[Cancer Biology & Therapy 4:7, 687-693, July 2005]; ©2005 Landes Bioscience

Review

PPARγ as a Therapeutic Target for Tumor Angiogenesis and Metastasis

Dipak Panigrahy[1,†]
Sui Huang[1,†]
Mark W. Kieran[1,2]
Arja Kaipainen[1,*]

[1]Vascular Biology Program; Children's Hospital; Department of Surgery; [2]Department of Pediatric Oncology; Dana-Farber Cancer Institute; Harvard Medical School; Boston, Massachusetts USA

†These authors contributed equally to this work.

*Correspondence to: Arja Kaipainen; 300 Longwood Avenue; Children's Hospital; Karp Research Building, Floor 12; Boston, Massachusetts USA 02115; Tel.: 617.919.2403; Fax: 617.730.0231; Email: arja.kaipainen@childrens.harvard.edu

Received 07/11/05; Accepted 07/13/05

Previously published online as a *Cancer Biology & Therapy* E-publication: http://www.landesbioscience.com/journals/cbt/abstract.php?id=2014

KEY WORDS

PPARγ ligand, PPARγ antagonist, angiogenesis, growth inhibition

ABSTRACT

Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors with pleiotropic effects on cell fate and metabolism. Because of its anti-proliferative, pro-apoptotic and differentiation promoting activities, PPARγ has been intensively evaluated as a target for anti-cancer therapy in preclinical models. However, PPARγ has been reported to act both as a promoter and suppressor of neoplasia, and the role of PPARγ activating ligands as well as antagonists in therapy remains controversial. In the past decade a new picture of tumors as a disease that involves changes in the non-cancerous tumor bed, including angiogenesis, inflammation and other stromal changes has emerged. PPARγ has strong anti-inflammatory and anti-angiogenic effects, extending the repertoire of potential targets of PPARγ ligands beyond cell autonomous mechanisms of cancer. The heterogeneous cellular targets and the biphasic effects of PPARγ on various pro and anti-tumor processes may account for the apparent paradoxical effects of PPARγ agonists. Here we review the action of PPARγ agonists on angiogenesis and inflammation in the context of tumorigenesis as an integrated tissue process and discuss potential explanations for the conflicting effects of PPARγ agonists on tumor progression and metastasis. Sorting out the various modes of action and defining their relative contribution in the context of tumor and host tissue as a heterogeneous target will therefore be crucial to understand the multi facetted effects of PPARγ. This will be paramount if the potent biological activity of PPARγ agonists are to be harnessed for cancer therapy.

PHARMACOLOGY OF PPARγ LIGANDS

Peroxisome proliferator activated receptors (PPARs) are a family of nuclear receptors comprising three isoforms, PPARα, PPARγ, and PPARβ/δ, which are encoded by separate genes (reviewed in refs. 1 and 2), but share a high degree of amino acid sequence homology resulting in some degree of cross reactivity.[3] PPARs act as ligand-activated transcriptional factors. PPARγ was originally discovered as the high affinity orphan receptor of the synthetic thiazolindinedione (TZD) class of agents used to treat type II diabetes.[4-6] Only later were natural PPARγ ligands discovered, which include polyunsaturated acids and essential fatty acids, such as linoleic acid and linolenic acid.[7] The most widely used natural ligand is prostaglandin 15 deoxy-$\Delta_{12,14}$ prostaglandin J_2 (15d-PGJ_2). However, 15d-PGJ_2 also potently inhibits NF-kβ dependent transcription via PPARγ independent mechanisms.[8]

The TZD family of PPARγ agonists includes rosiglitazone, pioglitazone, and troglitazone. Rosiglitazone binds PPARγ with a higher affinity (Kd = 40 nM) than troglitazone or pioglitazone. In general, they are selective for PPARγ at doses of 10 μM or less.[3,5] In contrast, non-TZD PPARγ agonists are in general less selective and also activate PPARα, albeit at 10 fold higher concentrations than those required to activate PPARγ.[9] Other PPARγ ligands, such as L 796449 (phenylacetic acid derivative), also activate PPARα and PPARδ at similar concentrations.[10,11] The natural ligand 15d-PGJ_2 activates PPARγ at low micromolar concentrations.[12] Several non-steroidal anti-inflammatory drugs (NSAIDs), in particular indomethacin and ibuprofen, bind to PPARγ and are weak PPARγ agonists at high micromolar concentrations.[13,14] Interestingly, NSAIDs share with PPARγ agonists both their anti-inflammatory and anti-angiogenic activity (see below).[15,16] For a comprehensive survey of cross-activation of PPARα and PPARδ by nominal PPARγ ligands (see refs. 1 and 3).

Because of its potent effects on cell fate regulation, PPARγ attracted interest as a potential target for cancer therapy.[17-20] Recent studies have shown that inhibition of PPARγ by PPARγ-specific antagonists induce cell death, apoptosis, anoikis and inhibit tumor cell invasion in squamous cell and hepatocellular carcinoma.[21,22] This approach follows the paradigm of the majority of target specific anti-cancer strategies which focus

on antagonizing signaling pathways to inhibit a cellular function that contributes to cell proliferation and survival. However, the first known PPARγ ligands were agonists and PPARγ activation has also been studied as a target in cancer therapy (discussed below).[17-19] Since PPARγ ligands, such as TZDs, activate a transcription factor that regulates a variety of cellular functions in many different cell types, their pharmacological properties are characterized by an extraordinary pleiotropy of qualitatively distinct biological effects across various tissues. These distinct effects often depend on the particular dose (reviewed in ref. 23). Therefore, dosage of PPARγ ligands in clinical trials for cancer therapy needs to be defined thoroughly and monitored closely. For instance, low concentrations of PPARγ ligands increase cell proliferation while higher concentrations block cell growth in breast cancer cells.[24] Conversely, we recently showed that higher doses of rosiglitazone were less anti-angiogenic than the lower doses that are actually comparable to the serum levels of rosiglitazone in humans.[25] Such a "biphasic" effect has been shown for many cytokines including those with anti-angiogenic effects, such as IFN-α, which has less anti-angiogenic activity at higher doses as well.[26,27]

Most in vitro studies of TZD effect on cancer cells utilize concentrations of TZDs higher than those typically required to trigger their action through PPARγ-which leads to cross-activation of PPARα and PPARδ[1]. This may produce qualitatively distinct effects at these higher doses compared to those elicited by the lower, "selective" doses at which only the PPARγ pathway is activated. Furthermore, PPARγ ligand concentrations that exhibit anti-tumor activity in mice are higher than the corresponding doses used in the treatment of Type II diabetes.[28-31] The effective clinical doses used in diabetes are 4–8 mg/day for rosiglitazone (0.11 mg/kg/day for a 70 kg human) and 15–45 mg/day for pioglitazone.[32] By contrast, the anti-tumor activity in mice is observed with rosiglitazone at 100-150 mg/kg/day,[28,30] which is 1000 fold higher.

COMPLEXITY OF TARGETS: CELL AUTONOMOUS AND NON-CELL AUTONOMOUS REGULATION

The notion of potential usefulness of PPARγ agonists in cancer stems from the indirect evidence that PPARγ may have tumor suppressive effects. Loss of function mutations and hemizygous deletions found in cancer cells and PAX-8/PPARγ fusion protein in thyroid cancer[33,34] gave a rise to the hypothesis that PPARγ may function as a tumor suppressor gene.[35] Similarly, PPARγ heterozygous knockout mice have increased susceptibility to chemical carcinogens.[36] However, no PPARγ mutations could be found in the analysis of 397 human tumors and cell lines,[37] questioning the idea that PPARγ may act as a classical tumor suppressor protein.

Nevertheless, PPARγ activation by ligands can induce cancer cell growth arrest, differentiation, apoptosis and non-apoptotic cell death.[18] These effects appear to be mediated through both PPARγ-dependent and PPARγ independent ("off target") pathway depending on the agonist type, concentration and tumor cell type.[1,20] Interestingly, some in vitro findings did not correlate with in vivo observations. For example, TZDs had minimal to no inhibitory activity on some tumor cell lines in vitro but potently inhibited the tumors derived from the same cells in animal models.[28] Importantly, some studies have shown that agonists possess inhibitory effects not only on tumors cells, but also on stromal cells, such as smooth muscle, endothelial, and inflammatory cells strongly suggesting that PPARγ (and ligands) may regulate tumor growth by targeting non-cell autonomous mechanisms.[38-40]

Over the past decades, starting from the recognition of the role of tumor angiogenesis in tumor progression[41] there has been an increasing awareness of alterations in the non-cancerous host tissue that promote tumor progression. Beyond tumor angiogenesis, infiltration of inflammatory and immune cells, changes in stromal fibroblasts and recruitment of bone marrow derived precursor cells all significantly modulate tumor progression (Fig. 1). Soluble growth factors secreted by cells from the altered tumor micro-environment in the surrounding host tissue as well as changes in extracellular matrix composition have tumor modulating effects.[42] Given the pleiotropic activity of PPARγ and the wide expression profile of PPARγ, many of the cells within the tumor bed, any cellular component of the tumor stroma in addition to the tumor cell, may be a target of PPARγ ligands and jointly respond to the diffuse presence of PPARγ agonists.

The action of PPARγ ligands on tumors highlights the limitations of the traditional concept of "one drug–one molecular target–one effect". The often counterintuitive, paradoxical effect of PPARγ agonists on tumors that has led to much controversy about their usefulness can essentially be explained by the following principles: (1) Cross-reactivity of PPARγ agonists with other PPAR family members; (2) Multiplicity of cell types (and their distinct response to PPARγ activation) that serve as targets; (3) Targeting of non-PPAR family molecules at higher dose (non-selective, or "off target" effects); (4) Bi (or multi) -phasic dose response relationships, in part due to heterogeneous sensitivity and opposite responsiveness of the various cellular targets mentioned above.

Some salient recently reported observations that illustrate the complexity of PPARγ action on tumors include the following: transcriptional activity and CD36 expression induced by the PPARγ agonist, 15d-PGJ_2 was reduced by a PPARγ antagonist, GW9662. However, the same antagonist did not block apoptosis induced by the same agonist in breast cancer cells.[43] In addition, the PPARγ antagonist GW9662 enhanced the inhibitory effect of the agonist rosiglitazone on breast cancer cells rather than rescued tumor growth, suggesting that PPARγ activation may not be involved in inhibition of survival and cell growth caused by TZDs.[44] Similar results were obtained in studies in which PC3, CaCO-2, T47D cancer cells were inhibited by both PPARγ agonists and antagonists separately and in co-treatments.[45] This apparent paradoxical synergism between a pair of nominal agonists and antagonists, respectively, is in line with the finding that while PPARγ agonists, as mentioned above, can have tumor suppressing effects, antagonists also can induce apoptosis in cancer cells.[21,22] Considering the pharmacological complexity discussed above, it is likely that non-PPARγ mediated, i.e., "off target" as well as biphasic effects are involved. Conversely, inhibition of cell proliferation by suppression of mRNA expression of integrin α5β1 by PPARγ agonists was reversed by an antagonist.[46] Finally, at the level of non-cell autonomous effects, higher doses of rosiglitazone appeared to be less anti-angiogenic (discussed below) and less potent in inhibiting lung metastasis than the lower doses that correspond to the serum levels of rosiglitazone achieved in humans in diabetes treatment.[25]

ANTI-ANGIOGENIC EFFECTS OF PPARγ AGONISTS

The process of neovascularization requires that endothelial cells proliferate, migrate, break matrix to invade, form tubes and mature (recruit pericytes around them).[41] Each one of these components of angiogenesis can be studied separately in vitro to determine the differential effect of anti-angiogenic agents on any of these processes in

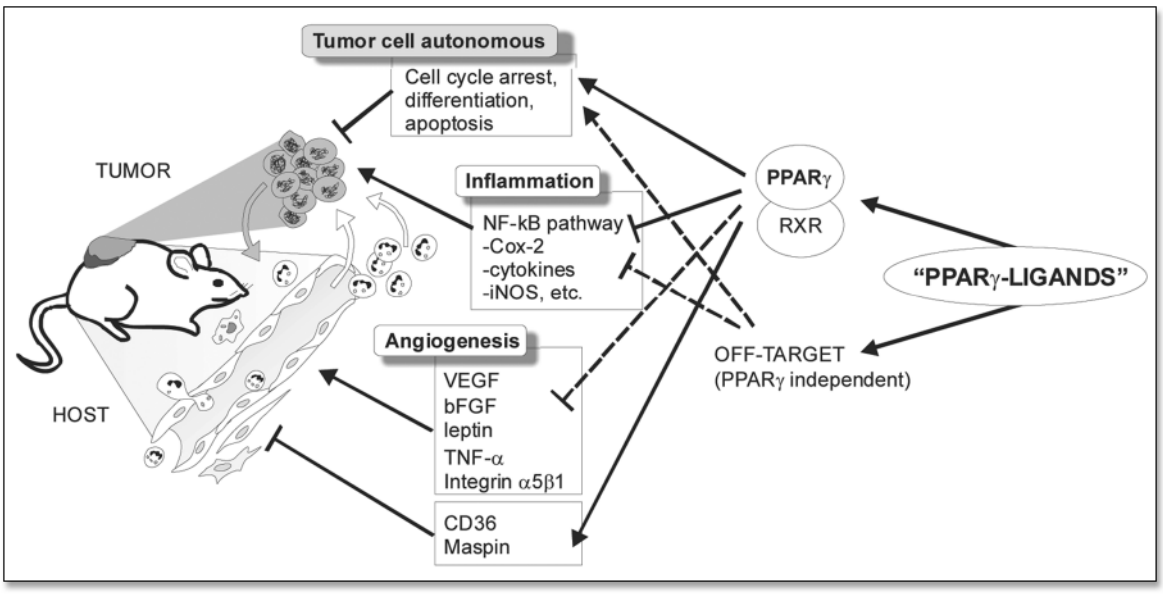

Figure 1. PPARγ-dependent and independent effects of PPARγ agonists on both tumor and host cells in the tumor bed. The figure shows selected examples of potential molecular targets of PPARγ agonists that mediate the anti-tumor, anti-angiogenic and anti-inflammatory effects. For the PPAR≥ target genes, solid arrows indicate direct regulation by PPARγ, dashed lines denote indirect regulation.

assays, such as endothelial cell (EC) proliferation, migration, tube formation, and aortic ring angiogenesis. Anti-angiogenic effects in vivo can be studied in the corneal neovascularization assay in which a stimulator (e.g., FGF2) incorporated into a polymer pellet that is implanted in a pocket in the normally avascular cornea.[47] This assay also allows one to assess the inflammatory component involved. In contrast, in the chorioallantoic membrane (CAM) assay, in which the same pellet is placed on a CAM of a 6-day-old chick embryo, no inflammatory component occurs before day 8.[48] Moreover, microvessel density, EC proliferation, and EC apoptosis can be monitored in histological sections of PPARγ ligand treated tumors.[28,49]

PPARγ is expressed in normal and tumor endothelial cells and influences angiogenesis at multiple steps. PPARγ agonists inhibit FGF2 and vascular endothelial growth factor (VEGF)-stimulated proliferation; they induce endothelial cell apoptosis at nanomolar doses (i.e., in the range of drug/ receptor binding affinity), suggesting a specific PPARγ mediated effect.[28,39,50-52] However, none of these studies have been done in the presence of an antagonist or in PPARγ deficient cells, as has been done in the case of treatment of tumor cells. As for EC migration and invasion, PPARγ ligands inhibit VEGF and leptin-induced endothelial cell migration.[53,54] The leptin-mediated angiogenesis inhibition is thought to occur via the Akt pathway.[54] EC tube formation induced by VEGF, FGF2 and PMA is also inhibited by PPARγ ligands. DNA microarray based gene expression profiling of EC induced to form capillary tubes on collagen matrix revealed that the ligand 15d-PGJ_2 stimulated transcription of TFPI-2 which is hypothesized to be involved in limiting extracellular matrix degradation and promoting the proliferation of mural cells, leading to the assembly of new vessel wall.[55] mRNA of another factor, laminin γ2 was increased 100 fold after the same treatment. While the role of laminin in EC differentiation is not clear, it may, since it is an essential part of the basement membrane lining blood vessels, have an important role in angiogenesis.[56]

Evidence of in vivo inhibition of angiogenesis by PPARγ agonists is also accumulating. 15d-PGJ_2 released by an implanted pellet inhibits corneal neovascularization in vivo.[39] Furthermore, PPARγ ligands inhibit choroidal, retinal, and corneal neovascularization when administered intraocularly.[57-59] In addition, systemic administration of rosiglitazone and troglitazone inhibits FGF2 induced angiogenesis.[28] Importantly, PPARγ ligands have been shown to inhibit angiogenesis in the CAM, indicating that this anti-angiogenic effect had a component that was independent of inflammatory processes. Conversely, in the corneal neovascularization assay a multiphasic effect on angiogenesis inhibition was observed: 100–200 mg/kg/day inhibited angiogenesis by 60–70%, while lower and higher doses had only 20–40% inhibition. These effects could be attributed to multiple pleiotropic effects of PPARγ: inhibition of VEGF expression in the tissue, inhibition of leukocyte extravasation, inhibition of cytokine secretion from the infiltrating leukocytes, or direct inhibition of endothelial functions.[28]

Immunohistochemical studies suggested that PPARγ is localized in tumor endothelial cells.[60] In fact, PPARγ was more highly expressed in endothelial cells of lung cancer and renal cell carcinoma than that in the corresponding normal tissue.[61] In addition to direct action of agents on the endothelium, tumor angiogenesis can also be regulated by indirect mechanisms. For instance, suppression of angiogenesis can result from a decrease in the local levels of stimulators (e.g., VEGF and FGF2) and/or an increase of endogenous inhibitors of angiogenesis (e.g., thrombospondin) produced by tumor cells. PPARγ ligands have been shown to suppress VEGF production in two tumor cell lines: glioblastoma (U87) and Lewis lung carcinoma. Similarly, pioglitazone and 15d-PGJ_2, at 10 μM, inhibited VEGF and FGF2 secretion by 70–84% in human renal cell carcinoma (RCC) cells.[62] In contrast, PPARγ ligands increased VEGF production in bladder and prostate cancer cell.[63,64] In addition, PPARγ ligands have also been shown to upregulate FGF2 induced VEGF release in osteoblasts.[65] These differences are most likely due to different cell types or variation in the number of days the tumor cells were treated.

INFLAMMATION MEDIATED EFFECTS OF PPARγ AGONISTS

In the past few years it has become evident that angiogenesis is not the only process in the non-cancerous compartment of the tumor tissue that influences tumorigenesis and tumor progression. It has long been known that inflammatory infiltrates in tumors can affect prognosis.[66] The observation of dramatic changes in the proteome and transcriptome of the tumor micro-environment with the upregulation of inflammatory cytokines suggest the presence of an inflammatory response in the host tissue surrounding the tumor.[42] Specifically, more recent studies link tumor initiation and tumor cell secretion of specific cytokines to tumor associated inflammation and neovascularization that promote tumor growth.[67,68] For instance, tumor derived IL-6 and -8 can induce migration of tumor inflammatory cells, which can activate angiogenesis and tumor growth. Both COX-2 and inducible nitric oxide syntheses (iNOS), central mediators of inflammatory responses, are also major regulators of angiogenesis and metastasis.[69] In fact, COX-2 activation can mediate the pro-angiogenic effect of nitric oxide in colorectal cancer.[70] The downregulation of these molecules can suppress the expression of adhesion molecules in leukocytes and endothelium, thus preventing inflammatory cell recruitment to the tumor and inhibiting inflammation and angiogenesis. These findings also suggest an intense cross-talk between inflammatory processes and angiogenesis, often blurring the line between the two.

The potent anti-inflammatory effects of PPARγ raise the possibility that part of the observed in vivo tumor suppressing effects is mediated by the inhibition of tumor promoting inflammatory processes. However, the molecular mechanisms by which PPARγ ligands prevent tumor growth through anti-inflammatory actions in vivo is not well understood, although its role is well characterized in inflammation as an underlying pathogenesis process in the case of cardiovascular diseases.[71-73] Anti-inflammatory effects of PPARγ ligands have been reported in animal models of atherosclerosis, arthritis, and inflammatory bowel disease.[74-77] For a recent review on the mechanistic role of PPARγ in inflammation see reference 78. In brief, PPARγ activation can produce anti-inflammatory effects via PPARγ receptor dependent trans-repression mechanisms: PPARγ activation downregulates the expression of stress kinase (e.g., JNK, p38 MAPK) and transcription factors, including NF-κB, AP-1, STAT[79] which govern the expression of pro-inflammatory cytokines, such as TNFα, IL-8, IL-6, IL-1β, as well as chamomiles and enzymes (iNOS, COX-2).

ANTI-ANGIOGENIC AND ANTI-INFLAMMATORY TARGET GENES

The precise, immediate molecular targets of PPARγ agonists that mediate their anti-tumor, anti-angiogenic and anti-inflammatory effects, and hence, their tumor suppressing activity remain elusive in many cases. However, several either PPARγ dependent or independent genes that are upregulated after treatment with PPARγ agonists have known biological functions that support the idea that PPARγ affects tumor growth not only via cell autonomous mechanisms but also through its anti-angiogenic or anti-inflammatory effects (Fig. 1). We briefly review a few interesting examples:

CD36 is a multifunctional cell surface protein which is also expressed on tumor micro-vascular endothelial cells and macrophages.[80,81] CD36 has a peroxisome proliferator response element (PPRE) in its promoter region and can therefore be directly regulated by PPARγ. As a receptor for the anti-angiogenic protein thrombospondin-1 (TSP-1) it may mediate the inhibition of tumor angiogenesis by PPARγ, which increases CD36 expression on endothelial cells. PPARγ ligands synergistically improve the anti-angiogenic and anti-tumor effects of TSP1 and the thrombospondin peptide ABT510 in tumor xenografts.[82]

Expression of maspin in tumor cells is upregulated by PPARγ activation.[83] Maspin is a member of the family of serine protease inhibitors which have been shown to possess tumor suppressor activity in breast and prostate cancer.[84] Maspin also inhibits mammary tumor cell motility in vitro, and primary tumor growth and metastasis in vivo.[85] In addition, maspin inhibits VEGF induced endothelial cell migration and FGF2 stimulated corneal neovascularization, and reduces microvessel density in tumors.[86,87] Furthermore, maspin overexpression targeted to endothelial cells induced EC apoptosis in mice bearing mammary tumors.[88]

Leptin is a hormone that regulates food intake. Interestingly, its receptor, OB-Rb, is also expressed on endothelial cells. Leptin can function as a potent angiogenic factor: it stimulates EC proliferation, migration and corneal angiogenesis.[89,90] PPARγ agonists have been shown to decrease mRNA expression of leptin.[1]

The pro-inflammatory cytokine TNFα is a central regulator of inflammation-mediated angiogenesis, but can also stimulate angiogenesis directly. PPARγ ligands have been shown to inhibit TNFα expression in inflammatory cells.[72]

Integrin α5β1 is expressed on several cell types, including tumor cells and endothelial cells. Overexpression of α5β1 is associated with a more malignant phenotype in various tumors.[46] It can promote angiogenesis, resulting in tumor growth in vivo.[91] PPARγ ligands inhibit fibronectin induced α5 integrin mRNA expression and the growth of non-small lung carcinoma cells (NSCLC).[46] These suppressive effects were reversed by a PPARγ antagonist GW9662.

Inducible nitric oxide synthase (iNOS) is expressed in several cells, including endothelial cells and plays a role in inflammation and immune defense but has also been suggested to be important for tumor angiogenesis.[92,93] PPARγ ligands inhibit iNOS promoter activity and expression in inflammatory cells.[71] A novel PPAR response element was recently identified in the murine iNOS promoter to which PPARγ directly binds.[94] PPARγ can repress the iNOS promoter in response to ligand binding.[95] PPARγ ligand administration decreased expression of iNOS in a colitis related mouse colon carcinogenesis model.[96] However, at PPARγ ligand concentrations of over 10 μM, PPARγ was not necessary for inhibition of iNOS expression.[94]

Matrix metalloproteinase-9 (MMP-9), is a 92-kDa gelatinase that is produced by endothelial cells, monocytes/macrophages and tumor cells and cleaves extracellular matrix proteins.[97,98] Degradation of matrix proteins is important for tumor or endothelial cell invasion into stromal tissue. The MMP-9 gene contains a PPRE sequence and thus, could be directly regulated by PPARγ, but appears to also be subjected to transrepressional activity of PPARγ on NF-κB activity which is required for MMP-9 expression.[98] TZDs have in fact been shown to inhibit MMP-9 secretion in macrophages and tumor cells.[71,72,99,100] However, PPARγ ligands did not affect MMP-9 levels in human microvascular endothelial cells.[28]

EFFECTS ON METASTASIS

Angiogenesis and invasion are two elementary processes that are essential for metastasis as well as local recurrence of a tumor.

In clinical samples of primary tumors PPARγ was expressed more often in low grade than in high grade tumors: in breast cancer, PPARγ expression was found to have a significant favorable impact on relapse free survival of patients.[101] Similarly PPARγ levels were lower in patients with local recurrence than those who stayed disease free[102] and PPARγ expression was found to be inversely associated with histological grade in invasive breast carcinoma.[101] The same type of correlation was found in samples from human lung tumors in that decreased expression of PPARγ was correlated with poor prognosis.[103]

When non-small cell lung cancer (NSCLC) cells overexpressing PPARγ were implanted in mice orthotopically, a dramatic inhibition of tumor number and metastasis from cells overexpressing PPARγ, which correlated with improved survival of the rats, was observed.[104] Preclinical studies with PPARγ ligands showed that they may be effective in preventing metastatic spread of cancer.[28,31] Troglitazone potently inhibited human papillary thyroid tumor growth and prevented distant metastasis of thyroid tumors to the liver.[31] In addition, PPARγ ligands suppressed the invasive potential of five anaplastic thyroid carcinoma cell lines.[105] Systemic therapy with PPARγ ligands prevented metastatic invasion after removal of primary Lewis lung carcinoma: no micrometastasis could be detected, only circulating tumor cells.[28] However, higher doses of rosiglitazone were less anti-angiogenic and less potent in inhibiting lung metastasis than the lower doses that are actually comparable to the serum levels of rosiglitazone in humans[25] revealing a biphasic behavior at the systemic level.

CONCLUSION

In conclusion, this review presents the conceptual challenges of placing the biology of PPARγ and its ligands into the traditional framework of a linear one drug–one target–one effect scheme. The potent modulatory effect of PPARγ on tumor growth that in vitro and animal studies on PPARγ agonists have revealed entails a broader view on drug action in cancer. First, tumorigenesis involves more than the cell autonomous acquisition of uncontrolled growth. Tissue response in the tumor bed, promoted and maintained by activated non-cancerous cells, notably angiogenesis and inflammatory processes, represent worthwhile targets for agents as pleiotropic as PPARγ agonists. Second, not all actions of nominal PPARγ–ligands are mediated by their cognate receptor, PPARγ. Non-selective, "off target" effects on still unknown molecules may either be responsible for the tumor inhibitory activity or counter it (with a different dose effect threshold), which would result in the observed biphasic dose effect relationships. In view of this complexity it may not be surprising that clinical trials in which PPARγ was activated to trigger cellular differentiation of cancer cells essentially failed.[106-109] As it has now been recognized for traditional chemotherapeutic agents, the dosing schedule may be optimized to target the endothelium rather than to achieve maximal killing solely of the tumor cells.[110,111] Given PPARγ's pleiotropic biological activity on a variety of cell types that play active roles in the tumor bed, there is certainly room for dose and schedule optimization. Moreover, as the early lessons that anti-angiogenic therapies has taught us, combining an attack on the endothelium and the tumor cells is most efficient. This should also apply to PPARγ. A joint multi-target attack on tumor cells, as well as on inflammatory response and angiogenesis may be an effective option. For instance, in addition to suppressing inflammation, PPARγ induced upregulation of CD36 and thus may enhance the anti-angiogenic effects of TSP-1 and consequently synergize with anti-angiogenic drugs. In fact, PPARγ ligands have been shown to synergistically improve the anti-angiogenic and anti-tumor effects of TSP-1 and the thrombospondin peptide ABT510 in tumor xenografts.[82] Thus, it is likely that PPARγ agonists, much as existing anti-angiogenic drugs, such as Avastin[112] will find clinical application in the context of multi-drug therapies. We are still at the beginning of unraveling the multifaceted activities of PPARγ in the complex tissue response in cancer. Elucidating the individual cellular targets of PPARγ agonists and defining the role of PPARγ in the various cell types will be paramount for a rational design of combinatorial therapy schemes that takes advantage of the potent and well-tolerated PPARγ agonists.

References

1. Berger J, Moller DE. Mechanism of action of PPARs. Ann Rev Med 2002; 53:409-35.
2. Debril MB, Renaud JP, Fajas L, Auwerx J. The pleiotropic functions of peroxisome proliferator-activated receptor gamma. J Mol Med 2001; 79:30-47.
3. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. J Med Chem 2000; 43:527-50.
4. Berger J, Bailey P, Biswas C, Cullinan CA, Doebber TW, Hayes NS, Saperstein R, Smith RG, Leibowitz MD. Thiazolidinediones produce a conformational change in peroxisomal proliferator-activated receptor-gamma: binding and activation correlate with antidiabetic actions in db/db mice. Endocrinology 1996; 137:4189-95.
5. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Wilson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor (PPARγ). J Biol Chem 1995; 270:12953-6.
6. Willson TM, Cobb JE, Cowan DJ, Wiethe RW, Correa ID, Prakash SR, Beck KD, Moore LB, Kliewer SA, Lehmann JM. The structure-activity relationship between peroxisome proliferator-activated receptor gamma agonism and the antihyperglycemic activity of thiazolidinediones. J Med Chem 1996; 39:665-8.
7. Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, Lehmann JM. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. Proc Natl Acad Sci USA 1997; 94:4318-23.
8. Straus DS, Pascual G, Li M, Welch JS, Ricote M, Hsiang CH, Sengchanthalangsy LL, Ghosh G, Glass CK. 15-deoxy-delta 12,14-prostaglandin J2 inhibits multiple steps in the NF-kappa B signaling pathway. Proc Natl Acad Sci USA 2000; 97:4844-9.
9. Shibata T, Matsui K, Nagao K, Shinkai H, Yonemori F, Wakitani K. Pharmacological profiles of a novel oral antidiabetic agent, JTT-501, an isoxazolidinedione derivative. Eur J Pharmacol 1999; 364:211-9.
10. Berger J, Tanen M, Elbrecht A, Hermanowski-Vosatka A, Moller DE, Wright SD, Thieringer R. Peroxisome proliferator-activated receptor-gamma ligands inhibit adipocyte 11beta -hydroxysteroid dehydrogenase type 1 expression and activity. J Biol Chem 2001; 276:12629-35.
11. Berger J, Leibowitz MD, Doebber TW, Elbrecht A, Zhang B, Zhou G, Biswas C, Cullinan CA, Hayes NS, Li Y, Tanen M, Ventre J, Wu MS, Berger GD, Mosley R, Marquis R, Santini C, Sahoo SP, Tolman RL, Smith RG, Moller DE. Novel peroxisome proliferator-activated receptor (PPAR) gamma and PPARdelta ligands produce distinct biological effects. J Biol Chem 1999; 274:6718-25.
12. Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. Cell 1995; 83:803-12.
13. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, Kliewer SA. Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. J Biol Chem 1997; 272:3406-10.
14. Adamson DJ, Frew D, Tatoud R, Wolf CR, Palmer CN. Diclofenac antagonizes peroxisome proliferator-activated receptor-gamma signaling. Mol Pharmacol 2002; 61:7-12.
15. Jones MK, Wang H, Peskar BM, Levin E, Itani RM, Sarfeh IJ, Tarnawski AS. Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs:Insight into mechanisms and implications for cancer growth and ulcer healing. Nat Med 1999; 5:1418-23.
16. Verheul HM, Panigrahy D, Yuan J, D'Amato RJ. Combination oral antiangiogenic therapy with thalidomide and sulindac inhibits tumour growth in rabbits. Br J Cancer 1999; 79:114-8.
17. Kopelovich L, Fay JR, Glazer RI, Crowell JA. Peroxisome proliferator-activated receptor modulators as potential chemopreventive agents. Mol Cancer Ther 2002; 1:357-63.
18. Koeffler HP. Peroxisome proliferator-activated receptor gamma and cancers. Clin Cancer Res 2003; 9:1-9.
19. Michalik L, Desvergne B, Wahli W. Peroxisome-proliferator-activated receptors and cancers: complex stories. Nat Rev Cancer 2004; 4:61-70.
20. Panigrahy D, Shen LQ, Kieran MW, Kaipainen A. Therapeutic potential of thiazolidinediones as anticancer agents. Expert Opin Investig Drugs 2003; 12:1925-37.
21. Masuda T, Wada K, Nakajima A, Okura M, Kudo C, Kadowaki T, Kogo M, Kamisaki Y. Critical role of peroxisome proliferator-activated receptor gamma on anoikis and invasion of squamous cell carcinoma. Clin Cancer Res 2005; 11:4012-21.

22. Schaefer KL, Wada K, Takahashi H, Matsuhashi N, Ohnishi S, Wolfe MM, Turner JR, Nakajima A, Borkan SC, Saubermann LJ. Peroxisome proliferator-activated receptor gamma inhibition prevents adhesion to the extracellular matrix and induces anoikis in hepatocellular carcinoma cells. Cancer Res 2005; 65:2251-9.
23. Rumi MA, Ishihara S, Kazumori H, Kadowaki Y, Kinoshita Y. Can PPAR gamma ligands be used in cancer therapy? Curr Med Chem Anti-Canc Agents 2004; 4:465-77.
24. Clay CE, Namen AM, Atsumi G, Trimboli AJ, Fonteh AN, High KP, Chilton FH. Magnitude of peroxisome proliferator-activated receptor-gamma activation is associated with important and seemingly opposite biological responses in breast cancer cells. J Investig Med 2001; 49:413-20.
25. Freed MI, Allen A, Jorkasky DK, DiCicco RA. Systemic exposure to rosiglitazone is unaltered by food. Eur J Clin Pharmacol 1999; 55:53-56.
26. Calabrese EJ, Baldwin LA. Toxicology rethinks its central belief. Nature 2003; 421:691-2.
27. Slaton JW, Perrotte P, Inoue K, Dinney C, Fidler IJ. Interferon-±-mediated downregulation of angiogenesis-related genes and therapy of bladder cancer are dependent on optimization of biological dose and schedule. Clin Cancer Res 1999; 5:2726-34.
28. Panigrahy D, Singer S, Shen LQ, Butterfield CE, Freedman DA, Chen JC, Moses MA, Kilroy S, Duensing S, Fltecher JA, Hlatky L, Hahnfeldt P, Folkman J, Kaipainen A. PPARγ ligands inhibit primary tumor growth and metastasis by inhibiting angiogenesis. J Clin Invest 2002; 110:923-32.
29. Sarraf P, Mueller E, Jones D, King FJ, DeAngelo DJ, Partridge JB, Holden SA, Chen LB, Singer S, Fletcher C, Spiegelman BM. Differentiation and reversal of malignant changes in colon cancer through PPARγ. Nature Med 1998; 4:1046-52.
30. Heaney AP, Fernando M, Melmed S. PPAR-gamma receptor ligands: novel therapy for pituitary adenomas. J Clin Invest 2003; 111:1381-888.
31. Ohta K, Endo T, Haraguchi K, Hershman JM, Onaya T. Ligands for peroxisome proliferator-activated receptor ≥ inhibit growth and induce apoptosis of human papillary thyroid carcinoma cells. J Clin Endocrinol Metab 2001; 86:2170-7.
32. Goldstein BJ. Differentiating members of the thiazolidinedione class: a focus on efficacy. Diabetes Metab Res Rev 2002; 18 Suppl 2:S16-22.
33. Kroll T, Sarraf P, Pecciarini L, Chen CJ, Mueller E, Spiegelman BM, Fletcher JA. PAX8-PPAR≥1 fusion oncogene in human thyroid carcinoma. Science 2000; 289:1357-60.
34. Sarraf P, Mueller E, Smith WM, Wright HM, Kum JB, Aaltonen LA, de la Chapelle A, Spiegelman BM, Eng C. Loss-of function mutations in PPAR≥ associated with human colon cancer. Mol Cell 1999; 3:799-804.
35. Girnun GD, Smith WM, Drori S, Sarraf P, Mueller E, Eng C, Nambiar P, Rosenberg DW, Bronson RT, Edelmann W, Kucherlapati R, Gonzalez FJ, Spiegelman BM. APC-dependent suppression of colon carcinogenesis by PPARγ. Proc Natl Acad Sci USA 2002; 99:13771-6.
36. Nicol CJ, Yoon M, Ward JM, Yamashita M, Fukamachi K, Peters JM, Gonzalez FJ. PPARgamma influences susceptibility to DMBA-induced mammary, ovarian and skin carcinogenesis. Carcinogenesis 2004; 25:1747-55.
37. Ikezoe T, Miller CW, Kawano S, Heaney A, Williamson EA, Hisatake J, Green E, Hofmann W, Taguchi H, Koeffler HP. Mutational analysis of the peroxisome proliferator-activated receptor gamma gene in human malignancies. Cancer Res 2001; 61:5307-10.
38. Wakino S, Kintscher U, Kim S, Yin F, Hsueh WA, Law RE. Peroxisome proliferator-activated receptor gamma ligands inhibit retinoblastoma phosphorylation and G1--> S transition in vascular smooth muscle cells. J Biol Chem 2000; 275:22435-41.
39. Xin X, Yang S, Kowalski J, Gerritsen ME. Peroxisome proliferator-activated receptor ligands are potent inhibitors of angiogenesis in vitro and in vivo. J Biol Chem 1999; 274:9116-21.
40. Delerive P, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors in inflammation control. J Endocrinol 2001; 169:453-9.
41. Folkman J. in Harrison's Textbook of Internal Medicine (eds. Braunwald, E. et al.) 517-30 (McGraw-Hill, 2001).
42. Liotta LA, Kohn EC. The microenvironment of the tumour-host interface. Nature 2001; 411:375-9.
43. Clay CE, Monjazeb A, Thorburn J, Chilton FH, High KP. 15-Deoxy-delta12,14-prostaglandin J2-induced apoptosis does not require PPARgamma in breast cancer cells. J Lipid Res 2002; 43:1818-28.
44. Seargent JM, Yates EA, Gill JH. GW9662, a potent antagonist of PPARgamma, inhibits growth of breast tumour cells and promotes the anticancer effects of the PPARgamma agonist rosiglitazone, independently of PPARgamma activation. Br J Pharmacol 2004; 143:933-7.
45. Lea MA, Sura M, Desbordes C. Inhibition of cell proliferation by potential peroxisome proliferator-activated receptor (PPAR) gamma agonists and antagonists. Anticancer Res 2004; 24:2765-71.
46. Han S, Rivera HN, Roman J. Peroxisome proliferator-activated receptor-gamma ligands inhibit alpha5 integrin gene transcription in non-small cell lung carcinoma cells. Am J Respir Cell Mol Biol 2005; 32:350-9.
47. Kenyon BM, Voest EE, Chen CC, Flynn E, Folkman J, D'Amato RJ. A model of angiogenesis in the mouse cornea. Invest Ophthalmol Vis Sci 1996; 37:1625-32.
48. Ribatti D, Vacca A, Roncali L, Dammacco F. The chick embryo chorioallantoic membrane as a model for in vivo research on antiangiogenesis. Curr Pharmacol Biotech 2000; 1:73-82.
49. Keshamouni VG, Arenberg DA, Reddy RC, Newstead MJ, Anthwal S, Standiford TJ. PPAR-gamma activation inhibits angiogenesis by blocking ELR+CXC chemokine production in non-small cell lung cancer. Neoplasia 2005; 7:294-301.
50. Marx N, Bourcier T, Sukhova GK, Libby P, Plutzky J. PPAR≥ activation in human endothelial cells increases plasminogen activator inhibitor type-1 expression:PPAR≥ as a potential mediator in vascular disease. Arterioscler Thromb Vasc Biol 1999; 19:546-51.
51. Bishop-Bailey D, Hla T. Endothelial cell apoptosis induced by the peroxisome proliferator-activated receptor (PPAR) ligand 15-deoxy-prostaglandin J2. J Biol Chem 1999; 274:17042-8.
52. Gralinski MR, Rowse PE, Breider MA. Effects of troglitazone and pioglitazone on cytokine-mediated endothelial cell proliferation in vitro. J Cardiovasc Pharmacol 1998; 31:909-13.
53. Goetze S, Eilers F, Bungenstock A, Kintscher U, Stawowy P, Blaschke F, Graf K, Law RE, Fleck E, Grafe M. PPAR activators inhibit endothelial cell migration by targeting Akt. Bioch Biol Res Comm 2002; 293:1431-7.
54. Goetze S, Bungenstock A, Czupalla C, Eilers F, Stawowy P, Kintscher U, Spencer-Hansch C, Graf K, Nurnberg B, Law RE, Fleck E, Grafe M. Leptin induces endothelial cell migration through Akt, which is inhibited by PPARgamma-ligands. Hypertension 2002; 40:748-54.
55. Kahn J, Mehraban F, Ingle G, Xin X, Bryant JE, Vehar G, Schoenfeld J, Grimaldi CJ, Peale F, Draksharabu A, Lewin DA, Gerritsen ME. Gene expression profiling in an in vitro model of angiogenesis. Am J Pathol 2000; 156:1887-900.
56. Patarroyo M, Tryggvason K, Virtanen I. Laminin isoforms in tumor invasion, angiogenesis and metastasis. Semin Cancer Biol 2002; 12:197-207.
57. Murata T, He S, Hangai M, Ishibashi T, Xi X, Kim S, Hsueh WA, Ryan SJ, Law RE, Hinton DR. Peroxisome proliferator-activated receptor-≥ ligands inhibit choroidal neovascularization. Invest Ophthalmol Vis Sci 2000; 41:2309-17.
58. Murata T, Hata Y, Ishibashi T, Kim S, Hsueh WA, Law RE, Hinton DR. Response of experimetal retinal neovascularization to thiazolidinediones. Arch Ophthalmol 2001; 119:709-17.
59. Sarayba MA, Li L, Tungsiripat T, Liu NH, Sweet PM, Patel AJ, Osann KE, Chittiboyina A, Benson SC, Pershadsingh HA, Chuck RS. Inhibition of corneal neovascularization by a peroxisome proliferator-activated receptor-gamma ligand. Exp Eye Res 2005; 80:435-42.
60. Inoue K, Kawahito Y, Tsubouchi Y, Yamada R, Kohno M, Hosokawa Y, Katoh D, Bishop-Bailey D, Hla T, Sano H. Expression of peroxisome proliferator-activated receptor (PPAR)-gamma in human lung cancer. Anticancer Res 2001; 21(4A):2471-6.
61. Inoue K, Kawahito Y, Sano H, Takano H, Yoshikawa T. New diagnostic tool for tumor angiogenesis. Chest 2003; 123:966-7.
62. Yuan J, Takahashi A, Masumori N, Uchida K, Hisasue S, Kitamura H, Itoh N, Tsukamoto T. Ligands for peroxisome proliferator-activated receptor gamma have potent antitumor effect against human renal cell carcinoma. Urology 2005; 65:594-9.
63. Fauconnet S, Lascombe I, Chabannes E, Adessi GL, Desvergne B, Wahli W, Bittard H. Differential regulation of vascular endothelial growth factor expression by peroxisome proliferator-activated receptors in bladder cancer cells. J Biol Chem 2002; 277:23534-43.
64. Haslmayer P, Thalhammer T, Jager W, Aust S, Steiner G, Ensinger C, Obrist P. The peroxisome proliferator-activated receptor gamma ligand 15-deoxy-Delta12,14-prostaglandin J2 induces vascular endothelial growth factor in the hormone-independent prostate cancer cell line PC 3 and the urinary bladder carcinoma cell line 5637. Int J Oncol 2002; 21:915-20.
65. Yasuda E, Tokuda H, Ishisaki A, Hirade K, Kanno Y, Hanai Y, Nakamura N, Noda T, Katagiri Y, Kozawa O. PPAR-gamma ligands up-regulate basic fibroblast growth factor-induced VEGF release through amplifying SAPK/JNK activation in osteoblasts. Biochem Biophys Res Commun 2005; 328:137-43.
66. Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, Makrigiannakis A, Gray H, Schlienger K, Liebman MN, Rubin SC, Coukos G. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003; 348:203-13.
67. Karin M. Inflammation and cancer: the long reach of Ras. Nat Med 2005; 11:20-1.
68. Sparmann A, Bar-Sagi D. Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. Cancer Cell 2004; 6:447-58.
69. Chiarugi V, Magnelli L, Gallo O. Cox-2, iNOS and p53 as play-makers of tumor angiogenesis (review). Int J Mol Med 1998; 2:715-9.
70. Cianchi F, Cortesini C, Fantappie O, Messerini L, Sardi I, Lasagna N, Perna F, Fabbroni V, Di Felice A, Perigli G, Mazzanti R, Masini E. Cyclooxygenase-2 activation mediates the proangiogenic effect of nitric oxide in colorectal cancer. Clin Cancer Res 2004; 10:2694-704.
71. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-≥ is a negative regulator of macrophage activation. Nature 1998; 391:79-82.
72. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 1998; 391:82-6.
73. Marx N, Libby P, Plutzky J. Peroxisome proliferator-activated receptors (PPARs) and their role in the vessel wall: possible mediators of cardiovascular risk? J Cardiovasc Risk 2001; 8:203-10.
74. Li AC, Brown KK, Silvestre MJ, Wilson TM, Palinski W, Glass CK. Peroxisome proliferator-activated receptor ≥ ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. J Clin Invest 2000; 106:523-31.
75. Su CG, Wen X, Bailey ST, Jiang W, Rangwala SM, Keilbaugh SA, Flanigan A, Murthy S, Lazar MA, Wu GD. A novel therapy for colitis utilizing PPAR-g ligands to inhibit the epithelial inflammatory response. J Clin Invest 1999; 104:383-9.
76. Sanchez-Hidalgo M, Martin AR, Villegas I, Alarcon De La Lastra C. Rosiglitazone, an agonist of peroxisome proliferator-activated receptor gamma, reduces chronic colonic inflammation in rats. Biochem Pharmacol 2005; 69:1733-44.

77. Cuzzocrea S, Mazzon E, Dugo L, Patel NS, Serraino I, Di Paola R, Genovese T, Britti D, De Maio M, Caputi AP, Thiemermann C. Reduction in the evolution of murine type II collagen-induced arthritis by treatment with rosiglitazone, a ligand of the peroxisome proliferator-activated receptor gamma. Arthritis Rheum 2003; 48:3544-56.
78. Alarcon de la Lastra C, Sanchez-Fidalgo S, Villegas I, Motilva V. New pharmacological perspectives and therapeutic potential of PPAR-gamma agonists. Curr Pharm Des 2004; 10:3505-24.
79. Kielian T, Drew PD. Effects of peroxisome proliferator-activated receptor-gamma agonists on central nervous system inflammation. J Neurosci Res 2003; 71:315-25.
80. Febbraio M, Hajjar DP, Silverstein RL. CD36: a class B scavenger receptor involved in angiogenesis, atherosclerosis, inflammation, and lipid metabolism. J Clin Invest 2001; 108:785-91.
81. Sund M, Hamano Y, Sugimoto H, Sudhakar A, Soubasakos M, Yerramalla U, Benjamin LE, Lawler J, Kieran M, Shah A, Kalluri R. Function of endogenous inhibitors of angiogenesis as endothelium-specific tumor suppressors. Proc Natl Acad Sci USA 2005; 102:2934-9.
82. Huang H, Campbell SC, Bedford DF, Nelius T, Veliceasa D, Shroff EH, Henkin J, Schneider A, Bouck N, Volpert OV. Peroxisome proliferator-activated receptor gamma ligands improve the antitumor efficacy of thrombospondin peptide ABT510. Mol Cancer Res 2004; 2:541-50.
83. Mueller E, Sarraf P, Tontonoz P, Evans RM, Martin KJ, Zhang M, Fletcher C, Singer S, Spiegelman BM. Terminal differentiation of human breast cancer through PPARγ. Mol Cell 1998; 1:465-70.
84. Zou Z, Anisowicz A, Hendrix MJ, Thor A, Neveu M, Sheng S, Rafidi K, Seftor E, Sager R. Maspin, a serpin with tumor-suppressing activity in human mammary epithelial cells. Science 1994; 263:526-9.
85. Schaefer JS, Zhang M. Role of maspin in tumor metastasis and angiogenesis. Curr Mol Med 2003; 3:653-8.
86. Zhang M, Volpert O, Shi YH, Bouck N. Maspin is an angiogenesis inhibitor. Nature Med 2000; 6:196-9.
87. Watanabe M, Nasu Y, Kashiwakura Y, Kusumi N, Tamayose K, Nagai A, Sasano T, Shimada T, Daida H, Kumon H. Adeno-associated virus 2-mediated intratumoral prostate cancer gene therapy: long-term maspin expression efficiently suppresses tumor growth. Hum Gene Ther 2005; 16:699-710.
88. Li Z, Shi HY, Zhang M. Targeted expression of maspin in tumor vasculatures induces endothelial cell apoptosis. Oncogene 2005; 24:2008-19.
89. Sietta-Honigmann MR, Nath AK, Murakami C, Garcia-Cardena G, Papapetropoulos A, Sessa WC, Madge LA, Schechner JS, Schwabb MB, Polverini PJ, Flores-Riveros JR. Biological action of leptin as an angiogenic factor. Science 1998; 281:1683-6.
90. Bouloumie A, Drexler HC, Lafontan M, Busse R. Leptin, the product of Ob gene, promotes angiogenesis. Circ Res 1998; 83:1059-66.
91. Kim S, Bell K, Mousa SA, Varner JA. Regulation of angiogenesis in vivo by ligation of integrin alpha5beta1 with the central cell-binding domain of fibronectin. Am J Pathol 2000; 156:1345-62.
92. Jenkins DC, Charles IG, Thomsen LL, Moss DW, Holmes LS, Baylis SA, Rhodes P, Westmore K, Emson PC, Moncada S. Roles of nitric oxide in tumor growth. Proc Natl Acad Sci U S A 1995; 92:4392-6.
93. Cianchi F, Cortesini C, Fantappie O, Messerini L, Schiavone N, Vannacci A, Nistri S, Sardi I, Baroni G, Marzocca C, Perna F, Mazzanti R, Bechi P, Masini E. Inducible nitric oxide synthase expression in human colorectal cancer: correlation with tumor angiogenesis. Am J Pathol 2003; 162:793-801.
94. Crosby MB, Svenson J, Gilkeson GS, Nowling TK. A novel PPAR response element in the murine iNOS promoter. Mol Immunol 2005; 42:1303-10.
95. Li M, Pascual G, Glass CK. Peroxisome proliferator-activated receptor gamma-dependent repression of the inducible nitric oxide synthase gene. Mol Cell Biol 2000; 20:4699-707.
96. Kohno H, Suzuki R, Sugie S, Tanaka T. Suppression of colitis-related mouse colon carcinogenesis by a COX-2 inhibitor and PPAR ligands. BMC Cancer 2005; 5:46.
97. Nagase H, Barrett AJ, Woessner JF, Jr. Nomenclature and glossary of the matrix metalloproteinases. Matrix Suppl 1992; 1:421-4.
98. Lee KJ, Kim HA, Kim PH, Lee HS, Ma KR, Park JH, Kim DJ, Hahn JH. Ox-LDL suppresses PMA-induced MMP-9 expression and activity through CD36-mediated activation of PPAR-g. Exp Mol Med 2004; 36:534-44.
99. Marx N, Sukhova G, Murphy C, Libby P, Plutzky J. 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 1998; 153:17-23.
100. Hashimoto K, Ethridge RT, Evers BM. Peroxisome proliferator-activated receptor gamma ligand inhibits cell growth and invasion of human pancreatic cancer cells. Int J Gastrointest Cancer 2002; 32:7-22.
101. Papadaki I, Mylona E, Giannopoulou I, Markaki S, Keramopoulos A, Nakopoulou L. PPARgamma expression in breast cancer: clinical value and correlation with ERbeta. Histopathology 2005; 46:37-42.
102. Jiang WG, Douglas-Jones A, Mansel RE. Expression of peroxisome-proliferator activated receptor-gamma (PPARgamma) and the PPARgamma co-activator, PGC-1, in human breast cancer correlates with clinical outcomes. Int J Cancer 2003; 106:752-7.
103. Sasaki H, Tanahashi M, Yukiue H, Moiriyama S, Kobayashi Y, Nakashima Y, Kaji M, Kiriyama M, Fukai I, Yamakawa Y, Fujii Y. Decreased perioxisome proliferator-activated receptor gamma gene expression was correlated with poor prognosis in patients with lung cancer. Lung Cancer 2002; 36:71-6.
104. Bren-Mattison Y, Van Putten V, Chan D, Winn R, Geraci MW, Nemenoff RA. Peroxisome proliferator-activated receptor-gamma (PPAR(gamma)) inhibits tumorigenesis by reversing the undifferentiated phenotype of metastatic non-small-cell lung cancer cells (NSCLC). Oncogene 2005; 24:1412-22.
105. Hayashi N, Nakamori S, Hiraoka N, Tsujie M, Xundi X, Takano T, Amino N, Sakon M, Monden M. Antitumor effects of peroxisome proliferator activate receptor gamma ligands on anaplastic thyroid carcinoma. Int J Oncol 2004; 24:89-95.
106. Kulke MH, Demetri GD, Sharpless NE, Ryan DP, Shivdasani R, Clark JS, Spiegelman BM, Kim H, Mayer RJ, Fuchs CS. A phase II study of troglitazone, an activator of the PPARgamma receptor, in patients with chemotherapy-resistant metastatic colorectal cancer. Cancer J 2002; 8:395-9.
107. Burstein HJ, Demetri GD, Mueller E, Sarraf P, Spiegelman BM, Winer EP. 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 2003; 79:391-97.
108. Debrock G, Vanhentenrijk V, Sciot R, Debiec-Rychter M, Oyen R, Van Oosterom A. A phase II trial with rosiglitazone in liposarcoma patients. Br J Cancer 2003; 89:1409-12.
109. Smith MR, Manola J, Kaufman DS, George D, Oh WK, Mueller E, Slovin S, Spiegelman B, Small E, Kantoff PW. Rosiglitazone versus placebo for men with prostate carcinoma and a rising serum prostate-specific antigen level after radical prostatectomy and/or radiation therapy. Cancer 2004; 101:1569-74.
110. Browder T, Butterfield CE, Kraling BM, Shi B, Marshall B, O'Reilly MS, Folkman J. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 2000; 60:1878-86.
111. Klement G, Baruchel S, Rak J, Man S, Clark K, Hicklin DJ, Bohlen P, Kerbel RS. Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity. J Clin Invest 2000; 105:15-24.
112. Marx J. Cancer. Encouraging results for second-generation antiangiogenesis drugs. Science 2005; 308:1248-9.