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INVITED REVIEW

Prostate Cancer

# The role of peroxisome proliferator-activated receptor gamma in prostate cancer

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**Despite great progress in the detection and treatment of prostate cancer, this disease remains an incredible health and economic burden. Although androgen receptor (AR) signaling plays a key role in the development and progression of prostate cancer, aberrations in other molecular pathways also contribute to the disease, making it essential to identify and develop drugs against novel targets, both for the prevention and treatment of prostate cancer. One promising target is the peroxisome proliferator-activated receptor gamma (PPARγ) protein. PPARγ was originally thought to act as a tumor suppressor in prostate cells because agonist ligands inhibited the growth of prostate cancer cells; however, additional studies found that PPARγ agonists inhibit cell growth independent of PPARγ. Furthermore, PPARγ expression increases with cancer grade/stage, which would suggest that it is not a tumor suppressor but instead that PPARγ activity may play a role in prostate cancer development and/or progression. Indeed, two new studies, taking vastly different, unbiased approaches, have identified PPARγ as a target in prostate cancer and suggest that PPARγ inhibition might be useful in prostate cancer prevention and treatment. These findings could lead to a new therapeutic weapon in the fight against prostate cancer.**

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## INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer mortality in men living in the developed world.[1] However, the majority of patients are likely to die with the disease rather than from the disease. If caught early, prostate cancer can often be cured with definitive local intervention via surgery or radiation. Despite great progress in developing novel treatments, once prostate cancer metastasizes, it remains incurable. The increasing treatment options and longer life span of men with prostate cancer have seen the total costs of treatment rise considerably. The US is expected to soon spend over $8 billion a year on prostate cancer screening and treatment.[2] The health and financial burdens associated with prostate cancer make it important to identify better treatments and chemopreventive strategies.

Prostate cancer is a multifaceted disease, with the greatest risk factors being age, race, inherited susceptibility, and environmental and behavioral factors such as diet. The development and growth of prostate cancer is uniquely dependent on androgens and the androgen receptor (AR).[3] Our most effective regimens for treating metastatic prostate cancer have arisen from the pioneering experiments in which suppression of testicular testosterone production was shown to cause tumor regression.[4] Since then, our ability to inhibit androgen synthesis and AR signaling has improved, and several agents are now approved for the treatment of metastatic prostate cancer.[5] AR also likely plays a key role in prostate cancer initiation and the early stages of disease, although little is known about this process. One early event that appears to occur in all prostate cancers is a transition from AR directing cytodifferentiation of luminal epithelial cells to AR driving the uncontrolled proliferation of these cells. This "malignancy switch" is likely a central event in tumorigenesis, as AR becomes the primary driver of neoplastic growth in malignant cells.[3] Indeed, the most successful prostate cancer prevention strategies to date have focused on inhibition of the AR via blockade of dihydrotestosterone (DHT) production using 5α-reductase inhibitors.[6,7]

While critical, changes in AR signaling alone are not likely sufficient to fully transform a benign prostate cell; other alterations are necessary. Many such alterations have been proposed to contribute to tumorigenesis, including phosphatase and tensin homolog (PTEN) loss,[8] NK3 homeobox 1 (Nkx3.1) loss,[9] Myc amplification,[10] Forkhead box protein M1 (FoxM1) overexpression,[11] and phosphoinositide 3-kinase/AKT serine/threonine kinase 1 (PI3K/AKT) activity,[12] among others. It is likely that various combinations of these alterations occur in different patients to cause tumorigenic transformation of cells, and that distinct alterations may dictate the course of disease progression and provide distinct therapeutic targets. We and others have recently identified the peroxisome proliferator-activated receptor gamma (PPARγ) as a potential contributor to prostate cancer development and progression.[13,14]

PPARγ is a ligand-dependent transcription factor belonging to the nuclear hormone receptor superfamily.[15] PPARγ is known to play a prominent role in adipocyte differentiation, the inflammatory response, and peripheral glucose utilization, and PPARγ agonists are widely used to treat type II diabetes. PPARγ exists in two protein isoforms, PPARγ1 and PPARγ2, which contains thirty additional amino

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acids at the N-terminus compared to isoform 1.[15] Most tissues express PPARγ1, while PPARγ2 is expressed selectively in adipocytes. A variety of fatty acids appear to be endogenous PPARγ ligands, but the only high-affinity ligands are synthetic, with the thiazolidinediones (TZDs) being among the most widely used clinically as insulin sensitizers in patients with type II diabetes.

Studies have suggested that PPARγ plays a key role in tumorigenesis as a tumor suppressor, and PPARγ agonists have shown antiproliferative and proapoptotic actions in many different cancers. For instance, PPARγ agonists have been shown to reduce the proliferation of colon cancer cells *in vitro* and *in vivo*[16,17] and have entered clinical trials for the treatment of colorectal and esophageal cancers.[18,19] There is also a strong evidence for beneficial effects of PPARγ agonists in head and neck[20] and lung[21] cancers. It was originally thought that PPARγ played a protective role in prostate cancer as well and that PPARγ agonists could be used as therapeutics. However, in this review, we will discuss how new studies have challenged the paradigm of the role of PPARγ in prostate cancer and strongly suggest a role for PPARγ antagonists to treat or prevent prostate cancer.

## PPARG AGONISTS IN PROSTATE CANCER

One of the first studies to investigate the role of PPARγ in prostate cancer stemmed from the observation that diets rich in ω-3 fatty acids appear to be linked to a lower incidence of prostate cancer compared with diets high in ω-6 fatty acids. One of these fatty acid metabolites, 15-Deoxy-$\Delta^{12,14}$-prostaglandin $J_2$ (15d-$PGJ_2$), is a specific activator of PPARγ[22] and had been shown to have antitumor activities,[23] leading Butler *et al.*[24] to test if the anti-tumor properties were due to activation of PPARγ. They found that 15d-$PGJ_2$ and other PPARγ activators including ciglitazone induced cell death in three prostate cancer cell lines but those ligands for PPARα and β did not. This initial study prompted others that investigated the efficacy of PPARγ activating ligands in prostate cancer, and these studies demonstrated that PPARγ agonists decreased AR levels and activity and inhibited prostate cancer cell growth.[25–27] However, later mechanistic studies clearly demonstrated that the effect of these molecules was PPARγ independent (**Figure 1**). One study found that PPARγ agonists inhibited cell growth by facilitating the proteasomal degradation of the transcription factor specificity protein 1 (SP1).[28] Other studies have proposed alternative means by which PPARγ agonists inhibit the growth of prostate cancer cells in a PPARγ-independent fashion, including inhibition of B-cell lymphoma-extra-large/B-cell lymphoma 2 (Bcl-xL/Bcl-2) functions,[29] inhibition of the C-X-C chemokine receptor type 4/C-X-C motif chemokine 12 (CXCR4/CXCL12) axis,[30] and inhibition of the AKT signaling pathway.[31] A further study demonstrated that PPARγ agonists actually increased AR signaling in C4-2 prostate cancer cells, and siRNA-based experiments demonstrated that this was PPARγ dependent.[32] Therefore, it is likely that the PPARγ agonists activate AR signaling, but effects on SP1 or other pathways in some cell types lead to indirect inhibition of AR and decreased prostate cancer cell proliferation.

## PPARG ACTIVITY IN PROSTATE CANCER AND A ROLE FOR ANTAGONISTS

The expression of tumor-suppressing proteins often decreases as cancers develop and progress. However, PPARγ expression appears to be positively correlated with increased stage and grade of prostate cancers, strongly suggesting that it is not a tumor suppressor. For instance, Segawa *et al.*[33] found that, in approximately 200 samples, PPARγ expression was significantly more extensive and intense in

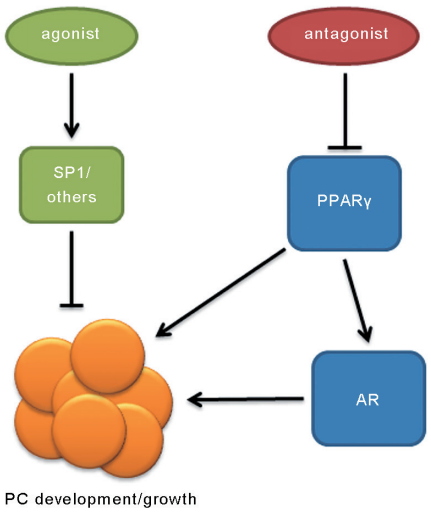


**Figure 1:** The role of PPARγ and ligands in prostate cancer growth: PPARγ agonists can inhibit the growth of prostate cancer cells, but this has been shown to be through PPARγ-independent mechanisms. New studies indicated that PPARγ played an oncogenic role in the development and progression of prostate cancer, both through AR-dependent and AR-independent means. Antagonists of PPARγ might be effective in the treatment of advanced prostate cancers and the prevention of prostate cancer development. PPARγ: peroxisome proliferator-activated receptor gamma; AR: androgen receptor; SP1: specificity protein 1; PC: prostate cancer.

prostate cancer and prostatic intraepithelial neoplasia (PIN) tissues than in benign prostatic hyperplasia (BPH) and normal prostate tissues. Likewise, using 232 samples, Rogenhofer *et al.*[34] found that PPARγ expression in advanced prostate cancer tissues was significantly higher than that in low-risk prostate cancer and BPH specimens ($P < 0.001$). Two smaller studies also found increased expression of PPARγ in malignant tissues compared to benign tissues.[35,36] These data strongly suggest that PPARγ is not a tumor suppressor but instead that its activity may be associated with prostate cancer development.

Two recent molecular studies further support an oncogenic role for PPARγ in prostate cancer. In the first study, Tew *et al.*[13] sought a molecular mechanism to explain the large retrospective studies that have shown that long-term use of warfarin reduced the risk of prostate cancer diagnosis.[37–40] Warfarin is an anticoagulant that disrupts the vitamin K cycle by inhibiting vitamin K epoxide reductase (VKOR) and preventing the γ-carboxylation of target proteins.[41] Although warfarin and the vitamin K cycle play an important role in blood coagulation, Tew *et al.*[13] identified additional pathways affected by warfarin treatment, including AR and PPARγ inhibition, that impact upon prostate cancer development.

Previous work in the laboratory had identified warfarin as an AR antagonist using a high throughput screen.[42] Tew *et al.*[13] hypothesized that AR antagonism was a potential mechanism by which warfarin reduced the risk of prostate cancer. They demonstrated that warfarin treatment inhibited the expression of AR target genes in mice and the growth of human prostate cancer cells *in vitro.* Using specialized mass spectrometry techniques, they found that AR was γ-carboxylated at amino acid E2, but that mutation of this residue did not prevent warfarin from inhibiting AR activity. This suggested that warfarin inhibited AR activity by a mechanism distinct from γ-carboxylation.

RNA sequencing of warfarin-treated mouse prostate tissues strongly suggested that warfarin inhibited PPARγ signaling even

more robustly than AR signaling. Warfarin treatment inhibited the expression of PPARγ and the PPARγ target genes lipase E (LIPE) and fatty acid synthase (FASN), both in cultured human cells and in mouse prostate tissue. Both LIPE and FASN are enzymes that play a role in fatty acid metabolism and are known to be upregulated in prostate and other cancers.[43–45] Importantly, Tew *et al.*[13] found that treatment with the PPARγ antagonist GW9662 decreased AR activity, which could not be further inhibited by the addition of warfarin, suggesting that warfarin acts through PPARγ to inhibit AR activity. This PPARγ inhibitor also decreased the growth of prostate cancer cells in culture. Tew *et al.*[13] proposed that inhibition of PPARγ could inhibit prostate cancer development by AR-dependent and AR-independent mechanisms but stopped short of testing PPARγ inhibitors in prostate cancer models.

Independently, Ahmad *et al.*[14] identified *PPARG* as a novel gene that drives prostate carcinogenesis using a Sleeping Beauty screen in prostate-specific *Pten*-/- mice. Mice with insertions upstream of the *PPARG* gene that caused increased expression of the PPARγ protein had decreased survival and increased metastases to the lungs and lymph nodes compared to littermate controls. Increased PPARγ expression in these mice was associated with increased levels of PPARγ target genes *FASN*, ATP citrate lyase (*ACYL*), and acetyl-CoA carboxylase (*ACC*). Overexpression of PPARγ in three prostate cancer cell lines, DU-145, PC3, and PC3M, increased cell proliferation and migration whereas siRNA knockdown of PPARγ had the opposite effect. Treatment with the PPARγ antagonist GW9662 was found to decrease the growth of PC3 xenografts in an orthotopic mouse model, but this decrease did not reach statistical significance.

Ahmad *et al*.[14] also found that levels of PPARγ positively correlated with prostate cancer grade and were associated with worse disease-specific survival in patients with low PTEN expression. In addition, PPARγ expression negatively correlated with PTEN levels, and positively correlated with the expression of phospho-AKT. Loss of PTEN function through deletion, epigenetic modification, or mutation causes activation of the PI3K/AKT pathway, which is well documented to contribute to prostate cancer progression and metastasis.[46,47] A recent study showed that abnormal activation of the PI3K/AKT pathway is seen in nearly all prostate cancer metastases and approximately 42% of primary tumors.[48] Ahmad *et al.*[14] also analyzed data from cBioportal (www.cbioportal.org) and demonstrated that the *PPARG* gene was amplified in 26% of advanced cancers and that the enzyme 15-lipoxygenase-2 (ALOX15B), which synthesizes 15-S-hydroxyeicosatetraenoic acid, an endogenous ligand of PPARγ, was upregulated in an additional 17% of cases. Furthermore, over half of all sequenced tumors demonstrated upregulation of one or more of the PPARγ target genes *FASN*, *ACC*, or *ACLY*, strongly suggesting a role for PPARγ activation in prostate cancer development and progression.

Despite the key observations of the two studies, several important questions remain. Ahmad *et al*.[14] study did not examine the contribution of AR signaling to the effects observed from altered PPARγ activity. Conversely, Tew *et al.*'s[13] study focused primarily on the ability of PPARγ to inhibit AR signaling and did not examine contributions of AR-independent PPARγ activities to the inhibition of prostate cancer cell growth. Therefore, it is of utmost importance to determine the relative contribution of AR-dependent and AR-independent effects of PPARγ antagonism and whether PPARγ antagonists are equally effective against AR-positive and AR-negative cancers. This could have important clinical implications, especially if PPARγ antagonists are effective against AR-negative cancers. Recent evidence suggests that truly AR-negative metastatic prostate cancers, which were once thought to be exceedingly rare, are on the rise with the use of advanced AR-targeting agents.[49] No effective treatments exist for this type of prostate cancer, and if PPARγ activity is driving cancer growth in these cancers, PPARγ antagonists could be useful in this setting.

Because AR is so intimately involved in prostate cancer development and progression, the AR-dependent effects of PPARγ activity have obvious connections to the disease process. AR-independent PPARγ effects on prostate cancer development and progression are not as clear and require more investigation. One possible AR-independent contribution to oncogenesis is increased fatty acid synthesis and lipogenesis, predominantly through direct transcriptional regulation of the enzymes ACLY, ACC, and FASN by PPARγ.[50] ACC is the rate-limiting step of fatty acid synthesis and ACYL links glucose metabolism to fatty acid metabolism.[51,52] Increased lipogenesis is observed in the very earliest stages of cancer development, even in PIN lesions,[50] suggesting an essential role in the development of prostate cancer by providing key membrane components such as phospholipids and cholesterol for prostate cancer cell growth. Pharmacologic or genetic inhibition of lipogenesis or of key lipogenic genes induces prostate cancer cell apoptosis and reduces tumor growth in xenograft models.[50] As such, FASN, ACYL, and ACC have all been implicated as important targets for cancer therapy.[52–54] Therefore, it is very likely that PPARγ activity contributes to prostate cancer cell growth by its lipogenesis-promoting effects. In addition to the fatty acid-related pathways, PPARγ has been found to regulate other pathways that could play a role in prostate cancer development and progression, including inflammation and regulation of tumor-infiltrating immune cells.[55]

Although Tew *et al.*[13] and others[32] have shown that PPARγ can regulate AR activity, AR may also influence the activity of PPARγ. Olokpa *et al.*[56] found that DHT treatment decreased PPARγ mRNA and protein levels in LNCaP C4-2 and VCaP cell lines, which could be blocked by competitive antagonists. Androgen treatment has also been associated with lower PPARγ mRNA and protein levels during myogenic differentiation of mouse C3H 10T1/2 pluripotent cells.[57] However, we have not observed that DHT-mediated decreases in PPARγ transcript levels nor in luciferase reporter activity in LNCaP prostate cancer cells or in HEK293 cells expressing AR. Further investigation into potential androgen-mediated inhibition of PPARγ activity is warranted though, as this could have important clinical implications, especially in the setting of androgen deprivation or treatment with second generation AR-targeting drugs. Such treatments could increase PPARγ expression and allow PPARγ activity to contribute to the proliferation of prostate cancers.

There is also an important question of whether the effects on prostate cancer, and the anti-tumor effects of antagonists, are mediated by PPARγ1, PPARγ2, or both. There has been very little study of the differences of the two isoforms in prostate cancer. Comprehensive IHC studies of PPARγ expression in human tissue have not attempted to delineate the two isoforms. Although PPARγ1 is presumed to be the predominant form in prostate and prostate cancer cells, PPARγ2 can be induced in these cells in culture.[24] Furthermore, PPARγ2 is expressed in normal C57/Bl6 mouse prostate tissue in addition to PPARγ1.[58] One elegant study has shed some light on the differing roles of the two isoforms in prostate tissue. Using prostate epithelial cells derived from mice with both PPARγ isoforms knocked out, Strand *et al.*[58] were able to selectively reintroduce PPARγ1 or γ2. Most strikingly, when recombined with fetal rat urogenital mesenchyme and grafted into the kidney capsule for 2 months, expression of PPARγ1 led to formation of adenocarcinoma while expression of PPARγ2 prevented the development of PIN that was observed in control cells. Recombinant tissue derived from PPARγ1-expressing cells exclusively

expressed luminal cytokeratins while that from PPARγ2-expressing cells expressed both luminal and basal cytokeratins, suggesting that PPARγ2 facilitated the development of both luminal and basal epithelial cells to produce benign prostate glands. These data suggest that PPARγ1 and PPARγ2 play opposing roles in the prostate, with PPARγ1 being oncogenic and PPARγ2 potentially playing a tumor suppressor role. While it is assumed that PPARγ1 is the predominant isoform in the human prostate, these results demand a thorough study of PPARγ1 and γ2 expression in human prostate cancer as well as in mouse models of prostate cancer. Should PPARγ2 be relevant in this setting, further molecular studies to better understand the potential opposing roles in prostate tissue are also warranted. It should be noted that our studies indicate that both PPARγ1 and PPARγ2 are inhibited by warfarin and GW9662 in prostate cancer cells, but we have yet to determine if they differentially regulate AR activity in this setting.

## POTENTIAL ACTIVATORS OF PPARG IN PROSTATE CANCER

While PPARγ activity is clearly associated with prostate cancer development and growth, thus making it an important new therapeutic target, exactly how PPARγ is activated and what cellular conditions lead to oncogenic activity are important questions as well. PPARγ is after all a fatty acid receptor, so it is very likely that fatty acids or associated molecules play a role in oncogenic activation of PPARγ. There have been extensive studies on links between obesity, fatty acids (especially ω-3 polyunsaturated fatty acids), and prostate cancer, but it has been difficult to discern correlations and mechanisms of action.[59,60] While connections between specific fatty acids and prostate cancer development are unclear, several key studies have linked fatty acid-binding proteins, which facilitate the nuclear transport of fatty acids to PPARs, to prostate cancer. Fatty acid-binding protein 5 (FABP5) is a 15 kDa cytosolic protein of the fatty acid-binding protein family that binds a wide array of ligands, including fatty acids and fatty acid metabolites spanning 10–22 carbons in length with various saturation states, as well as all-trans-retinoic acid and numerous synthetic drugs and probes.[61] FABP5 overexpression has been linked to worse outcomes in several cancers.[61] Specifically, in prostate cancer, levels of both nuclear and cytoplasmic FABP5 were significantly higher in cancerous tissues than in normal and BPH tissues and increased expression was significantly associated with a reduced patient survival time.[44,62] Additional studies demonstrated that increased FABP5 and PPARγ levels were significantly correlated with increased Gleason score and that expression of cytoplasmic FABP5 was significantly correlated with nuclear PPARγ expression.[63] While expression of PPARβ/δ in carcinomas did not correlate with patient outcome, the increased levels of both FABP5 and PPARγ were associated with shorter patient survival. Multivariate analysis indicated that FABP5 was independently associated with patient survival, whereas PPARγ was confounded by FABP5 in predicting patient survival, suggesting that FABP5 may interact with PPARγ in a coordinated mechanism to promote progression of prostatic cancer. Several studies demonstrated that suppression of FABP5 expression in PC3-M cells inhibited their tumorigenicity.[62,64] Bao *et al*.[61] found that overexpression of FABP5 or stimulation with recombinant FABP5 stimulated growth, colony formation, anchorage-independent growth, and invasion of LNCaP cells. These conditions also decreased apoptosis, which could be blocked by the PPARγ inhibitor GW9662. FABP5 mutants that had reduced fatty acid-binding capabilities did not increase these malignant measures to the extent of wild-type FABP5. FABP5 overexpression also increased the subcutaneous growth and vascularization of LNCaP xenografts. Another recent study by the same group found that PPARγ, stimulated by FABP5, can bind to and activate transcription from the VEGF promoter, which might promote angiogenesis.[65] Similar to Ahmad *et al*.'s[14] study, the authors found that suppression of PPARγ in prostate cancer cells reduced proliferation, invasiveness, and anchorage-independent growth *in vitro*. Knockdown of PPARγ in PC3-M cells by siRNA significantly reduced tumor size and incidence. These data strongly implicate FABP5 as a key player in the activation of PPARγ in prostate cancer.

FABP4 is approximately 50% similar to FABP5 in terms of amino acid sequence and has a similar structure, and it has been shown to directly interact with and transactivate PPARγ in a ligand-selective fashion.[66] Treatment of DU145 prostate cancer cells with exogenous FABP4 promoted serum-induced prostate cancer cell invasion *in vitro*, and an FABP4 inhibitor reduced the subcutaneous growth and lung metastasis of the cells in xenografted mice.[67] Although there is much less known about FABP4 in prostate cancer, these limited data suggest that FABP4 might also lead to activation of PPARγ in prostate tissue to drive tumorigenesis. Analysis of publically available datasets on cBioportal (www.cbioportal.org) reveals that both *FABP5* and *FABP4* genes are frequently amplified or have increased transcript levels in prostate cancer. *FABP5* was found to be altered in 37 (11.1%) of 333 samples from the final TCGA dataset,[68] 34 (22.7%) of 150 samples from the SU2C/PCF dataset,[69] 37 (43.5%) of 85 samples from the MSKCC dataset,[48] 14 (23.7%) of 59 samples from the University of Michigan dataset,[70] 22 (36.1%) of 61 from the Fred Hutchinson dataset,[71] and 41 (50.6%) of 81 samples from the Neuroendocrine Prostate Cancer dataset,[72] perhaps the dataset representing the most advanced disease state. Likewise, *FABP4* was found to be amplified or overexpressed in 8.1%, 23.3%, 11.6%, 25.4%, 41.3%, and 53.8% of these datasets, respectively. These are truly astounding findings, and while more analysis must be done to determine if the increased expression of these proteins is associated with increased PPARγ activity in these samples, these data strongly suggest that FABP4 and FABP5 could be important drivers of PPARγ activation and prostate cancer progression.

## POTENTIAL CLINICAL IMPLEMENTATION OF PPARG ANTAGONISTS

Ahmad *et al*.'s[14] study suggested a role for PPARγ antagonists in the treatment of metastatic disease but did not examine the potential of these compounds to prevent the development of prostate cancer. Conversely, Tew *et al*.'s[13] study, by way of its dissection of the mechanism of action of warfarin to prevent prostate cancer, focused solely on preventive potential of PPARγ antagonists. These studies left open the question as to whether PPARγ antagonists are best used to prevent the development of prostate cancer or are they best used to treat metastatic disease, or can they be used for both? It will be essential to thoroughly test PPARγ antagonists in appropriate models of prostate cancer prevention and advanced disease.

The publically available databases suggest that PPARγ or downstream targets are involved in many, but not all advanced cancers. Identifying which patients might be the best candidates for PPARγ-targeted therapy will be essential for clinical implication in this setting, and future work should focus on the identification of useful biomarkers, especially as several agents already exist to treat castration-resistant prostate cancer. At the opposite end of the disease spectrum, there are no approved therapies to prevent or reduce the risk of developing prostate cancer. While 5α reductase inhibitors demonstrated an ability to reduce the detection of low-grade prostate cancers, they were never widely adopted due to adverse effects and a lack of efficacy at reducing the detection of high-grade cancers. However, there is a strong reason to believe that

PPARγ antagonists will be more effective at preventing the development of prostate cancer than previous trials with 5α reductase inhibitors. In the retrospective trials, warfarin was found to reduce the detection of both low- and high-grade tumors, suggesting that it has chemopreventive properties distinct from 5α reductase inhibitors. The additional chemopreventive properties could be due to the dual inhibition of PPARγ and AR. It must now be determined if PPARγ inhibition is an effective therapy in prostate cancer prevention models. Interestingly, heterozygous deletion of the *Pparg* gene in the TRAMP mouse prostate cancer model did not increase prostate cancer development or progression.[73] However, it is not clear that PPARγ activity was meaningfully decreased in this model, as PPARγ transcript levels and the expression of PPARγ target genes expression appeared to be reduced only 2–3 times. Furthermore, it is unclear which isoforms were targeted. However, it is clear that multiple mouse prostate cancer models express at least some PPARγ isoform in normal prostate tissue, so treatment of these mice, or other mouse prostate cancer models, with PPARγ antagonists will help determine the potential for chemoprevention.

Other hurdles exist in the development of PPARγ antagonists for clinical use in prostate cancer. While adverse effects in the treatment of end-stage disease are more tolerable, PPARγ antagonists will need to have very little negative impact on the health of individuals if they are to be used chronically to prevent the development of cancer. The known effects on fatty acid synthesis and storage may need to be mitigated or the drugs may have to be targeted specifically to prostate tissue. In addition, few PPARγ antagonists have been developed, and those that have do not have ideal drug-like properties. A concerted medicinal chemistry effort will be needed to create clinical candidates. Despite these challenges, the new data regarding the role of PPARγ in prostate cancer offer great hope for a new, effective treatment for advanced disease and potentially a way to reduce the risk of developing prostate cancer (**Figure 1**).

## EXPERT COMMENTARY

The paradigm for the role of PPARγ in prostate cancer has shifted. What was once thought to be a tumor suppressor now has been shown to have an oncogenic role in the development and progression of prostate cancer. Many genes have been postulated as important targets in prostate cancer, but to date, AR stands alone as the only clinically validated molecular target. Despite this, the identification of PPARγ as an important accessory to prostate cancer development by two unbiased and completely different approaches lends credence to it being a true and important target in prostate cancer. While much work remains to be done to fully understand the role of PPARγ in prostate cancer and to develop PPARγ antagonists with suitable clinical properties, there is great promise for the treatment and prevention of prostate cancer by targeting PPARγ.

## AUTHOR CONTRIBUTIONS

JOJ and CE performed primary literature searches and assembled data. JOJ created the figure. CE, SKP and JOJ wrote and edited the manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declare no competing interests.

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