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Review Article

Peroxisome Proliferator-Activated Receptor Gamma (Pparγ) and Prostate Cancer

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Abstract

The fatty acid receptor peroxisome proliferator-activated receptor gamma (PPARγ) is a transcription factor, which includes two isoforms named PPARγ1 and PPARγ2 respectively. In human body, PPARγ involves in metabolic disorder, neurodegenerative disease and inflammation. Recent advance in PPARγ study has led to the discoveries of several genes that are regulated by PPARγ in prostate cancer cells. Evidence showed that PPARγ plays important roles in development and in malignant progression of prostate cancer. In this mini-review, we described the PPARγ structure and summarized their involvement in different diseases. Our focus is on the roles of PPARγ isoforms in prostate cancer.

Peroxisome Proliferator-Activated Receptor Gamma

Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) is a transcription factor that is ligand dependent and is a member of the nuclear hormone receptor superfamily. PPARγ is expressed in two isoforms: PPARγ1 and PPARγ2, the latter contains thirty extra amino acids (Figure 1). Both synthetic and endogenous ligands can band to and activate PPARγ [1]. When activated, PPARγ is translocated into the nucleus and forms a heterodimer with the retinoid X receptor (RXR), where it serves as a transcriptional regulator of genes via DNA binding [2]. It is well established that PPARγ plays a critical role in adipocyte differentiation, the inflammatory response, and peripheral glucose consumption. PPARγ agonists are frequently utilised to treat type II diabetes [1]. Diabetes type II is the most prevalent endocrine-metabolic condition worldwide, characterised by insulin resistance and insulin secretion abnormalities. PPARγ agonists were utilised to sensitise tissues (muscle, adipose tissue, and liver) to insulin stimulation. However, these PPARγ agonist medicines were associated with significant side effects such as increased weight, oedema, heart failure, and an increased risk of myocardial infarction [3]. The role of PPARγ in prostate cancer (PCa) has been controversial. Initially, it was believed that PPARγ functioned as a tumour suppressor in prostate cells since agonist ligands suppressed the proliferation of PCa cells. However, further investigations revealed that these agonists suppressed cell growth in a manner independent of PPARγ [4-8]. Furthermore, PPARγ expression rises with the grade/stage of cancer cases [9-11]. These results suggested that it is not a tumour suppressor. In the contrary, studies also find PPARγ activity may contribute to the development and the progression of the prostate cancer. While a tumour suppressor expression level frequently reduced as the develop and progress of the malignancies, PPARγ expression level appeared to be significantly increased with elevated PCa stage and grade, strongly implying that it is cancer-promoter or oncogene. For example, it was discovered by immunohistochemical staining that PPARγ expression was significantly greater and more intense in prostate cancer and prostatic intraepithelial neoplasia (PIN) tissues than in benign prostatic hyperplasia (BPH) and normal prostate tissues samples [11]. Similarly, utilising more tissue samples in a separate investigation by a different group, it was discovered that PPARγ expression was substantially higher in advanced PCa tissues than in low-risk PCa and BPH specimens ($P < 0.001$) [10]. In addition, two smaller investigations found higher

PPARγ expression in malignant versus benign tissues [12,13]. When taken all these studies together, these findings strongly suggested that PPARγ is not a tumour suppressor and that its activation may play a promotive role in the development of PCa.

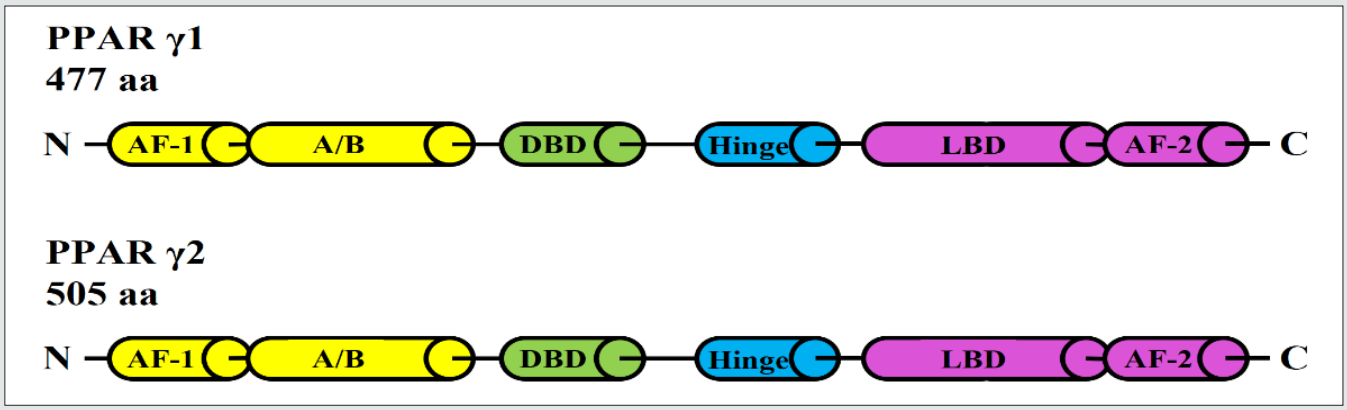

Figure 1: Structures of PPARγ1 and PPARγ2. At protein level, PPARγ consists of an activation function 1 (AF-1) region, a variable or Hinge (A/B) region, a DNA-binding domain (DBD). a ligand-binding domain (LDB), and an activation function 2 (AF-2) region. PPARγ2 has an extra of 30 Amino acids.

The Role of PPARγ in PCa

Using a Sleeping Beauty screen in prostate-specific Pten/ mice, Ahmad et al. identified PPARγ as a new gene that promoted prostate carcinogenesis [9]. In comparison to littermate controls, mice having insertions upstream of the PPARγ gene that increased PPAR protein expression had lower survival rate with increased lung and lymph node metastases [9]. In these animals, increased PPARγ expression was correlated with increasing expression of PPARγ targeting genes for FASN, ATP citrate lyase (ACYL), and acetylCoA carboxylase (ACC) [9]. Overexpression of PPARγ promoted cell proliferation and migration in three PCa cell lines, DU145, PC3, and PC3M, while siRNA knockdown of PPAR had the opposite effect [9] Ahmad et al. also discovered a significant positive correlation between PPARγ levels and PCa grades, as well as a link between low PTEN expression and poor disease-specific survival in patients with low PTEN expression [9]. Furthermore, Ahmad et al. also analysed data from the cBioportal (www.cbioportal.org) and discovered that the PPARγ gene was amplified in 26% of advanced cancers and that the enzyme 15lipoxygenase 2 (ALOX15B), an endogenous PPARγ ligand, which reconstructs 15S hydroxyeicosatetraenoic acid, was upregulated in an extra 17% of cases [9]. Additionally, over half of all sequenced tumours expressed one or more of the PPAR target genes for FASN, ACC, or ACLY, strongly suggested a promotive role for PPARγ activation in the development and progression of PCa [9].

One of the very first studies to examine the involvement of PPAR in PCa was motivated by the fact that diets high in omega-3 fatty acids appear to be associated with a reduced incidence of PCa than diets high in omega-6 fatty acids. One of these fatty acid metabolites, 15-Deoxy-Δ12,14-prostaglandin J2 (15dPGJ2), is a particular PPAR activator [14] and was found to have anticancer activity [15], prompting Butler et al. to investigate if the antitumor qualities were attributable to PPAR activation [16]. They discovered that while 15dPGJ2 and other PPARγ activators such as ciglitazone promoted cell death in three PCa cell lines, PPARα and β ligands did not. This initial discovery sparked more research on the usefulness of PPARγ activating ligands in PCa, which revealed that PPARγ agonists reduced androgen receptor (AR) level and activity while inhibiting PCa cell growth [17-19]. Furthermore, further mechanistic studies proved unequivocally that these compounds had an impact independent of the PPARγ (Figure 1.17). According to one study, PPAR agonists reduced cell proliferation by promoting the proteasomal degradation of transcription factor specificity protein 1. (SP1) [20]. Other studies suggested alternative mechanisms by which PPARγ agonists inhibited PCa cell growth in a PPARγ-independent manner, which include the inhibition of BclxL/ Bcl2 functions [21], the inhibition of the CXC chemokine receptor type 4/CXC motif chemokine 12 (CXCR4/CXCL12) axis [22], and the inhibition of the AKT signalling pathway [23]. A further study indicated that PPARγ agonists promoted AR signalling in C42 PCa cells, and that this was PPARγ dependent [24]. As a result, it is probable that PPARγ agonists stimulate AR signalling, but their effects on SP1 or other pathways in some cell types result in indirect AR suppression and lower PCa cell growth. The role of PPARγ and its ligands in PCa development can be shown in [Figure 2].

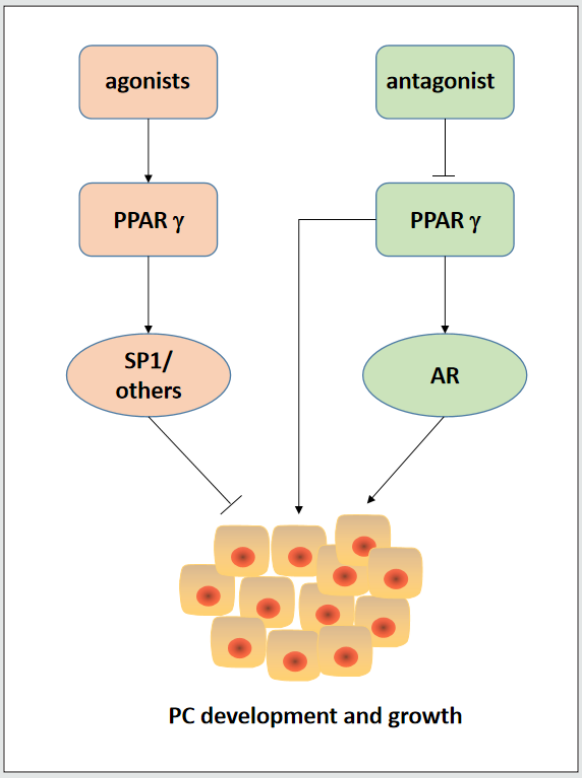

Figure 2: The role of PPARγ and its ligands in PCa growth: PPARγ has an oncogenic role in the development and progression of PCa through both AR-dependent and AR-independent mechanisms. PPARγ agonists were found to reduce PCa cell growth through PPARγ-independent pathways. PPARγ antagonists may be useful in treatment of advanced PCa as well as the prevention of PCa. PPARγ: peroxisome proliferator activated receptor gamma, AR: androgen receptor, SP1: specificity protein 1, and PC: prostate cancer.

Previous work demonstrated that elevated FABP5 levels contributed significantly to malignant progression in castration-resistant PC (CRPC) model cell systems by binding and transferring larger amounts of fatty acids, which stimulated the nuclear receptor PPARγ [26]. It is also demonstrated that treatment of PC3-M cells with PPARγ antagonist GW9662 resulted in a similar inhibition of tumour growth to that observed with a FABP5 inhibitor named dmrFABP5. These results suggested that the inhibitory mechanism of dmrFABP5 is connected to the FABP5-PPARγ-signaling pathway [27]. Experiments proved that the cellular uptake of fatty acids was increased as the increasing malignancy of the tested PCa cells, indicating that increased amounts of fatty acids were taken up by the cancer cells and that at least some of excessive amount of fatty acids was used as signalling molecules to stimulate and thus to activate PPARγ [28]. Chemically synthesized FABP5 inhibitor SB-FI-26 was shown to reduce significantly the amount of fatty acids uptake into PC3M cells. So, it was suggested that SB-FI-26 acts as a competitive inhibitor of fatty acids for FABP5 and thus inhibited the transport of intra- and extracellular fatty acids into the cytoplasm [29]. It was suggested that the competitive inhibition of fatty acid uptake by SB-FI-26 may result in a deacress or discontinuation of fatty acid-induced PPARγ activation. Thus, PPARγ may lose its ability to upregulate downstream cancer-promoting genes (such as VEGF), or to downregulate downstream tumour-suppressor genes (such as apoptotic genes) [27, 28]. Previous investigation demonstrated FABP5-PPAR-VEGF signalling axis, rather than the AR-initiated pathways, is the predominant pathway for malignant signal transduction in CRPC cells [27]. Therefore, PPARγ seems to play a critical role in this axis. Interestingly, the bio-inhibitor dmrFABP5 was much stronger than the chemical inhibitor SB-FI-26 in suppressing CRPC developed in nude mice, unlike SB-FI-26, dmrFABP5 did not have an inhibitive effect in cellular fatty acid uptake [28].

Role of PPARγ isoforms in prostate cancer

Because PPARγ agonists reduce AR activity and PCa cell proliferation, it was initially assumed to be tumour suppressors in prostate cells [30-34]. But, PPARγ agonists, on the other hand, were shown to suppress cell growth and AR activity in an independent manner of PPAR activity [35-37]. In addition, PPARγ expression also rises with PC grade/stage [38-40], indicating that the opposite to the initial assumption is true. In order to study PPARγ as a functional target in PCa, it is vital to notice the fact that PPARγ has two isoforms. PPARγ2 which looks exactly like PPARγ1, but is 30 amino acids longer than PPARγ1 at the amino terminus. PPARγ1 is found in many organs, whereas PPARγ2 is found primarily in adipocytes

and regulates their differentiation [40, 41]. A recent study by Strand et al [42]. revealed that the two PPARγ isoforms had significant variations. In this study, the PPAR gene was first knocked out in mouse prostate epithelial cells, and then the individual PPARγ1 and PPARγ2 transcripts were subsequently reintroduced. When these modified cells were used in a prostate reconstitution assay, it was discovered that restoring PPARγ1 resulted in the development of adenocarcinoma, whereas restoring PPARγ2 led to the formation of benign glands. According to a recent study, in many but not all local and metastatic malignancies, both isoforms of PPARγ are expressed in human tissue, with PPARγ1 predominating in PCa cells. Researchers further show that both PPARγ1 and PPARγ2 are expressed in epithelial cells of isolated benign prostate glands using IHC and RNA in situ hybridization. These results suggested that PPARγ1 is more important than PPARγ2 in the malignant progression of PCa. Indeed, such functional characterisation tests by Strand et al [42]. clearly suggested that PPARγ1 had an oncogenic capability in prostate cells while PPARγ2 had a tumour suppressive property. This conclusion was supported by some recent studies [28]. In a mouse prostate reconstitution test, Strand et al colleagues clearly proved that expression of PPARγ1 alone in benign mouse prostate epithelial cells resulted in the formation of adenocarcinoma-like tissue, whereas expression of PPARγ2 alone resulted in a highly differentiated phenotype [42]. In the soft agar colony formation assay, the addition of PPARγ1, but not PPARγ2, boosted the proliferation of BPH1 cells. It was also discovered that inhibiting PPARγ1 reduced the proliferation of PCa cell lines with endogenous or constitutive expression of PPARγ1. This supports the concept that PPARγ1 is an oncogene. The introduction of PPARγ2 inhibited the proliferation of LNCaP cells, further supporting the idea of PPARγ2 as a tumour suppressor.

The functional role of PPARγ played in malignant progression of PCa cells has been a controversial issue for quite a long time [4]. Recent functional characterisation of PPARγ isoforms greatly facilitated the clarification on the functional roles of this gene. However there still are many issues requiring further study on PPARγ's functional role in PCa and the underlying molecular mechanisms. The recent encouraging advances in more reliable and efficient gene-editing techniques, such as crispr/cas9, provided better methods to evaluate functional role of PPARγ and will help the research community to understand this gene better and to develop better strategies for therapeutic interventions.

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Competing Interest

The authors declare no conflict of interest.

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