. Among these is the promotion of apoptosis, although this does not occur with all agonists or in all conditions (29). The reasons for this will be discussed in the Mechanisms of PPARgamma Activity section. PPARgamma agonists may also influence tumors *in vivo* by inhibiting angiogenesis through their activity in endothelial cells (33). In glioblastomas, PPARgamma agonists also reportedly block the promotion of the cancer stem cell subpopulation by growth factors *in vitro*, an important effect since this subpopulation is responsible for both metastasis and resistance to chemotherapy (34).

3.2. Characterizing PPARgamma activity in tumors

3.2.1. Early attempts to characterize PPARgamma activity in tumors

The effects of PPARgamma activation in early experiments with troglitazone led researchers to search for a loss of PPARgamma expression in both cell lines and clinical samples. In one of the early studies, 4 out of 55 clinical samples of sporadic colon cancer were found to have either missense or nonsense mutations, all of which resulted in a loss of PPARgamma activity (25). Another study found non-intragenic hemizygous deletions of PPARgamma in 8 of 38 prostate tumor samples and noted a reduction of PPARgamma protein levels in a few of these samples relative to the normal prostate tissue (26). A following study, however, failed to find either mutations or losses of expression at the mRNA level in both cell lines and clinical samples from several types of cancer including carcinomas of the colon, breast, lung and prostate; gliomas; osteosarcomas; myelodysplastic syndrome; and several leukemias (27). When compared with patient prognosis, however, a clear correlation emerged as PPARgamma mRNA transcript levels were found to be a favorable indicator in lung carcinomas (35). Only within the last 2-3 years have reliable correlations linking markers of PPARgamma activity to patient prognosis been constructed for other cancers.

3.2.2. Recent immunohistochemistry correlations

While most clinicopathological correlations involving PPARgamma appear to be inconclusive at the DNA/RNA level, those involving immunohistochemistry (IHC) data have been much more informative. In breast cancer, for example, the level of PPARgamma staining in clinical tumor samples is strongly positively correlated with the patients' survival ($p<0.001$), with a higher independent predictive value than tumor size, axillary lymph node status, TNM stage, Histologic grade, ER, or Ki-67 in a combined model (36). Likewise, in colon cancer overall survival is significantly higher in patients whose tumors demonstrate higher PPARgamma staining (37). Similar findings have also been demonstrated in mobile tongue squamous cell carninoma (38). As for prostate cancer, IHC staining is detectable in the nuclei of tumor cells in clinical samples, whereas it is absent in the adjacent, non-malignant epithelial tissue; however, the expression level is highly inversely correlated with PSA level (39). This would suggest that in prostate cancer PPARgamma functions as an inducible tumor suppressor triggered by malignancy, while its expression is down-regulated during tumor progression. A direct survival correlation, however, was not constructed in this study. In pancreatic cancer the expression of PPARgamma is *inversely* associated with patients' survival time (40). Most likely, PPARgamma exerts similar tumor-suppressive activity in these tumors, while this activity is down-regulated through mechanisms independent of changes in its protein level.

3.2.3. Expression of dominant negative splice variants

Studies examining the alternative splicing of PPARgamma have yielded results consistent with a tumor suppressive role in all tumor types studied. In one such study, mRNA transcripts encoding the dominant negative splice variant gammaORF4 were expressed in 16 of 25 clinical specimens of sporadic colorectal cancer at high levels relative to the adjacent nonmalignant tissue (10). It is unknown, however, whether the protein expression profile mirrored that of the mRNA. Shortly after this study, another group identified PPARgamma1_{tr} (another dominant-negative splice variant) and noted its expression in the cell lines K562 (myelogenous leukemia), THP-1

(monocytic leukemia), A549 (alveolar adenocarcinoma), and HeLa (cervical cancer) (11). Expression of this splice variant was later detected in 8 of 9 clinical lung tumor samples at the protein level, whereas it was absent in the adjacent nonmalignant tissue (41). Importantly, there is no conclusive evidence that the expression level of either dominant negative isoform in clinical samples was sufficient to significantly reduce wild-type PPARgamma activity. Several hypothesized mechanisms for the repression of nuclear receptors by their respective dominant-negative splice variants have been reviewed by others and may lead to a method for conclusively confirming their suppression of PPARgamma activity *in vivo (*12).

3.3. Animal models

3.3.1. Early controversy over PPARgamma's influence in colorectal cancer

Given the complexity of clinicopathological data regarding PPARgamma, observations drawn from controlled experiments using animal models should be more informative. Such studies examining PPARgamma's role in colorectal cancer, however, have yielded mixed results, although more recent evidence appears to support a tumor suppressive role. In two nearly identical early studies, long-term treatment of APC (+/-) mice with PPARgamma agonists increased the frequency of spontaneous polyps in the colon (42, 43). Saez and colleagues used troglitazone exclusively, while the others used both troglitazone and rosiglitazone. In a subsequent model, however, treatment of mice with the PPARgamma agonist pioglitazone was able to reduce the number of spontaneous tumors induced by dimethylhydrazine (44). Taken together without further evidence, these studies might have suggested that PPARgamma activation generally suppresses tumorigenesis in tumors driven by random mutations, whereas it contributes to malignancy when coupled to an APC mutation. Subsequent studies, however, have rejected this conclusion. Another group of researchers using APC (+/-) mice replaced PPARgamma agonists with intestine-specific PPARgamma haploinsufficiency and found that this increased the rate of tumor formation (45), although a previous theoretically redundant experiment had failed to observe this difference (46). In yet another study employing the agonist MCC-555 in APC (+/-) mice, PPARgamma activation reduced the rate of tumor-formation (32). Other studies employing animal models have established the efficacy of PPARgamma-specific agonists in suppressing colitis, an established risk factor for colorectal cancer (47-49). Rosiglitazone has also been approved as a clinical treatment for colitis, although it has not become a mainstream treatment because of adverse effects on the cardiovascular system (50). Even more recently, a diet rich in conjugated linoleic acid (another PPARgamma ligand) has been shown to suppress tumor formation (in addition to colitis) in mice during long-term azoxymethane treatment, an effect which is abrogated by PPARgamma deficiency (50).

3.3.2. Animal models for carcinomas, aside from colon cancer

Studies employing animal models for other types of cancer have similarly characterized PPARgamma as a tumor suppressor. The agonists rosiglitazone and fenretinide, for example, have been shown to exert a protective effect in a rat model for mammary carcinogenesis (51). Similarly, in a gastric carcinoma chemoprevention model, PPARgamma (+/-) mice displayed an enhanced generation of tumors during treatment with N-methyl-N-nitrosourea (52). In lung cancer, lung-specific overexpression of PPARgamma in transgenic mice reduced the formation of tumors induced by ethyl carbamate treatment (53).

3.4. Epidemiological correlations and clinical trials

Clinical data regarding the effects of PPARgamma activation clearly indicate the potential for modulation of PPARgamma as a chemopreventive strategy, although an effective treatment using PPARgamma agonists against established tumors has not been developed. One study employing data on 87,678 male diabetic patients correlated the use of TZDs (PPARgamma ligands) with the risk of developing cancer, finding a risk factor-adjusted 29% reduction in lung cancer for all patients, a 45% reduction in colorectal cancer for African Americans, an insignificant reduction in colorectal cancer for whites, and an *increase* in prostate cancer at 15% (P=0.03) for whites and 18% (not statistically significant) for African Americans (54). Unfortunately, the data for this study included patients treated with troglitazone, which can no longer be used clinically and may not accurately reflect the effects of other PPARgamma agonists. In an early clinical trial with prostate cancer, long-term treatment with troglitazone prevented the rise of PSA levels, especially for androgen-dependent tumors (26). For more advanced, late stage tumors that are refractory to either chemotherapy or hormone therapy, however, clinical trials using PPARgamma agonists alone have shown little success. In one such study, troglitazone treatment of patients with metastatic colorectal cancer resulted in no partial responses (55). In a separate trial, breast cancer patients with either stage IV or stage IIIB tumors also showed no partial responses to troglitazone treatment, although this study was discontinued prematurely because the drug was withdrawn from the market (56). In yet another trial using the PPARgamma agonist rosiglitazone to treat recurrent prostate cancer, a small, statistically insignificant increase in survival time was observed relative to a placebo group (57).

3.5. Combination therapies

Subsequent attempts have been made to develop combination therapies in which PPARgamma activation synergizes or potentiates other drugs. Since much of the genomic activity of PPARgamma is achieved through a heterodimer with RXRalpha, treatment strategies employing agonists for both receptors have been proposed (58). A phase I trial using this approach, however, failed to demonstrate any partial responses in a group of patients with refractory solid tumors (59). The most widely accepted explanation for this failure will be discussed in the PPARgamma-RXR part of the Mechanisms of PPARgamma Activity section.

Another promising combination treatment strategy is co-administration with conventional chemotherapy drugs (30). Treatments combining rosiglitazone with the platinum-based drug carboplatin, for

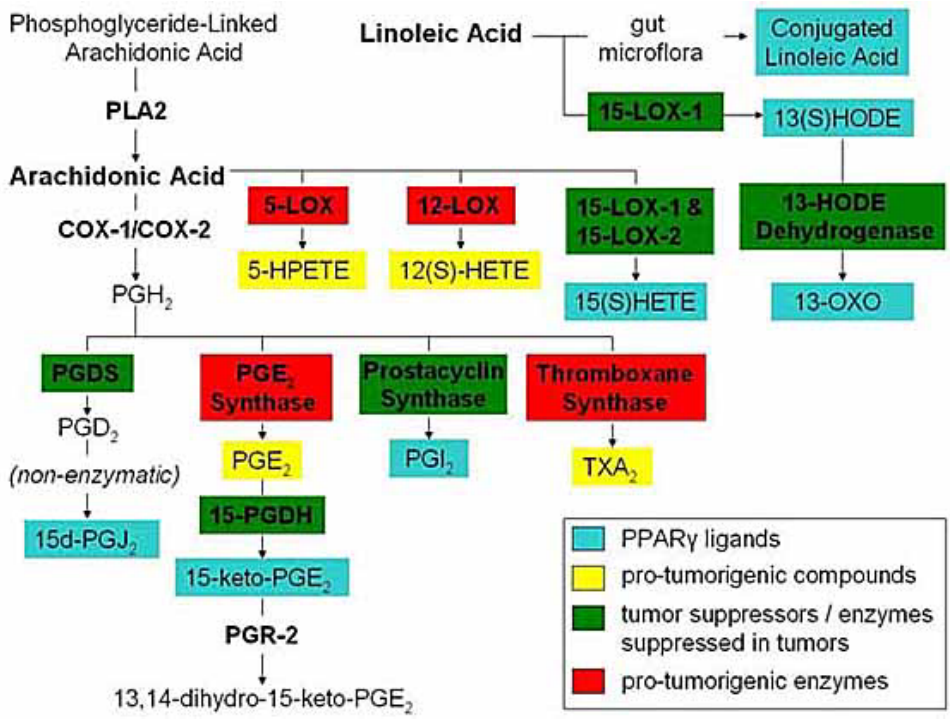

Figure 1. Naturally occurring PPARgamma ligands arising from the metabolism of arachidonic acid and linoleic acid are shown. Several of the enzymes in these pathways are associated with tumorigenesis, and some of them have well described tumor-suppressive functions.

example, result in a marked improvement over either individual compound both in cell lines and in vivo in a murine model with KRAS-induced tumors (60, 61). Cisplatin also shows synergistic combination effects with rosiglitazone in DMBA-induced murine mammary tumors (62), and with troglitazone in a mesothelioma cell line (63). A similar combination effect occurs between rosiglitazone and 5-fluorouracil in colon cancer and liver cancer cell lines (64, 65). 15d-PGJ2, an endogenous PPARgamma ligand, also reportedly acts synergistically with docetaxel in lung cancer cell lines (66). Antagonism, however, likely occurs for compounds removed from the cell by the ATP cassette transporter ABCG2, since PPARgamma-RXR directly transactivates this gene (67). Such drugs include irinotecan (68), daunorubicin, doxorubicin, and mitoxantrone (69). Among these, doxorubicin is antagonized by rosiglitazone in HT-29 cells (70), while, to our knowledge, no report exists regarding combination effects between specific PPARgamma agonists and the remaining compounds from this group. The agonists ciglitazone and rosiglitazone have also been reported to antagonize gamma radiation-induced cell death in Caco2 cells in vitro by up-regulating Hsp70 (71). Additional proposals for combination treatments have been reviewed by others (30). Many more of these approaches will likely emerge as the mechanisms of PPARgamma activity are further elucidated.

4. REGULATION OF PPARgamma

4.1. Ligands

4.1.1. Lipoxygenase products

PPARgamma is activated by several known endogenous ligands emerging from the metabolism of arachadonic acid and linoleic acid. A map of these pathways is shown in Figure 1.

Among the ligands represented are the lipoxygenase products 13 (S)HODE (produced from linoleic acid by 15-LOX-1) and 15 (S)HETE (produced from arachidonic acid by both 15-LOX-1 and 15-LOX-2, although 15-LOX-2 catalyzes this reaction much more efficiently) (72). Induction of 15-LOX-1 activity has actually been shown to mediate the promotion of apoptosis by non-steroidal anti-inflammatory drugs (NSAIDs) in certain tumor cell lines and to occur independently of COX-2 inhibition (73, 74). Although this finding was originally demonstrated only in colon cancer cell lines, it has been repeated in cell lines from both esophageal cancer and gastric cancer (75, 76). Supposedly, apoptosis is achieved through the activity of 13 (S)HODE because, unlike 15 (S)HETE, its level is induced by these treatments, while inhibition of 15-LOX-1 reverses this effect (73, 74). Additional compounds produced either in parallel to these products by 15-LOX-1 or downstream of them, however, may account for this effect. 13 (S)HODE is, in fact, degraded by 13-HODE dehydrogenase to form 13-oxooctadecadienoic acid (13-OXO) (77), another PPARgamma ligand (78). Seeing as the expression of 13-HODE dehydrogenase is reportedly reduced in colon cancer samples relative to nonmalignant tissue (79), 13-OXO likely influences additional mechanisms. In contrast to its role as a ligand, 13 (S)HODE can also *suppress* PPARgamma activity through a poorly understood, context-dependent MAPK activation (80). Because a pro-

tumorigenic effect has been demonstrated for 15-LOX-1 in PC-3 cells, it has been hypothesized that this activity reverses its role in prostate cancer, causing it to enhance, rather than suppress, tumorigenesis (81). Importantly, the role of 15-LOX-1 has not been firmly established in prostate cancer.

15 (S)HETE is believed to play a less significant role in activating PPARgamma, at least in colorectal cancer (73, 74). While the ability of 13 (S)HODE and 15 (S)HETE to activate PPARgamma at concentrations of 5μM appears to be roughly comparable (82), the endogenous concentration of 13 (S)HODE has been determined to be about 4-5 times that of 15 (S)HETE in clinical samples from both colorectal tumors and paired non-malignant epithelium (83). Roughly the same ratio has been reported for mice lungs, both for non-malignant tissue and for tumors generated through treatment with 4-(methylnitrosamino)-1- (3-pyridyl)-1-butanone (84). This difference has been attributed to a much higher availability of linoleic acid than arachidonic acid in the diet (83). A decrease of 13 (S)HODE production has also been observed in clinical colorectal tumor samples relative to paired nonmalignant epithelium samples, whereas no discernable difference has been observed with respect to the concentration of 15 (S)HETE, suggesting that 15 (S)HETE plays a less significant role in suppressing these tumors (83). In a lung carcinogenesis model, however, a statistically significant decrease was detected in the levels of both 13 (S)HODE and 15 (S)HETE (84). While the concentration of 15 (S)HETE appears to be low in tumors, it is possible that the downstream metabolites are more prevalent. Among these, both 15-oxo-ETE and 5-oxo-15 (S)-OH-ETE have been characterized as PPARgamma ligands, although extremely high concentrations are required for their activity (85). It is unlikely that the local concentrations of these compounds are ever sufficient to activate PPARgamma.

Interestingly, in assays measuring the endogenous production of 15 (S)HETE, about 95% of this product is detected in the medium, although the efficiency of its secretion appears to vary between cell lines (72). Such variation may indicate that this process is regulated, in part, by an active transport mechanism. Recently, it has also been demonstrated that 15 (S)HETE preferentially activates PPARbeta/delta over PPARgamma (86). While the expression and activation of PPARbeta/delta are down-regulated by 13 (S)HODE during the induction of 15-LOX-1 in colon cancer cells (where PPARbeta/delta activity favors malignant characteristics) (87), activation may occur within neighboring cells that lack 13 (S)HODE. Interestingly, PPARbeta/delta activation specifically within stromal cells has been shown to alter cytokine production so as to *reduce* mitogenic paracrine signals when cultured with multiple myeloma cells (88). Although 15 (S)HETE may not play a significant role in the activation of PPARgamma in most tumors, it could conceivably exert a similar tumor-suppressive effect through such paracrine signaling.

4.1.2. Prostaglandins

Several arachidonic acid metabolites generated downstream of the COX enzymes can also act as PPARgamma ligands. Among these, 15d-PGJ2 appears to be the most prevalent in the literature, probably because it was the first endogenous ligand discovered for PPARgamma (89). Prostacyclin (PGI2), another downstream product of the COXs, is also believed to activate PPARgamma as its stable analog iloprost has been shown to activate a PPARgamma reporter in both a bronchial epithelial cell line and two lung adenocarcinoma cell lines (53). Furthermore, it has been suggested that this activity mediates prostacyclin's well-established tumor suppressive activity, since knock-down of the IP receptor (a G-protein-coupled receptor for prostacyclin) fails to reduce the protective effect of prostacyclin synthase over-expression (53). The evidence for this, however, is still inconclusive because the effect of PPARgamma knockdown on prostacyclin synthase-mediated suppression of tumorigenesis has never been determined. Increased activity of a PPARgamma reporter has also been observed upon treatment of 3T3-L1 cells with 15-keto-PGE2, an arachidonic acid product generated through conversion of PGE2 by 15-PGDH (90). This particular ligand is believed to be indispensible for at least a subset of endogenous processes that require PPARgamma activation, seeing as exogenous over-expression of the downstream enzyme PGR-2 (which metabolizes 15-keto-PGE2 to form 13,14-dihydro-15-keto-PGE2) blocks hormone-induced differentiation of 3T3-L1 cells into adipocytes (90). On the other hand, the activity of 13,14-dihydro-15-keto-PGE2 may be responsible for this effect, rather than the absence of 15-keto-PGE2.

4.1.3. Importance of arachidonic acid products

Given PPARgamma's role in adipocyte differentiation, it is interesting that siRNA-mediated knockdown of phospholipase A2, the initiator of arachidonic acid signaling, is able to block hormone-induced differentiation of 3T3-L1 preadipocytes (91). It is also worth noting that this differentiation is rescued through treatment with the PPARgamma agonist troglitazone. These observations provide highly suggestive, circumstantial evidence that at least one of the known PPARgamma ligands generated through arachidonic acid metabolism is necessary for endogenous induction of PPARgamma activity. This conclusion is also consistent with *in vivo* observations in animal models, although these can be readily explained by at least one other mechanism. In the aforementioned adipocyte-specific PPARgamma double knockout study in mice, for example, increases in body weight due to a high fat diet were attenuated relative to a control group, as was the total body fat weight (92). Similarly, adipocyte-specific phospholipase A2 knockout mice had a normal body weight when fed a standard diet, but they failed to develop obesity in response to a high fat diet (93). Although the results of the latter study were consistent with the effects of decreased PPARgamma activity, the researchers explained them through an elevation of lipolysis due to decreased PGE2 production. Nonetheless, current evidence appears to support the hypothesis that ligands originating from arachidonic acid metabolism are the principal means of inducing PPARgamma activity for most organs *in vivo,* whereas other mechanisms only modulate this activation. In the colon, however, an exception emerges in that natural PPARgamma ligands from the diet complement those from

the arachidonic acid pathway. As mentioned previously, dietary supplementation with conjugated linoleic acid, has been shown to reduce colorectal tumorigenesis induced by azoxymethane in mice, presumably through an observed suppression of colitis (a known risk factor for colorectal cancer), whereas this effect is absent in PPARgamma-deficient mice (50).

4.2. Phosphorylation

Phosphorylation of PPARgamma also plays a significant role in its regulation. Not long after PPARgamma's discovery, treatment of NIH3T3 and 293T cells with either EGF or PDGF was shown to down-regulate the activity of PPARgamma, an event which was attributed to MAPK-mediated phosphorylation of PPARgamma1 at Ser82 (94). In breast cancer, it has actually been hypothesized that a loss of PPARgamma activity is achieved entirely through MAPK activation, as evidenced by the fact that the growth inhibition effect of troglitazone treatment in an otherwise resistant cell line can be rescued through the addition of the MAPK inhibitor PD98059 (24). More recent studies have found that this effect can be achieved through phosphorylation of RXR (part of an important heterodimer with PPARgamma) under the same conditions, while it can also be reduced through transfection with an RXR mutant protected against phosphorylation (95, 96). The two mechanisms are, in fact, complementary; several lines of evidence confirming an independent role for the phosphorylation of PPARgamma in modulating its activity have been reviewed (97).

4.3. Corepressors

The activity of PPARgamma is also modulated through interaction with corepressors, either through a repression of PPARgamma activity or through PPARgamma's enhancement of the ability of these corepressors to transrepress other genes (98). PPARgamma's affinity for these proteins can be modulated by numerous factors. For example, most of these corepressors lose their affinity for nuclear receptors when these receptors are activated by their respective ligands (98), while some of these interactions are *enhanced* by ligands. The binding of the corepressor RIP140 to ternary complexes of PPARgamma and RXR, for example, is enhanced by the addition of RXR ligands (99). Additionally, at least one protein is known to block the interaction between PPARgamma and its corepressors. Direct interaction with phosphorylated extracellular signal-related kinase 5 (ERK5) has been observed to increase the activity of PPARgamma1 in reporter assays, presumably by blocking its interaction with the corepressor SMRT (100). Seeing as an elevation of this mitogenic kinase's expression has been observed in prostate tumor samples relative to the corresponding nonmalignant tissue, this type of mechanism could be prevalent in cancer (101). This fact may also explain why a suppression of PPARgamma protein level would be necessary for highly malignant prostate tumors, seeing as ERK5 would reduce the ability of these corepressors to suppress PPARgamma activity.

4.4. Repression of PPREs by other proteins

The genomic activity of PPARgamma can also be blocked through binding of other proteins to PPREs. This behavior has been reported for the estrogen receptor (102). A similar repression of PPREs has been reported for a thyroid receptor beta mutant observed clinically, in which either a homodimer or heterodimers with either PPARgamma or RXR could bind and repress PPREs (103). Whether such a direct repression of PPREs is common clinically remains to be seen.

4.5. Proteasomal degradation

PPARgamma activity is also regulated through proteasomal degradation. Targeting of PPARgamma to the proteasome occurs through ubiquitylation of the AF-2 segment of its ligand binding domain (104). This process is counterintuitively enhanced by the addition of TZDs, an effect which contrasts with their effect on the activation of PPREs (105). In cancer cell lines, however, the influence of this process often appears to be overcome by a competing mechanism. PC-3 cells, for example, show no change in the protein level of PPARgamma upon treatment with troglitazone (21), while a similar treatment elicits an *increase* in PPARgamma protein in 21MT cells (24).

4.6. Transcriptional regulation

Little is known regarding control of PPARgamma transcription in epithelial cells. The C2H2 zinc finger transcription factor Zac, which is known to play a role in apoptosis, has been reported to activate the transcription of PPARgamma and is expressed in some colon cancer cell lines (106). Additionally, during the well studied process in which NIH-3T3 cells are differentiated into adipocytes through activation of PPARgamma, a positive feedback loop emerges in which PPARgamma and its target gene C/EBPalpha up-regulate the transcription of each other (107). In light of the effect ligands have in promoting PPARgamma degradation (105), this process likely proceeds after a transient induction by endogenous ligands. A similar loop may be active during the treatment of carcinomas with synthetic PPARgamma agonists. Two transcription factors modulated by TGFbeta, Egr-1 and AP1, are also considered to be important regulators of PPARgamma transcription in smooth muscles; however, their importance in epithelial cells has not been established (108). Likewise, the circadian clock transcription factors DBP and E4BP4 have been shown to regulate the PPARgamma6 mRNA transcript level (15), while their role in PPARgamma regulation in epithelial cells and tumors has not been characterized.

5. MECHANISMS OF PPARgamma ACTIVITY

5.1. Is PPARgamma responsible for the antitumor effects of its agonists?

Many researchers have speculated that the anticancer effects elicited by PPARgamma agonists are independent of this receptor's activity. This conclusion was reached in an early study after growth inhibition was elicited by both troglitazone and ciglitazone in PPARgamma (-/-) mouse ES cells (28). Another group of researchers extended this finding to other agonists upon finding that the anticancer effects elicited by troglitazone, ciglitazone, and 15-d-PGJ2 (an endogenous ligand) on several prostate and bladder carcinoma cell lines varied qualitatively (growth inhibition vs. apoptosis), while rosiglitazone and pioglitazone elicited no effects

whatsoever (29). An interpretation of these discrepancies, however, should account for the fact that different agonists can influence independent mechanisms of PPARgamma activity. In one study, for example, treatment of a myeloid leukemia cell line with either 15-d-PGJ2 or troglitazone resulted in a repression of STAT3 reporter activity, an effect which was reversed by the PPARgamma antagonist GW9662 (109). 15-d-PGJ2, however, caused direct binding of PPARgamma to STAT3, whereas troglitazone increased the binding of NCoR to STAT3, presumably through the observed release of this corepressor from PPARgamma. Considering that all of the known mechanisms of PPARgamma's activity are also context-dependent, much of the variability in the effects of PPARgamma ligands is likely caused by an interaction between off-target mechanisms and the activity of PPARgamma.

5.2. PPARgamma-RXR heterodimer

Among the mechanisms of PPARgamma activity, the most prevalent in the literature is that of the PPARgamma-RXR heterodimer, which is known to promote the transcription of genes whose promoters contain peroxisome proliferator response elements (PPREs) (98). In adipocytes several genes, such as aPC, are constitutively bound to PPARgamma-coactivator complexes, among which PPARgamma-RXR is highly prevalent (110). The significance of the activity of this heterodimer in clinical tumors, however, has not been established. This uncertainty stems from the fact that treatments combining ligands for PPARgamma and RXR result in an additive or synergistic induction of the dimer's activity (6). In early studies on the effects of PPARgamma activation in cancer, this behavior was observed in a liposarcoma cell line (22). Recently, however, the activity of this heterodimer has been shown to be absent in several cancer cell lines due to growth factor-triggered phosphorylation of RXRalpha, while the synergy between ligands for the two receptors can be restored through either the withdrawal of growth factors or the addition of MAPK inhibitors (95, 96). An elevation of RXRalpha phosphorylation has actually been observed in clinical colorectal tumor samples relative to nonmalignant epithelial colon tissue (95). Much research has, therefore, focused upon the prospect of developing combination therapies that reduce the phosphorylation of RXR to potentiate the effect of PPARgamma agonists (58). Importantly, the activity resulting from PPARgamma's interaction with RXR is not restricted to the induction of PPREs. The oncogenic protein beta-Catenin, for example, has been shown to interact with both RXR and PPARgamma (111-113). Moreover, treatment of cells with PPARgamma ligands during exogenous expression of PPARgamma and RXR decreases the ability of beta-Catenin to transactivate its target genes (114). Much of PPARgamma's anticancer activity, however, is achieved through mechanisms independent of RXR. This is evident in the antitumor effects elicited by troglitazone in MDA-MB-231 breast cancer cells (115), which lack a detectable level of RXRalpha expression (116).

5.3. Coactivators

The transcription activity of PPARgamma's target genes can also be achieved through complexes containing PPARgamma and various coactivators, although the specificity of the target genes may vary. A complex with PGC-1alpha, for example, activates the transcription of UCP-1, which is inaccessible to PPARgamma-RXR (117). Different coactivators also have different modes of activity. Many of the classical coactivators, such as CBP/p300 and SRC-1, achieve this activity through their histone acetyl transferase (HAT) activity, while others like PGC-1alpha simply recruit other coactivators to complexes with PPARgamma (118). The influence of PPARgamma ligands on the activity of these coactivators also varies. In most cases, interaction between PPARgamma and its coactivators is enhanced by ligand activation (98). Some coactivators, however, activate PPARgamma constitutively. Among these are ARA70 and SHP (119, 120). Additionally, interaction with certain coactivators may be enhanced by only a subset of the PPARgamma ligands. For example, binding to PGC-1alpha is reportedly enhanced by the addition of 15d-PGJ2 and troglitazone (121), but not rosiglitazone (117). This contrast, however, may not be valid because the effects of 15d-PGJ2 and troglitazone were determined through an endogenous immunoprecipitation of PGC-1alpha, whereas the absence of this activity for rosiglitazone was determined through an exogenous immunoprecipitation of GST-tagged PGC-1alpha. Importantly, many of PPARgamma's co-activators are promiscuous, a fact exemplified by PGC-1alpha's binding to NF-kappaB (121), nuclear respiratory factor-1 (NRF-1) (118), estrogen receptor alpha (ERalpha), the retinoic acid (RA) receptor, and thyroid receptor beta (117). Clearly the availability of these coactivators is an important determinant of PPARgamma's activity in tumors. Madjalaweih and Ro provide a much more extensive review of PPARgamma's coactivators, as well as its corepressors (122).

5.4. Corepressors

Any PPARgamma that is not part of an active complex normally exists in an inactive form, bound to a corepressor, such as SMRT or NCoR (98). Under most circumstances, interaction with a ligand causes PPARgamma to dissociate from the corepressor and bind to a coactivator (98). The corepressor, in turn, may be freed to bind to other transcription factors, thereby transrepressing their target genes, an effect which, as previously mentioned, was observed during treatment of a multiple myeloma cell line with troglitazone (109). Ligand activation also enhances SUMOylation of PPARgamma, a change which initiates the recruitment of PPARgamma to NCoR-HDAC3 complexes associated with specific genes, thereby repressing their transcription by blocking the ubiquitylation-mediated destruction of the complexes (123). An extensive list of PPARgamma corepressers is included in a review by Madjalaweih and Ro (122).

6. PPARgamma TARGET PATHWAYS

6.1. Overview

Microarray studies have hinted at numerous pathways that may be modulated by PPARgamma ligands. The first of these papers characterized the effect on known markers of differentiation, such as RegIA and keratin20, in Moser and COS7 cells, finding that these differentiation markers were mostly up-regulated (124). A more recent

paper profiled the influence of three different PPARgamma agonists on several pathways in HCT116 colon cancer cells, based on changes in the levels of mRNA transcripts of representative genes (125). Some of the processes characterized and the accompanying genes used as markers are as follows: the cell cycle (MDM2 decreased, CHEK2 and RBX1 somehow altered), cytokine-cytokine receptor interaction (IL18 and VEGFB somehow altered), ubiquitin-mediated proteolysis (UBE2E1 and RBX1 somehow altered), phosphotydlinositol signaling (INPP5D decreased), Wnt signaling (RBX1 somehow altered), the "colorectal cancer pathway" (APPL decreased), and calcium signaling (SLC25A4 somehow altered). Several genes involved in apoptosis, such as BCL-X (L), MCL-1, BAX (126), XIAP (127), and Survivin (128), are also reportedly modulated by PPARgamma so as to favor this process. In contrast, PPARgamma has been shown to up-regulate Hsp70 in Caco2 colon cancer cells and MCF7 breast cancer cells (71, 129), an affect which *prevents* radiation-induced apoptosis (71). Although these observations provide promising directions for future research, their reliability is unknown. Numerous mechanisms of PPARgamma activity are already known to be context-dependent and may, therefore, vary widely between individual tumors. Accordingly, the development of clinical treatments exploiting this receptor will depend upon understanding the precise mechanisms by which these pathways are influenced. The pathways that follow are more thoroughly researched and include discussions of their mechanisms.

6.2. Well studied non-genomic targets

6.2.1. Beta-catenin

PPARgamma is believed to inhibit signaling by the beta-Catenin pathway, whose contribution to tumor biology is well established. The activity of beta-Catenin is important in promoting epithelial-mesenchymal transition (130), an important process in tumor progression. The protumorigenic activity of Wnt/beta-Catenin signaling arises from the nuclear localization of beta-Catenin, which activates the TCF/LEF families of transcription factors by displacing them from the corepressor Groucho/TLE (131). This results in an up-regulation of cyclin D and c-myc, both of which exert pro-tumorigenic effects (132). In non-malignant cells this event is prevented by a destruction complex containing Axin, APC, and the kinase GSK-3beta, which phosphorylates beta-Catenin, thereby targeting it for proteasomal degradation (133). Cannonical Wnt signaling, however, leads to the formation of a membrane-bound complex containing Fz, LRP6, Dvl, and Axin (134), effectively removing Axin from the destruction complex and deactivating it (135).

Speculation regarding PPARgamma's influence on the Wnt/beta-Catenin pathway began when early APC (+/-) mice models failed to demonstrate a chemopreventive effect for PPARgamma ligands against colorectal carcinogenesis, whereas a protective effect was observed during treatment of wild-type mice with mutagenic agents (46). Importantly, APC is an established tumor suppressor that is necessary for the proper function of the beta-catenin destruction complex (136); a loss-of-function mutation of this gene increases the nuclear localization of beta-Catenin within a subset of cells in the tumor (137). In one study seeking to resolve this issue, tumors were induced in both wild-type and PPARgamma (+/-) mice through treatment with azoxymethane (46). Tumor formation was enhanced in the PPARgamma (+/-) mice, relative to the wild-type mice, while beta-Catenin was up-regulated in their colon epithelial tissue prior to the onset of these tumors. The next year, PPARgamma activation by both troglitazone and GW7845 was found to increase the proteasomal degradation of beta-Catenin in NIH 3T3-L1 cells (138). Interaction between beta-catenin and PPARgamma was also soon demonstrated through immunoprecipitation in two other laboratories (112, 113). Another group of researchers failed to repeat the PPARgamma-mediated degradation of beta-Catenin; however, they found that the PPARgamma ligands troglitazone, rosiglitazone, and GW1929 all repressed the activity of a beta-Catenin transcription complex during co-expression of PPARgamma and RXR (114). Repression of the Wnt signaling pathway, therefore, would appear to require sufficient expression of both PPARgamma and RXR. Importantly, the nuclear localization of beta-Catenin is strongly modulated by both intrinsic and paracrine signals, even in the presence of an APC mutation (139); therefore, PPARgamma's influence on such signals may partially mediate PPARgamma's impact on beta-Catenin activity. On the other hand, such signals may completely abrogate PPARgamma's influence on this pathway. It should be mentioned that in clinical colorectal cancer samples, nuclear-localized beta-Catenin immunohistochemistry staining reportedly shows no significant correlation with overall PPARgamma staining intensity (37).

The process of sorting through the mechanisms of PPARgamma activity on this pathway is further complicated by its effect on E-Cadherin. E-Cadherin is a membrane protein whose expression is inversely correlated with malignancy, while restored expression of this receptor reduces malignant characteristics (140). Importantly, E-Cadherin sequesters beta-Catenin at the cell membrane, thereby preventing its localization to the nucleus (140). A recent paper has found that ciglitazone and linoleic acid treatments in several prostate cancer cell lines lead to an up-regulation of E-Cadherin, along with an even more reliable down-regulation of N-Cadherin (141). The effects of these ligands, moreover, are PPARgamma dependent, since they are reversed by the PPARgamma antagonist GW9662 (141). They also lead to a repression of both beta-Catenin and c-myc expression, indicating that the full pathway is, in fact, influenced by these treatments. The clinical relevance of this mechanism is supported by the fact that the overall PPARgamma immunoreactivity in clinical breast tumor samples is positively correlated with the localization of beta-Catenin to the membrane as well as the cytoplasm (36). One group has attributed this effect to a repression of Snail observed in non-small cell lung carcinoma cell lines (142). Snail otherwise directly represses the transcription of E-Cadherin (142). This repression is believed to have been somehow mediated by an inhibition of ERK through an unknown phosphatase, although the mechanism connecting these events is unknown.

6.2.2. STAT3/NF-kappaB

PPARgamma's ability to inhibit IL-6/STAT3/NF-kappaB signaling has been reported by numerous laboratories in a wide variety of cell types. The prospect of targeting this pathway is particularly exciting because it is part of an important epigenetic positive feedback loop (IL6→STAT3→NF-kappaB→Lin28→Let-7→IL6) that has been found to be active in half of all cancer cell lines screened (143). Among PPARgamma's effects on this pathway is an inhibition of STAT3's promotion of its target genes (109). These treatments, however, do not appear to impact STAT3's ability to activate NF-kappaB (109). STAT3-mediated processing of NF-kappaB requires the acetylation of STAT3 (144), an event which PPARgamma has not been shown to disrupt. Importantly, PPARgamma ligands appear to influence the binding of proteins to STAT3, rather than STAT3 phosphorylation (109).

Treatments with PPARgamma agonists have also been observed to reduce the ability of NF-kappaB to promote its target genes, an effect which has been established both *in vitro* in cell lines from multiple tissue sources (47, 121, 145, 146), and *in vivo* in an experimentally induced colitis model in mice (147). Among these agonists, 15d-PGJ2 is unique in that it has been observed to block NF-kappaB-mediated transcription in the absence of PPARgamma (although repression is enhanced through exogenous expression of PPARgamma), supposedly through direct inhibition of IKK (145). Importantly, this mechanism reduces the nuclear localization of NF-kappaB in the cell (145). In contrast, activation of PPARgamma by all ligands tested appears to block the interaction between NF-kappaB and its target genes (145). One mechanism that may explain this activity is a ligand-induced SUMOylation of PPARgamma that causes it to bind corepressor complexes associated with NF-kappaB target genes, an event which inhibits the transcription of these genes by blocking the degradation of the complexes (123). Alternatively, ligand activation of PPARgamma has been reported to promote its association with PGC-1, thus, reducing the availability of this coactivator for binding with NF-kappaB (121). While it has been reported that PPARgamma ligands can block the induction of IL-6 by stromal cells in a multiple myeloma cell line (supposedly through inhibition of NF-kappaB) (121), such treatments have not been reported to disrupt autocrine loops involving IL-6 in carcinoma cell lines. This effect would lead to a much more pronounced inhibition of their proliferation. PPARgamma may repress only a subset of NF-kappaB target genes that does not include Lin28. Importantly, the inhibition effects of PPARgamma agonists on both STAT3 and NF-kappaB are context-dependent, since repression of STAT3 through troglitazone depends upon the level of SMRT (109), while the trans-repression of NF-kappaB target genes is attenuated by knockdown of NCoR (123). Interference with STAT3/NF-kappaB signaling through these mechanisms, therefore, may be highly variable and unreliable in a clinical setting if not somehow guided by molecular profiling.

Alternatively, PPARgamma agonists can also block Tyk2-mediated phosphorylation of STAT3 through an unknown mechanism (34, 148). This mechanism is believed to mediate the growth inhibition effects that PPARgamma agonists have on the CD133+ subpopulation of glioblastoma cell lines during treatment with specific growth factors *in vitro* (34). Some other studies have established that Tyk2 expression contributes to metastasis (149, 150). Tyk2 is also reportedly expressed in an appreciable fraction of clinical prostate tumors, although thorough clinicopathological correlations have not been constructed (149). More recently, a head and neck cancer cell line has been reported to dependent upon the combination of pSrc and Tyk2 for STAT3 activation; therefore, it is likely that manipulation of this mechanism by PPARgamma agonists would depend upon combinations with other treatments for its effectiveness (151). Importantly, the inhibition of Tyk2 activity by PPARgamma agonists has not been reported in carcinoma cell lines.

6.2.3. Androgen receptor

For prostate cancer, the most attractive effect of PPARgamma ligands is their interference with androgen receptor signaling. Upon stimulation by androgen, this membrane-bound nuclear receptor internalizes and acts as a transcription factor for genes whose promoters contain androgen responsive elements (152). Among these is PSA (152), an important marker for detecting prostate cancer (153). Suppression of this activity was first noted when treatment of the androgen-dependent LNCaP cells with troglitazone caused a marked reduction of their PSA level (21). Likewise, an early clinical trial found that patients with androgen-dependent prostate cancer, as well as a subset of patients with androgen-refractory prostate cancer, encountered a drop in their PSA levels during troglitazone treatment (26). In yet another study, treatment of LNCaP cells with the PPARgamma agonists troglitazone, pioglitazone, and 15-d-PGJ2 reduced both the PSA level and the activity of an ARE reporter without altering the androgen receptor protein level (154). It has also been demonstrated through chromatin immunoprecipitation experiments that both troglitazone and ciglitazone block the recruitment of the androgen receptor to androgen responsive elements on the promoters of its target genes (155). The authors who performed the latter study have argued that this activity is independent of PPARgamma because the same effect was achieved by structurally similar analogues that failed to "activate" PPARgamma. In a previously mentioned study examining immunohistochemistry staining of PPARgamma in clinical tumor samples, however, it was argued that the tight inverse correlation observed between PPARgamma immunoreactivity and PSA level suggests that the effects of PPARgamma ligands on PSA are dependent upon binding of these ligands to PPARgamma (39).

6.3. Verified genomic targets

6.3.1. P53

Rosiglitazone reportedly promotes p53 expression at the transcriptional level in MCF7 breast cancer cells through recruitment of PPARgamma to an NF-

kappaB site on its promoter (156). A well described tumor suppressor gene, p53 is important for the induction of apoptosis, cell cycle arrest, and autophagy during various types of stress (157). This activity is likely mediated by its transrepression activity on Bcl-2, survivin, IGFR, Mcl-1, and PIK3CA and its transactivation of such targets such as p21, PTFG, Gadd45, and 14-3-3σ (157). This mechanism, however, is unlikely to account for many of the effects previously observed, seeing as loss-of-function p53 mutations are ubiquitous in most types of cancer. Certain types of tumors usually lack this mutation, and may, therefore, be more susceptible to this mechanism.

6.3.2. PTEN

Among the most attractive antitumor mechanisms arising from PPARgamma's genomic activity is a direct activation of the PTEN promoter by the PPARgamma-RXR heterodimer, an event which should exert pleotropic effects through a suppression of Akt (158). As with p53, mutations of PTEN are highly frequent in most types of cancer. For pancreatic cancer, however, it has been reported that activation of PPARgamma in the cell line PANC-1 through treatment with rosiglitazone increases the protein level of PTEN, while the reverse is true for the addition of PPARgamma antagonist GW9662 (159). The growth suppression effects elicited by rosiglitazone in this cell line are especially pronounced, with almost no measureable growth in xenografts after the initiation of treatment (160). Although the immunoreactivity of PTEN has been found to be significantly reduced in clinical samples of pancreatic cancer (161), the cancer genome project has found that loss-of-function mutations of this gene are a rare event, occurring in only 1 out of 66 clinical samples in the COSMIC_pancreas data set of the Cancer Genome Workbench. It is, therefore, conceivable that the repression of PTEN may be overcome through activation of PPARgamma in these tumors. If population mutation rates prove to be a reliable predictor of PTEN induction through PPARgamma activity, then data from the Cancer Genome Workbench Datadump indicate that carcinomas of the oesophagus, head and neck, ovary, and lung may also be potential candidates for this mechanism, with PTEN mutation rates ≤ 2%. The directions for accessing this site are detailed in the Acknowledgements section.

7. PERSPECTIVE

Aside from its role as a specific target for anticancer treatments, PPARgamma is now emerging as a potential biomarker for predicting patient prognosis. PPARgamma staining may also become a useful tool for selecting treatments. Activation of PPARgamma, for example, should lead to the up-regulation of ABCG2, which antagonizes several prominent chemotherapy drugs (67). PPARgamma might also regulate additional multidrug resistance (MDR) proteins. A role for the PPARs in regulating MDR proteins has been reviewed by others (161). Considering the fact that other drugs are synergized by PPARgamma activity (60, 62, 64, 66), if additional multidrug resistance proteins are not influenced by PPARgamma, then PPARgamma staining is most likely an independent predictor of drug resistance when combined with these other markers. No correlation, however, has been constructed at present. PPARgamma may also be useful for predicting resistance to radiotherapy, since it reportedly activates Hsp70 (71). Additionally, as the drive to develop inhibitors for targets downstream of COX-1/COX-2 progresses, an understanding of both the effect of such inhibitors on the expression of the lipoxygenases and the clinical significance of the various prostaglandins as PPARgamma ligands will be important for optimizing such treatments. Biomarkers should also be established to predict which PPARgamma target pathways are responsive to PPARgamma activation within a given tumor, since nearly all of these pathways are context-dependent. Establishing the exact mechanisms of PPARgamma activity in each target pathway, therefore, will likely be necessary.

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9. REFERENCES

1. I. Issemann and S. Green: Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature* 347, 645-50 (1990)

2. C. Dreyer, G. Krey, H. Keller, F. Givel, G. Helftenbein and W. Wahli: Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors. *Cell* 68, 879-87 (1992)

3. J.D. Tugwood, I. Issemann, R.G. Anderson, K.R. Bundell, W.L. McPheat and S. Green: The mouse peroxisome proliferator activated receptor recognizes a response element in the 5' flanking sequence of the rat acyl CoA oxidase gene. *Embo J* 11, 433-9 (1992)

4. S. Kersten, B. Desvergne and W. Wahli: Roles of PPARs in health and disease. *Nature* 405, 421-4 (2000)

5. F. Chen, S.W. Law and B.W. O'Malley: Identification of two mPPAR related receptors and evidence for the existence of five subfamily members. *Biochem Biophys Res Commun* 196, 671-7 (1993)

6. P. Tontonoz, E. Hu, R.A. Graves, A.I. Budavari and B.M. Spiegelman: mPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer. *Genes Dev* 8, 1224-34 (1994)

7. P. Tontonoz, E. Hu and B.M. Spiegelman: Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell* 79, 1147-56 (1994)

8. L.A. Stanton, J.R. Li and F. Beier: PPARgamma2 expression in growth plate chondrocytes is regulated by p38 and GSK-3. *J Cell Mol Med* 14, 242-56 (2010)

9. S.S. Deeb, L. Fajas, M. Nemoto, J. Pihlajamaki, L. Mykkanen, J. Kuusisto, M. Laakso, W. Fujimoto and J. Auwerx: A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 20, 284-7 (1998)

10. L. Sabatino, A. Casamassimi, G. Peluso, M.V. Barone, D. Capaccio, C. Migliore, P. Bonelli, A. Pedicini, A. Febbraro, A. Ciccodicola and V. Colantuoni: A novel peroxisome proliferator-activated receptor gamma isoform with dominant negative activity generated by alternative splicing. *J Biol Chem* 280, 26517-25 (2005)

11. H.J. Kim, I.S. Woo, E.S. Kang, S.Y. Eun, J.H. Lee, K.C. Chang, J.H. Kim and H.G. Seo: Identification of a truncated alternative splicing variant of human PPARgamma1 that exhibits dominant negative activity. *Biochem Biophys Res Commun* 347, 698-706 (2006)

12. M. van der Vaart and M.J. Schaaf: Naturally occurring C-terminal splice variants of nuclear receptors. *Nucl Recept Signal* 7, e007 (2009)

13. L. Fajas, J.C. Fruchart and J. Auwerx: PPARgamma3 mRNA: a distinct PPARgamma mRNA subtype transcribed from an independent promoter. *FEBS Lett* 438, 55-60 (1998)

14. H. Sundvold and S. Lien: Identification of a novel peroxisome proliferator-activated receptor (PPAR) gamma promoter in man and transactivation by the nuclear receptor RORalpha1. *Biochem Biophys Res Commun* 287, 383-90 (2001)

15. S. Takahashi, I. Inoue, Y. Nakajima, M. Seo, T. Nakano, F. Yang, M. Kumagai, T. Komoda, T. Awata, M. Ikeda and S. Katayama: A promoter in the novel exon of hPPARgamma directs the circadian expression of PPARgamma. *J Atheroscler Thromb* 17, 73-83 (2010)

16. A.J. Vidal-Puig, R.V. Considine, M. Jimenez-Linan, A. Werman, W.J. Pories, J.F. Caro and J.S. Flier: Peroxisome proliferator-activated receptor gene expression in human tissues. Effects of obesity, weight loss, and regulation by insulin and glucocorticoids. *J Clin Invest* 99, 2416-22 (1997)

17. J.M. Lehmann, L.B. Moore, T.A. Smith-Oliver, W.O. Wilkison, T.M. Willson and S.A. Kliewer: An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 270, 12953-6 (1995)

18. A.R. Saltiel and J.M. Olefsky: Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes* 45, 1661-9 (1996)

19. N. Marx, G. Sukhova, C. Murphy, P. Libby and J. Plutzky: Macrophages in human atheroma contain PPARgamma: differentiation-dependent peroxisomal proliferator-activated receptor gamma (PPARgamma) expression and reduction of MMP-9 activity through PPARgamma activation in mononuclear phagocytes *in vitro*. *Am J Pathol* 153, 17-23 (1998)

20. U. Krause, S. Harris, A. Green, J. Ylostalo, S. Zeitouni, N. Lee and C.A. Gregory: Pharmaceutical modulation of canonical Wnt signaling in multipotent stromal cells for improved osteoinductive therapy. *Proc Natl Acad Sci U S A* 107, 4147-52 (2010)

21. T. Kubota, K. Koshizuka, E.A. Williamson, H. Asou, J.W. Said, S. Holden, I. Miyoshi and H.P. Koeffler: Ligand for peroxisome proliferator-activated receptor gamma (troglitazone) has potent antitumor effect against human prostate cancer both *in vitro* and *in vivo*. *Cancer Res* 58, 3344-52 (1998)

22. P. Tontonoz, S. Singer, B.M. Forman, P. Sarraf, J.A. Fletcher, C.D. Fletcher, R.P. Brun, E. Mueller, S. Altiok, H. Oppenheim, R.M. Evans and B.M. Spiegelman: Terminal differentiation of human liposarcoma cells induced by ligands for peroxisome proliferator-activated receptor gamma and the retinoid X receptor. *Proc Natl Acad Sci U S A* 94, 237-41 (1997)

23. P. Sarraf, E. Mueller, D. Jones, F.J. King, D.J. DeAngelo, J.B. Partridge, S.A. Holden, L.B. Chen, S. Singer, C. Fletcher and B.M. Spiegelman: Differentiation and reversal of malignant changes in colon cancer through PPARgamma. *Nat Med* 4, 1046-52 (1998)

24. E. Mueller, P. Sarraf, P. Tontonoz, R.M. Evans, K.J. Martin, M. Zhang, C. Fletcher, S. Singer and B.M. Spiegelman: Terminal differentiation of human breast cancer through PPAR gamma. *Mol Cell* 1, 465-70 (1998)

25. P. Sarraf, E. Mueller, W.M. Smith, H.M. Wright, J.B. Kum, L.A. Aaltonen, A. de la Chapelle, B.M. Spiegelman and C. Eng: Loss-of-function mutations in PPAR gamma associated with human colon cancer. *Mol Cell* 3, 799-804 (1999)

26. E. Mueller, M. Smith, P. Sarraf, T. Kroll, A. Aiyer, D.S. Kaufman, W. Oh, G. Demetri, W.D. Figg, X.P. Zhou, C. Eng, B.M. Spiegelman and P.W. Kantoff: Effects of ligand activation of peroxisome proliferator-activated receptor gamma in human prostate cancer. *Proc Natl Acad Sci U S A* 97, 10990-5 (2000)

27. T. Ikezoe, C.W. Miller, S. Kawano, A. Heaney, E.A. Williamson, J. Hisatake, E. Green, W. Hofmann, H. Taguchi and H.P. Koeffler: Mutational analysis of the peroxisome proliferator-activated receptor gamma gene in human malignancies. *Cancer Res* 61, 5307-10 (2001)

28. S.S. Palakurthi, H. Aktas, L.M. Grubissich, R.M. Mortensen and J.A. Halperin: Anticancer effects of thiazolidinediones are independent of peroxisome proliferator-activated receptor gamma and mediated by

inhibition of translation initiation. *Cancer Res* 61, 6213-8 (2001)

29. C.L. Chaffer, D.M. Thomas, E.W. Thompson and E.D. Williams: PPARgamma-independent induction of growth arrest and apoptosis in prostate and bladder carcinoma. *BMC Cancer* 6, 53 (2006)

30. D. Veliceasa, F.T. Schulze-Hoepfner and O.V. Volpert: PPARgamma and Agonists against Cancer: Rational Design of Complementation Treatments. *PPAR Res* 2008, 945275 (2008)

31. S. Wei, J. Yang, S.L. Lee, S.K. Kulp and C.S. Chen: PPARgamma-independent antitumor effects of thiazolidinediones. *Cancer Lett* 276, 119-24 (2009)

32. K. Yamaguchi, M. Cekanova, M.F. McEntee, J.H. Yoon, S.M. Fischer, I.B. Renes, I. Van Seuningen and S.J. Baek: Peroxisome proliferator-activated receptor ligand MCC-555 suppresses intestinal polyps in ApcMin/+ mice via extracellular signal-regulated kinase and peroxisome proliferator-activated receptor-dependent pathways. *Mol Cancer Ther* 7, 2779-87 (2008)

33. C. Giaginis, A. Tsantili-Kakoulidou and S. Theocharis: Peroxisome Proliferator-Activated Receptor-gamma Ligands: Potential Pharmacological Agents for Targeting the Angiogenesis Signaling Cascade in Cancer. *PPAR Res* 2008, 431763 (2008)

34. W. Chearwae and J.J. Bright: PPARgamma agonists inhibit growth and expansion of CD133+ brain tumour stem cells. *Br J Cancer* 99, 2044-53 (2008)

35. H. Sasaki, M. Tanahashi, H. Yukiue, S. Moiriyama, Y. Kobayashi, Y. Nakashima, M. Kaji, M. Kiriyama, I. Fukai, Y. Yamakawa and Y. Fujii: Decreased perioxisome proliferator-activated receptor gamma gene expression was correlated with poor prognosis in patients with lung cancer. *Lung Cancer* 36, 71-6 (2002)

36. Y. Jiang, L. Zou, C. Zhang, S. He, C. Cheng, J. Xu, W. Lu, Y. Zhang, H. Zhang, D. Wang and A. Shen: PPARgamma and Wnt/beta-Catenin pathway in human breast cancer: expression pattern, molecular interaction and clinical/prognostic correlations. *J Cancer Res Clin Oncol* 135, 1551-9 (2009)

37. S. Ogino, K. Shima, Y. Baba, K. Nosho, N. Irahara, S. Kure, L. Chen, S. Toyoda, G.J. Kirkner, Y.L. Wang, E.L. Giovannucci and C.S. Fuchs: Colorectal cancer expression of peroxisome proliferator-activated receptor gamma (PPARG, PPARgamma) is associated with good prognosis. *Gastroenterology* 136, 1242-50 (2009)

38. S. Theocharis, J. Klijanienko, C. Giaginis, J. Rodriguez, T. Jouffroy, A. Girod, D. Point, G. Tsourouflis and X. Satre-Garau: Peroxisome proliferator-activated receptor-gamma in mobile tongue squamous cell carcinoma: associations with clinicopathological parameters and patients survival. *J Cancer Res Clin Oncol* (2010)

39. Y. Nakamura, T. Suzuki, A. Sugawara, Y. Arai and H. Sasano: Peroxisome proliferator-activated receptor gamma in human prostate carcinoma. *Pathol Int* 59, 288-93 (2009)

40. C. Giaginis, E. Katsamangou, G. Tsourouflis, D. Zizi-Serbetzoglou, G. Kouraklis and S. Theocharis: Peroxisome proliferator-activated receptor-gamma and retinoid X receptor-alpha expression in pancreatic ductal adenocarcinoma: association with clinicopathological parameters, tumor proliferative capacity, and patients' survival. *Med Sci Monit* 15, BR148-56 (2009)

41. H.J. Kim, J.Y. Hwang, W.S. Choi, J.H. Lee, K.C. Chang, T. Nishinaka, C. Yabe-Nishimura and H.G. Seo: Expression of a peroxisome proliferator-activated receptor gamma 1 splice variant that was identified in human lung cancers suppresses cell death induced by cisplatin and oxidative stress. *Clin Cancer Res* 13, 2577-83 (2007)

42. A.M. Lefebvre, I. Chen, P. Desreumaux, J. Najib, J.C. Fruchart, K. Geboes, M. Briggs, R. Heyman and J. Auwerx: Activation of the peroxisome proliferator-activated receptor gamma promotes the development of colon tumors in C57BL/6J-APCMin/+ mice. *Nat Med* 4, 1053-7 (1998)

43. E. Saez, P. Tontonoz, M.C. Nelson, J.G. Alvarez, U.T. Ming, S.M. Baird, V.A. Thomazy and R.M. Evans: Activators of the nuclear receptor PPARgamma enhance colon polyp formation. *Nat Med* 4, 1058-61 (1998)

44. J. Li, Y. Lv, X. Dong and Z. Jin: (Pioglitazone, a peroxisome proliferators-activated receptor gamma ligand, inhibits dimethylhydrazine (DMH) induced aberrant crypt foci in rats). *Beijing Da Xue Xue Bao* 35, 537-9 (2003)

45. C.A. McAlpine, Y. Barak, I. Matise and R.T. Cormier: Intestinal-specific PPARgamma deficiency enhances tumorigenesis in ApcMin/+ mice. *Int J Cancer* 119, 2339-46 (2006)

46. G.D. Girnun, W.M. Smith, S. Drori, P. Sarraf, E. Mueller, C. Eng, P. Nambiar, D.W. Rosenberg, R.T. Bronson, W. Edelmann, R. Kucherlapati, F.J. Gonzalez and B.M. Spiegelman: APC-dependent suppression of colon carcinogenesis by PPARgamma. *Proc Natl Acad Sci U S A* 99, 13771-6 (2002)

47. C.G. Su, X. Wen, S.T. Bailey, W. Jiang, S.M. Rangwala, S.A. Keilbaugh, A. Flanigan, S. Murthy, M.A. Lazar and G.D. Wu: A novel therapy for colitis utilizing PPAR-gamma ligands to inhibit the epithelial inflammatory response. *J Clin Invest* 104, 383-9 (1999)

48. L.J. Saubermann, A. Nakajima, K. Wada, S. Zhao, Y. Terauchi, T. Kadowaki, H. Aburatani, N. Matsuhashi, R. Nagai and R.S. Blumberg: Peroxisome proliferator-activated receptor gamma agonist ligands stimulate a Th2 cytokine response and prevent acute colitis. *Inflamm Bowel Dis* 8, 330-9 (2002)

49. K. Katayama, K. Wada, A. Nakajima, H. Mizuguchi, T. Hayakawa, S. Nakagawa, T. Kadowaki, R. Nagai, Y.

Kamisaki, R.S. Blumberg and T. Mayumi: A novel PPAR gamma gene therapy to control inflammation associated with inflammatory bowel disease in a murine model. *Gastroenterology* 124, 1315-24 (2003)

50. N.P. Evans, S.A. Misyak, E.M. Schmelz, A.J. Guri, R. Hontecillas and J. Bassaganya-Riera : Conjugated linoleic acid ameliorates inflammation-induced colorectal cancer in mice through activation of PPARgamma. *J Nutr* 140, 515-21 (2010)

51. H. Kocdor, M.A. Kocdor, T. Canda, D. Gurel, R. Cehreli, O. Yilmaz, M. Alakavuklar and G. Guner: Chemopreventive efficacies of rosiglitazone, fenretinide and their combination against rat mammary carcinogenesis. *Clin Transl Oncol* 11, 243-9 (2009)

52. J. Lu, K. Imamura, S. Nomura, K. Mafune, A. Nakajima, T. Kadowaki, N. Kubota, Y. Terauchi, G. Ishii, A. Ochiai, H. Esumi and M. Kaminishi: Chemopreventive effect of peroxisome proliferator-activated receptor gamma on gastric carcinogenesis in mice. *Cancer Res* 65, 4769-74 (2005)

53. R. Nemenoff, A.M. Meyer, T.M. Hudish, A.B. Mozer, A. Snee, S. Narumiya, R.S. Stearman, R.A. Winn, M. Weiser-Evans, M.W. Geraci and R.L. Keith: Prostacyclin prevents murine lung cancer independent of the membrane receptor by activation of peroxisomal proliferator--activated receptor gamma. *Cancer Prev Res (Phila Pa)* 1, 349-56 (2008)

54. R. Govindarajan, L. Ratnasinghe, D.L. Simmons, E.R. Siegel, M.V. Midathada, L. Kim, P.J. Kim, R.J. Owens and N.P. Lang: Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. *J Clin Oncol* 25, 1476-81 (2007)

55. M.H. Kulke, G.D. Demetri, N.E. Sharpless, D.P. Ryan, R. Shivdasani, J.S. Clark, B.M. Spiegelman, H. Kim, R.J. Mayer and C.S. Fuchs: A phase II study of troglitazone, an activator of the PPARgamma receptor, in patients with chemotherapy-resistant metastatic colorectal cancer. *Cancer J* 8, 395-9 (2002)

56. H.J. Burstein, G.D. Demetri, E. Mueller, P. Sarraf, B.M. Spiegelman and E.P. Winer: Use of the peroxisome proliferator-activated receptor (PPAR) gamma ligand troglitazone as treatment for refractory breast cancer: a phase II study. *Breast Cancer Res Treat* 79, 391-7 (2003)

57. M.R. Smith, J. Manola, D.S. Kaufman, D. George, W.K. Oh, E. Mueller, S. Slovin, B.M. Spiegelman, E. Small and P.W. Kantoff: Rosiglitazone versus placebo for men with prostate carcinoma and a rising serum prostate-specific antigen level after radical prostatectomy and/or radiation therapy. *Cancer* 101, 1569-74 (2004)

58. M. Shimizu and H. Moriwaki: Synergistic Effects of PPARgamma Ligands and Retinoids in Cancer Treatment. *PPAR Res* 2008, 181047 (2008)

59. W.L. Read, M.Q. Baggstrom, P.M. Fracasso and R. Govindan: A phase I study of bexarotene and rosiglitazone in patients with refractory cancers. *Chemotherapy* 54, 236-41 (2008)

60. G.D. Girnun, E. Naseri, S.B. Vafai, L. Qu, J.D. Szwaya, R. Bronson, J.A. Alberta and B.M. Spiegelman: Synergy between PPARgamma ligands and platinum-based drugs in cancer. *Cancer Cell* 11, 395-406 (2007)

61. G.D. Girnun, L. Chen, J. Silvaggi, R. Drapkin, L.R. Chirieac, R.F. Padera, R. Upadhyay, S.B. Vafai, R. Weissleder, U. Mahmood, E. Naseri, S. Buckley, D. Li, J. Force, K. McNamara, G. Demetri, B.M. Spiegelman and K.K. Wong: Regression of drug-resistant lung cancer by the combination of rosiglitazone and carboplatin. *Clin Cancer Res* 14, 6478-86 (2008)

62. K. Tikoo, P. Kumar and J. Gupta: Rosiglitazone synergizes anticancer activity of cisplatin and reduces its nephrotoxicity in 7, 12-dimethyl benz{a}anthracene (DMBA) induced breast cancer rats. *BMC Cancer* 9, 107 (2009)

63. N. Hamaguchi, H. Hamada, S. Miyoshi, K. Irifune, R. Ito, T. Miyazaki and J. Higaki: *In vitro* and *in vivo* therapeutic efficacy of the PPAR-gamma agonist troglitazone in combination with cisplatin against malignant pleural mesothelioma cell growth. *Cancer Sci* (2010)

64. Y.Q. Zhang, X.Q. Tang, L. Sun, L. Dong, Y. Qin, H.Q. Liu, H. Xia and J.G. Cao: Rosiglitazone enhances fluorouracil-induced apoptosis of HT-29 cells by activating peroxisome proliferator-activated receptor gamma. *World J Gastroenterol* 13, 1534-40 (2007)

65. L.Q. Cao, X.L. Wang, Q. Wang, P. Xue, X.Y. Jiao, H.P. Peng, H.W. Lu, Q. Zheng, X.L. Chen, X.H. Huang, X.H. Fu and J.S. Chen: Rosiglitazone sensitizes hepatocellular carcinoma cell lines to 5-fluorouracil antitumor activity through activation of the PPARgamma signaling pathway. *Acta Pharmacol Sin* 30, 1316-22 (2009)

66. S.V. Fulzele, A. Chatterjee, M.S. Shaik, T. Jackson, N. Ichite and M. Singh: 15-Deoxy-Delta12,14-prostaglandin J2 enhances docetaxel anti-tumor activity against A549 and H460 non-small-cell lung cancer cell lines and xenograft tumors. *Anticancer Drugs* 18, 65-78 (2007)

67. I. Szatmari, G. Vamosi, P. Brazda, B.L. Balint, S. Benko, L. Szeles, V. Jeney, C. Ozvegy-Laczka, A. Szanto, E. Barta, J. Balla, B. Sarkadi and L. Nagy: Peroxisome proliferator-activated receptor gamma-regulated ABCG2 expression confers cytoprotection to human dendritic cells. *J Biol Chem* 281, 23812-23 (2006)

68. S. Kawabata, M. Oka, K. Shiozawa, K. Tsukamoto, K. Nakatomi, H. Soda, M. Fukuda, Y. Ikegami, K. Sugahara, Y. Yamada, S. Kamihira, L.A. Doyle, D.D. Ross and S. Kohno: Breast cancer resistance protein directly confers

SN-38 resistance of lung cancer cells. *Biochem Biophys Res Commun* 280, 1216-23 (2001)

69. L.A. Doyle, W. Yang, L.V. Abruzzo, T. Krogmann, Y. Gao, A.K. Rishi and D.D. Ross: A multidrug resistance transporter from human MCF-7 breast cancer cells. *Proc Natl Acad Sci U S A* 95, 15665-70 (1998)

70. L. Tencer, E. Burgermeister, M.P. Ebert and M. Liscovitch: Rosiglitazone induces caveolin-1 by PPARgamma-dependent and PPRE-independent mechanisms: the role of EGF receptor signaling and its effect on cancer cell drug resistance. *Anticancer Res* 28, 895-906 (2008)

71. P. Pierzchalski, A. Krawiec, J. Gawelko, W.W. Pawlik, S.J. Konturek and M. Gonciarz: Molecular mechanism of protection against chemically and gamma-radiation induced apoptosis in human colon cancer cells. *J Physiol Pharmacol* 59 Suppl 2, 191-202 (2008)

72. V. Subbarayan, X.C. Xu, J. Kim, P. Yang, A. Hoque, A.L. Sabichi, N. Llansa, G. Mendoza, C.J. Logothetis, R.A. Newman, S.M. Lippman and D.G. Menter: Inverse relationship between 15-lipoxygenase-2 and PPAR-gamma gene expression in normal epithelia compared with tumor epithelia. *Neoplasia* 7, 280-93 (2005)

73. I. Shureiqi, D. Chen, R. Lotan, P. Yang, R.A. Newman, S.M. Fischer and S.M. Lippman: 15-Lipoxygenase-1 mediates nonsteroidal anti-inflammatory drug-induced apoptosis independently of cyclooxygenase-2 in colon cancer cells. *Cancer Res* 60, 6846-50 (2000)

74. I. Shureiqi, D. Chen, J.J. Lee, P. Yang, R.A. Newman, D.E. Brenner, R. Lotan, S.M. Fischer and S.M. Lippman: 15-LOX-1: a novel molecular target of nonsteroidal anti-inflammatory drug-induced apoptosis in colorectal cancer cells. *J Natl Cancer Inst* 92, 1136-42 (2000)

75. I. Shureiqi, X. Xu, D. Chen, R. Lotan, J.S. Morris, S.M. Fischer and S.M. Lippman: Nonsteroidal anti-inflammatory drugs induce apoptosis in esophageal cancer cells by restoring 15-lipoxygenase-1 expression. *Cancer Res* 61, 4879-84 (2001)

76. J. Wu, H.H. Xia, S.P. Tu, D.M. Fan, M.C. Lin, H.F. Kung, S.K. Lam and B.C. Wong: 15-Lipoxygenase-1 mediates cyclooxygenase-2 inhibitor-induced apoptosis in gastric cancer. *Carcinogenesis* 24, 243-7 (2003)

77. S.M. Earles, J.C. Bronstein, D.L. Winner and A.W. Bull: Metabolism of oxidized linoleic acid: characterization of 13-hydroxyoctadecadienoic acid dehydrogenase activity from rat colonic tissue. *Biochim Biophys Acta* 1081, 174-80 (1991)

78. R. Altmann, M. Hausmann, T. Spottl, M. Gruber, A.W. Bull, K. Menzel, D. Vogl, H. Herfarth, J. Scholmerich, W. Falk and G. Rogler: 13-Oxo-ODE is an endogenous ligand for PPARgamma in human colonic epithelial cells. *Biochem Pharmacol* 74, 612-22 (2007)

79. A.L. Silverman, J.C. Bronstein, S. Krymgold, D. Kahlon and A.W. Bull: Decreased levels of 13-hydroxyoctadecadienoic acid (13-HODE) dehydrogenase in neoplastic tissue of human colon biopsies. *Cancer Epidemiol Biomarkers Prev* 5, 53-6 (1996)

80. L.C. Hsi, L. Wilson, J. Nixon and T.E. Eling: 15-lipoxygenase-1 metabolites down-regulate peroxisome proliferator-activated receptor gamma via the MAPK signaling pathway. *J Biol Chem* 276, 34545-52 (2001)

81. U.P. Kelavkar, J.B. Nixon, C. Cohen, D. Dillehay, T.E. Eling and K.F. Badr: Overexpression of 15-lipoxygenase-1 in PC-3 human prostate cancer cells increases tumorigenesis. *Carcinogenesis* 22, 1765-73 (2001)

82. J.B. Nixon, H. Kamitani, S.J. Baek and T.E. Eling: Evaluation of eicosanoids and NSAIDs as PPARgamma ligands in colorectal carcinoma cells. *Prostaglandins Leukot Essent Fatty Acids* 68, 323-30 (2003)

83. I. Shureiqi, D. Chen, R.S. Day, X. Zuo, F.L. Hochman, W.A. Ross, R.A. Cole, O. Moy, J.S. Morris, L. Xiao, R.A. Newman, P. Yang and S.M. Lippman: Profiling lipoxygenase metabolism in specific steps of colorectal tumorigenesis. *Cancer Prev Res (Phila Pa)* 3, 829-38 (2010)

84. H. Yuan, M.Y. Li, L.T. Ma, M.K. Hsin, T.S. Mok, M.J. Underwood and G.G. Chen: 15-Lipoxygenases and its metabolites 15 (S)-HETE and 13 (S)-HODE in the development of non-small cell lung cancer. *Thorax* 65, 321-6 (2010)

85. J.T. O'Flaherty, L.C. Rogers, C.M. Paumi, R.R. Hantgan, L.R. Thomas, C.E. Clay, K. High, Y.Q. Chen, M.C. Willingham, P.K. Smitherman, T.E. Kute, A. Rao, S.D. Cramer and C.S. Morrow: 5-Oxo-ETE analogs and the proliferation of cancer cells. *Biochim Biophys Acta* 1736, 228-36 (2005)

86. S. Naruhn, W. Meissner, T. Adhikary, K. Kaddatz, T. Klein, B. Watzer, S. Muller-Brusselbach and R. Muller: 15-hydroxyeicosatetraenoic acid is a preferential peroxisome proliferator-activated receptor beta/delta agonist. *Mol Pharmacol* 77, 171-84 (2010)

87. I. Shureiqi, W. Jiang, X. Zuo, Y. Wu, J.B. Stimmel, L.M. Leesnitzer, J.S. Morris, H.Z. Fan, S.M. Fischer and S.M. Lippman: The 15-lipoxygenase-1 product 13-S-hydroxyoctadecadienoic acid down-regulates PPAR-delta to induce apoptosis in colorectal cancer cells. *Proc Natl Acad Sci U S A* 100, 9968-73 (2003)

88. H.C. Chong, M.J. Tan, V. Philippe, S.H. Tan, C.K. Tan, C.W. Ku, Y.Y. Goh, W. Wahli, L. Michalik and N.S. Tan: Regulation of epithelial-mesenchymal IL-1 signaling by PPARbeta/delta is essential for skin homeostasis and wound healing. *J Cell Biol* 184, 817-31 (2009)

89. S.A. Kliewer, J.M. Lenhard, T.M. Willson, I. Patel, D.C. Morris and J.M. Lehmann: A prostaglandin J2

metabolite binds peroxisome proliferator-activated receptor gamma and promotes adipocyte differentiation. *Cell* 83, 813-9 (1995)

90. W.L. Chou, L.M. Chuang, C.C. Chou, A.H. Wang, J.A. Lawson, G.A. FitzGerald and Z.F. Chang: Identification of a novel prostaglandin reductase reveals the involvement of prostaglandin E2 catabolism in regulation of peroxisome proliferator-activated receptor gamma activation. *J Biol Chem* 282, 18162-72 (2007)

91. X. Su, D.J. Mancuso, P.E. Bickel, C.M. Jenkins and R.W. Gross: Small interfering RNA knockdown of calcium-independent phospholipases A2 beta or gamma inhibits the hormone-induced differentiation of 3T3-L1 preadipocytes. *J Biol Chem* 279, 21740-8 (2004)

92. W. He, Y. Barak, A. Hevener, P. Olson, D. Liao, J. Le, M. Nelson, E. Ong, J.M. Olefsky and R.M. Evans: Adipose-specific peroxisome proliferator-activated receptor gamma knockout causes insulin resistance in fat and liver but not in muscle. *Proc Natl Acad Sci U S A* 100, 15712-7 (2003)

93. K. Jaworski, M. Ahmadian, R.E. Duncan, E. Sarkadi-Nagy, K.A. Varady, M.K. Hellerstein, H.Y. Lee, V.T. Samuel, G.I. Shulman, K.H. Kim, S. de Val, C. Kang and H.S. Sul: AdPLA ablation increases lipolysis and prevents obesity induced by high-fat feeding or leptin deficiency. *Nat Med* 15, 159-68 (2009)

94. H.S. Camp and S.R. Tafuri: Regulation of peroxisome proliferator-activated receptor gamma activity by mitogen-activated protein kinase. *J Biol Chem* 272, 10811-6 (1997)

95. K. Yamazaki, M. Shimizu, M. Okuno, R. Matsushima-Nishiwaki, N. Kanemura, H. Araki, H. Tsurumi, S. Kojima, I.B. Weinstein and H. Moriwaki: Synergistic effects of RXR alpha and PPAR gamma ligands to inhibit growth in human colon cancer cells--phosphorylated RXR alpha is a critical target for colon cancer management. *Gut* 56, 1557-63 (2007)

96. P. Shankaranarayanan, A. Rossin, H. Khanwalkar, S. Alvarez, R. Alvarez, A. Jacobson, A. Nebbioso, A.R. de Lera, L. Altucci and H. Gronemeyer: Growth factor-antagonized rexinoid apoptosis involves permissive PPARgamma/RXR heterodimers to activate the intrinsic death pathway by NO. *Cancer Cell* 16, 220-31 (2009)

97. K.A. Burns and J.P. Vanden Heuvel: Modulation of PPAR activity via phosphorylation. *Biochim Biophys Acta* 1771, 952-60 (2007)

98. N.S. Tan, L. Michalik, B. Desvergne and W. Wahli: Multiple expression control mechanisms of peroxisome proliferator-activated receptors and their target genes. *J Steroid Biochem Mol Biol* 93, 99-105 (2005)

99. E. Treuter, T. Albrektsen, L. Johansson, J. Leers and J.A. Gustafsson: A regulatory role for RIP140 in nuclear receptor activation. *Mol Endocrinol* 12, 864-81 (1998)

100. M. Akaike, W. Che, N.L. Marmarosh, S. Ohta, M. Osawa, B. Ding, B.C. Berk, C. Yan and J. Abe: The hinge-helix 1 region of peroxisome proliferator-activated receptor gamma1 (PPARgamma1) mediates interaction with extracellular signal-regulated kinase 5 and PPARgamma1 transcriptional activation: involvement in flow-induced PPARgamma activation in endothelial cells. *Mol Cell Biol* 24, 8691-704 (2004)

101. C. Clape, V. Fritz, C. Henriquet, F. Apparailly, P.L. Fernandez, F. Iborra, C. Avances, M. Villalba, S. Culine and L. Fajas: miR-143 interferes with ERK5 signaling, and abrogates prostate cancer progression in mice. *PloS one* 4, e7542 (2009)

102. D. Bonofiglio, S. Gabriele, S. Aquila, S. Catalano, M. Gentile, E. Middea, F. Giordano and S. Ando: Estrogen receptor alpha binds to peroxisome proliferator-activated receptor response element and negatively interferes with peroxisome proliferator-activated receptor gamma signaling in breast cancer cells. *Clin Cancer Res* 11, 6139-47 (2005)

103. O. Araki, H. Ying, F. Furuya, X. Zhu and S.Y. Cheng: Thyroid hormone receptor beta mutants: Dominant negative regulators of peroxisome proliferator-activated receptor gamma action. *Proc Natl Acad Sci U S A* 102, 16251-6 (2005)

104. G.E. Kilroy, X. Zhang and Z.E. Floyd: PPAR-gamma AF-2 domain functions as a component of a ubiquitin-dependent degradation signal. *Obesity (Silver Spring)* 17, 665-73 (2009)

105. S. Hauser, G. Adelmant, P. Sarraf, H.M. Wright, E. Mueller and B.M. Spiegelman: Degradation of the peroxisome proliferator-activated receptor gamma is linked to ligand-dependent activation. *J Biol Chem* 275, 18527-33 (2000)

106. T. Barz, A. Hoffmann, M. Panhuysen and D. Spengler: Peroxisome proliferator-activated receptor gamma is a Zac target gene mediating Zac antiproliferation. *Cancer Res* 66, 11975-82 (2006)

107. E.D. Rosen, C.H. Hsu, X. Wang, S. Sakai, M.W. Freeman, F.J. Gonzalez and B.M. Spiegelman: C/EBPalpha induces adipogenesis through PPARgamma: a unified pathway. *Genes Dev* 16, 22-6 (2002)

108. M. Fu, J. Zhang, Y. Lin, X. Zhu, L. Zhao, M. Ahmad, M.U. Ehrengruber and Y.E. Chen: Early stimulation and late inhibition of peroxisome proliferator-activated receptor gamma (PPAR gamma) gene expression by transforming growth factor beta in human aortic smooth muscle cells: role of early growth-response factor-1 (Egr-1), activator protein 1 (AP1) and Smads. *Biochem J* 370, 1019-25 (2003)

109. L.H. Wang, X.Y. Yang, X. Zhang, J. Huang, J. Hou, J. Li, H. Xiong, K. Mihalic, H. Zhu, W. Xiao and W.L. Farrar: Transcriptional inactivation of STAT3 by

PPARgamma suppresses IL-6-responsive multiple myeloma cells. *Immunity* 20, 205-18 (2004)

110. H.P. Guan, T. Ishizuka, P.C. Chui, M. Lehrke and M.A. Lazar: Corepressors selectively control the transcriptional activity of PPARgamma in adipocytes. *Genes Dev* 19, 453-61 (2005)

111. J.H. Xiao, C. Ghosn, C. Hinchman, C. Forbes, J. Wang, N. Snider, A. Cordrey, Y. Zhao and R.A. Chandraratna: Adenomatous polyposis coli (APC)-independent regulation of beta-catenin degradation via a retinoid X receptor-mediated pathway. *J Biol Chem* 278, 29954-62 (2003)

112. E.A. Jansson, A. Are, G. Greicius, I.C. Kuo, D. Kelly, V. Arulampalam and S. Pettersson: The Wnt/beta-catenin signaling pathway targets PPARgamma activity in colon cancer cells. *Proc Natl Acad Sci U S A* 102, 1460-5 (2005)

113. D. Lu, H.B. Cottam, M. Corr and D.A. Carson: Repression of beta-catenin function in malignant cells by nonsteroidal antiinflammatory drugs. *Proc Natl Acad Sci U S A* 102, 18567-71 (2005)

114. D. Lu and D.A. Carson: Repression of beta-catenin signaling by PPAR gamma ligands. *Eur J Pharmacol* 636, 198-202 (2010)

115. H.N. Yu, Y.R. Lee, E.M. Noh, K.S. Lee, J.S. Kim, E.K. Song, M.K. Han, Y.C. Lee, K.B. Kwon, S.J. Lee, H.J. Youn and S.H. Jung: Induction of G1 phase arrest and apoptosis in MDA-MB-231 breast cancer cells by troglitazone, a synthetic peroxisome proliferator-activated receptor gamma (PPARgamma) ligand. *Cell Biol Int* 32, 906-12 (2008)

116. D.L. Crowe and R.A. Chandraratna: A retinoid X receptor (RXR)-selective retinoid reveals that RXR-alpha is potentially a therapeutic target in breast cancer cell lines, and that it potentiates antiproliferative and apoptotic responses to peroxisome proliferator-activated receptor ligands. *Breast Cancer Res* 6, R546-55 (2004)

117. P. Puigserver, Z. Wu, C.W. Park, R. Graves, M. Wright and B.M. Spiegelman: A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* 92, 829-39 (1998)

118. P. Puigserver, G. Adelmant, Z. Wu, M. Fan, J. Xu, B. O'Malley and B.M. Spiegelman: Activation of PPARgamma coactivator-1 through transcription factor docking. *Science* 286, 1368-71 (1999)

119. C.A. Heinlein, H.J. Ting, S. Yeh and C. Chang: Identification of ARA70 as a ligand-enhanced coactivator for the peroxisome proliferator-activated receptor gamma. *J Biol Chem* 274, 16147-52 (1999)

120. H. Nishizawa, K. Yamagata, I. Shimomura, M. Takahashi, H. Kuriyama, K. Kishida, K. Hotta, H. Nagaretani, N. Maeda, M. Matsuda, S. Kihara, T. Nakamura, H. Nishigori, H. Tomura, D.D. Moore, J. Takeda, T. Funahashi and Y. Matsuzawa: Small heterodimer partner, an orphan nuclear receptor, augments peroxisome proliferator-activated receptor gamma transactivation. *J Biol Chem* 277, 1586-92 (2002)

121. L.H. Wang, X.Y. Yang, X. Zhang and W.L. Farrar: Inhibition of adhesive interaction between multiple myeloma and bone marrow stromal cells by PPARgamma cross talk with NF-kappaB and C/EBP. *Blood* 110, 4373-84 (2007)

122. A. Majdalawieh and H.S. Ro: PPARgamma1 and LXRalpha face a new regulator of macrophage cholesterol homeostasis and inflammatory responsiveness, AEBP1. *Nucl Recept Signal* 8, e004 (2010)

123. G. Pascual, A.L. Fong, S. Ogawa, A. Gamliel, A.C. Li, V. Perissi, D.W. Rose, T.M. Willson, M.G. Rosenfeld and C.K. Glass: A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. *Nature* 437, 759-63 (2005)

124. R.A. Gupta, J.A. Brockman, P. Sarraf, T.M. Willson and R.N. DuBois: Target genes of peroxisome proliferator-activated receptor gamma in colorectal cancer cells. *J Biol Chem* 276, 29681-7 (2001)

125. M. Cekanova, J.S. Yuan, X. Li, K. Kim and S.J. Baek: Gene alterations by peroxisome proliferator-activated receptor gamma agonists in human colorectal cancer cells. *Int J Oncol* 32, 809-19 (2008)

126. S. Dionne, E. Levy, D. Levesque and E.G. Seidman: PPARgamma ligand 15-deoxy-delta 12,14-prostaglandin J2 sensitizes human colon carcinoma cells to TWEAK-induced apoptosis. *Anticancer Res* 30, 157-66 (2010)

127. C.J. Lee, J.S. Han, C.Y. Seo, T.H Park, H.C. Kwon, J.S. Jeong, I.H. Kim, J. Yun, Y.S. Bae, J.Y. Kwak and J.I. Park: Pioglitazone, a synthetic ligand for PPARgamma, induces apoptosis in RB-deficient human colorectal cancer cells. *Apoptosis* 11, 401-11 (2006)

128. M. Lu, T. Kwan, C. Yu, F. Chen, B. Freedman, J.M. Schafer, E.J. Lee, J.L. Jameson, V.C. Jordan and V.L. Cryns: Peroxisome proliferator-activated receptor gamma agonists promote TRAIL-induced apoptosis by reducing survivin levels via cyclin D3 repression and cell cycle arrest. *J Biol Chem* 280, 6742-51 (2005)

129. S.J. Crabb, A. Hague, P.W. Johnson and G. Packham: BAG-1 inhibits PPARgamma-induced cell death, but not PPARgamma-induced transcription, cell cycle arrest or differentiation in breast cancer cells. *Oncol Rep* 19, 689-96 (2008)

130. K. Kim, Z. Lu and E.D. Hay: Direct evidence for a role of beta-catenin/LEF-1 signaling pathway in induction of EMT. *Cell Biol Int* 26, 463-76 (2002)

131. D.L. Daniels and W.I. Weis: Beta-catenin directly displaces Groucho/TLE repressors from Tcf/Lef in Wnt-

mediated transcription activation. *Nat Struct Mol Biol* 12, 364-71 (2005)

132. N.A. Wong and M. Pignatelli: Beta-catenin--a linchpin in colorectal carcinogenesis? *Am J Pathol* 160, 389-401 (2002)

133. A. Reinacher-Schick and B.M. Gumbiner: Apical membrane localization of the adenomatous polyposis coli tumor suppressor protein and subcellular distribution of the beta-catenin destruction complex in polarized epithelial cells. *J Cell Biol* 152, 491-502 (2001)

134. J. Bilic, Y.L. Huang, G. Davidson, T. Zimmermann, C.M. Cruciat, M. Bienz and C. Niehrs: Wnt induces LRP6 signalosomes and promotes dishevelled-dependent LRP6 phosphorylation. *Science* 316, 1619-22 (2007)

135. Y. Ying and Q. Tao: Epigenetic disruption of the WNT/beta-catenin signaling pathway in human cancers. *Epigenetics* 4, 307-12 (2009)

136. M. Peifer and P. Polakis: Wnt signaling in oncogenesis and embryogenesis--a look outside the nucleus. *Science* 287, 1606-9 (2000)

137. T. Brabletz, A. Jung, K. Hermann, K. Gunther, W. Hohenberger and T. Kirchner: Nuclear overexpression of the oncoprotein beta-catenin in colorectal cancer is localized predominantly at the invasion front. *Pathol Res Pract* 194, 701-4 (1998)

138. M. Moldes, Y. Zuo, R.F. Morrison, D. Silva, B.H. Park, J. Liu and S.R. Farmer: Peroxisome-proliferator-activated receptor gamma suppresses Wnt/beta-catenin signalling during adipogenesis. *Biochem J* 376, 607-13 (2003)

139. R. Fodde and T. Brabletz: Wnt/beta-catenin signaling in cancer stemness and malignant behavior. *Curr Opin Cell Biol* 19, 150-8 (2007)

140. G. Christofori and H. Semb: The role of the cell-adhesion molecule E-cadherin as a tumour-suppressor gene. *Trends Biochem Sci* 24, 73-6 (1999)

141. P. Laidler, J. Dulinska and S. Mrozicki: Does the inhibition of c-myc expression mediate the anti-tumor activity of PPAR's ligands in prostate cancer cell lines? *Arch Biochem Biophys* 462, 1-12 (2007)

142. R. Choudhary, H. Li, R.A. Winn, A.L. Sorenson, M.C. Weiser-Evans and R.A. Nemenoff: Peroxisome proliferator-activated receptor-gamma inhibits transformed growth of non-small cell lung cancer cells through selective suppression of Snail. *Neoplasia* 12, 224-34 (2010)

143. D. Iliopoulos, H.A. Hirsch and K. Struhl: An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. *Cell* 139, 693-706 (2009)

144. N. Nadiminty, W. Lou, S.O. Lee, X. Lin, D.L. Trump and A.C. Gao: Stat3 activation of NF-{kappa}B p100 processing involves CBP/p300-mediated acetylation. *Proc Natl Acad Sci U S A* 103, 7264-9 (2006)

145. D.S. Straus, G. Pascual, M. Li, J.S. Welch, M. Ricote, C.H. Hsiang, L.L. Sengchanthalangsy, G. Ghosh and C.K. Glass: 15-deoxy-delta 12,14-prostaglandin J2 inhibits multiple steps in the NF-kappa B signaling pathway. *Proc Natl Acad Sci U S A* 97, 4844-9 (2000)

146. W.K. Jung, I.S. Park, S.J. Park, S.S. Yea, Y.H. Choi, S. Oh, S.G. Park and I.W. Choi: The 15-deoxy-Delta12,14-prostaglandin J2 inhibits LPS-stimulated AKT and NF-kappaB activation and suppresses interleukin-6 in osteoblast-like cells MC3T3E-1. *Life Sci* 85, 46-53 (2009)

147. T. Takagi, Y. Naito, N. Tomatsuri, O. Handa, H. Ichikawa, N. Yoshida and T. Yoshikawa: Pioglitazone, a PPAR-gamma ligand, provides protection from dextran sulfate sodium-induced colitis in mice in association with inhibition of the NF-kappaB-cytokine cascade. *Redox Rep* 7, 283-9 (2002)

148. J. Rajasingh and J.J. Bright: 15-Deoxy-delta12,14-prostaglandin J2 regulates leukemia inhibitory factor signaling through JAK-STAT pathway in mouse embryonic stem cells. *Exp Cell Res* 312, 2538-46 (2006)

149. H. Ide, T. Nakagawa, Y. Terado, Y. Kamiyama, S. Muto and S. Horie: Tyk2 expression and its signaling enhances the invasiveness of prostate cancer cells. *Biochem Biophys Res Commun* 369, 292-6 (2008)

150. C. Schuster, M. Muller, M. Freissmuth, V. Sexl and D. Stoiber: Commentary on H. Ide *et al.*, "Tyk2 expression and its signaling enhances the invasiveness of prostate cancer cells". *Biochem Biophys Res Commun* 366, 869-70 (2008)

151. B. Sen, B. Saigal, N. Parikh, G. Gallick and F.M. Johnson: Sustained Src inhibition results in signal transducer and activator of transcription 3 (STAT3) activation and cancer cell survival via altered Janus-activated kinase-STAT3 binding. *Cancer Res* 69, 1958-65 (2009)

152. N. Nadiminty, W. Lou, M. Sun, J. Chen, J. Yue, H.J. Kung, C.P. Evans, Q. Zhou and A.C. Gao: Aberrant activation of the androgen receptor by NF-kappaB2/p52 in prostate cancer cells. *Cancer Res* 70, 3309-19 (2010)

153. E.L. Paquette, L. Sun, L.R. Paquette, R. Connelly, D.G. McLeod and J.W. Moul: Improved prostate cancer-specific survival and other disease parameters: impact of prostate-specific antigen testing. *Urology* 60, 756-9 (2002)

154. J.I. Hisatake, T. Ikezoe, M. Carey, S. Holden, S. Tomoyasu and H.P. Koeffler: Down-Regulation of prostate-specific antigen expression by ligands for peroxisome proliferator-activated receptor gamma in human prostate cancer. *Cancer Res* 60, 5494-8 (2000)

155. C.C. Yang, C.Y. Ku, S. Wei, C.W. Shiau, C.S. Chen, J.J. Pinzone and M.D. Ringel: Peroxisome proliferator-activated receptor gamma-independent repression of prostate-specific antigen expression by thiazolidinediones in prostate cancer cells. *Mol Pharmacol* 69, 1564-70 (2006)

156. D. Bonofiglio, S. Aquila, S. Catalano, S. Gabriele, M. Belmonte, E. Middea, H. Qi, C. Morelli, M. Gentile, M. Maggiolini, S. Ando: Peroxisome proliferator-activated receptor-gamma activates p53 gene promoter binding to the nuclear factor-kappaB sequence in human MCF7 breast cancer cells. *Mol Endocrinol* 20, 3083-92 (2006)

157. Z. Wang and Y. Sun: Targeting p53 for Novel Anticancer Therapy. *Transl Oncol* 3, 1-12 (2010)

158. S.J. Lee, E.K. Yang and S.G. Kim: Peroxisome proliferator-activated receptor-gamma and retinoic acid X receptor alpha represses the TGFbeta1 gene via PTEN-mediated p70 ribosomal S6 kinase-1 inhibition: role for Zf9 dephosphorylation. *Mol Pharmacol* 70, 415-25 (2006)

159. M.H. Bai, H.B. Ma, X.J. Wang, X.X. Liu, X.H. Xue and F.J. Xue: (Effects of activated PPARgamma on the expression of PTEN gene in pancreatic cancer cells). *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 24, 717-20 (2008)

160. Y.W. Dong, X.P. Wang and K. Wu: Suppression of pancreatic carcinoma growth by activating peroxisome proliferator-activated receptor gamma involves angiogenesis inhibition. *World J Gastroenterol* 15, 441-8 (2009)

161. J. Tao, J. Xiong, T. Li, Z. Yang, X. Li, K. Li, H. Wu and C. Wang: Correlation between protein expression of PTEN in human pancreatic cancer and the proliferation, infiltration, metastasis and prognosis. *J Huazhong Univ Sci Technolog Med Sci* 26, 444-7 (2006)

162. A. Konieczna, R. Lichnovka, B. Erdosova and J. Ehrmann: The Role of PPARs in MDR - a lesson from embryonic development. *Neoplasma* 56, 279-83 (2009)

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