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# Molecular Cross-regulation Between PPAR-γ and other Signaling Pathways: Implications for Lung Cancer Therapy

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## Abstract

Peroxisome Proliferator-Activated Receptors (PPAR)-γ belongs to the nuclear hormone receptor superfamily of ligand-dependent transcription factors. It is a mediator of adipocyte differentiation, regulates lipid metabolism and macrophage function. The ligands of PPAR-γ have long been in the clinic for the treatment of type II diabetes and have a very low toxicity profile. Activation of PPAR-γ was shown to modulate various hallmarks of cancer through its pleiotropic affects on multiple different cell types in the tumor microenvironment. An overwhelming number of preclinical-studies demonstrate the efficacy of PPAR-γ ligands in the control of tumor progression through their affects on various cellular processes, including cell proliferation, apoptosis, angiogenesis, inflammation and metastasis. A variety of signaling pathways have been implicated as potential mechanisms of action. This review will focus on the molecular basis of these mechanisms; primarily PPAR-γ cross-regulation with other signaling pathways and its relevance to lung cancer therapy will be discussed.

### Keywords

PPAR; Lung cancer therapy; Synergistic drug interactions; tumor microenvironment; TZDs; PPAR-gamma ligands

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The authors declare no conflict of interest.

## Introduction

Lung cancer is the leading cause of cancer death, [1] and every year 1.2 million new cases are diagnosed worldwide. Despite improvements in diagnostic imaging, surgery, radiotherapy and chemotherapy, the overall survival for lung cancer remains poor with only 14% of patients surviving 5 years from the date of diagnosis. This underscores the desperate need for novel strategies for early detection, prevention and treatment of this disease. PPAR-γ is known to be expressed in both human SCLC and NSCLC cell lines [2,3]. The expression status of PPAR-γ was shown to correlate with differentiation status and survival in the lung cancer patients [4,5]. Many PPAR-γ ligands were shown to inhibit tumor growth and progression in preclinical models of lung cancer, by modulating various cellular processes in cancer cells, stromal cells and tumor microenvironment. They do so by influencing various signaling pathways in a PPAR-γ-dependent manner (Figure 1). In addition, these ligands also employ other novel mechanisms including PPAR-γ-independent mechanisms to exert their anti-neoplastic affects.

PPARs are members of the nuclear hormone receptor superfamily that includes receptors for steroids, thyroid hormone, vitamin D, and retinoic acid [6]. PPARs are transcription factors that upon ligand binding regulate both target gene expression and repression [7]. To date, three isotypes of PPARs called PPAR-α, PPAR-γ and PPAR-δ have been identified [8,9]. Each of these three subtypes display differential tissue distribution and mediate specific functions such as early development, cell proliferation, differentiation, apoptosis and metabolic homeostasis [10]. PPAR-γ is highly expressed in adipose tissue and it is a master regulator of adipocyte differentiation [11,12]. PPAR-γ is also expressed in multiple other tissues, such as breast, colon, lung, ovary, prostate and thyroid [13]. A single PPAR-γ gene is transcribed into three isoforms namely PPAR-γ1, PPAR-γ2, PPAR-γ3 and PPAR-γ4 utilizing four different promoters [8]. However PPAR-γ1 and γ3 transcripts both translate into the same PPAR-γ1 protein. PPAR-γ2 protein contains an additional 30 aminoacids at N-terminus compared to PPAR-γ1, which contribute to its constitutive transcription activation function that is 5–6-fold greater than PPAR-γ1 [14].

PPAR-γ receptors are activated by several lipophilic ligands, including long-chain polyunsaturated fatty acids and several eicosanoids. The cyclopentone prostaglandin J2, was suggested to be the most potent endogenous ligand for the PPAR-γ receptor and is the most commonly used naturally occurring PPAR-γ agonist [15,16]. A wide range of synthetic PPAR-γ ligands have been developed. The most widely used synthetic agents belong to the thiazolidinedione class of antidiabetic drugs, that include ciglitazone, troglitazone, pioglitazone and rosiglitazone (also referred to as glitazones or TZDs). Some of the glitazones were already in clinical use as insulin sensitizers in type 2 diabetic patients [17]. Non-thiozolidinedione compounds such as isoxazolidinedione JTT-501 [18] and the tyrosine-based GW7845 [19] are also identified as PPAR-γ ligands along with several plant derived compounds. [20–22].

Activation of PPAR-γ plays an inhibitory role in cell proliferation and growth by virtue of its differentiation inducing ability. This property makes PPAR-γ activation by natural and synthetic ligands an attractive tool in cancer treatment and prevention. The precise mechanism(s) linking modulation of PPAR-γ with cancer growth inhibition is been elucidated. PPAR-γ ligands exert their effects through both PPAR-γ dependent and independent pathways, often triggering crosstalk with other signaling pathways (Figure 1). Better understanding of the biological role of PPAR-γ and its ability to trigger crosstalk with other cell signaling pathways would allow rational development of selective PPAR-γ modulators, and for targeting aspects of PPAR-γ biology that are implicated in tumor progression. This review will focus on the mechanisms of cross-regulation between PPAR-γ

activation and signaling pathways that regulate hallmarks of a cancer cell and will discuss the implications of this cross-talk for lung cancer therapy.

## Mode of Action

Similar to other nuclear hormone receptors, PPARs contain five distinct regions A/B, C, D, E and F [23]. C and E domains contain a highly conserved DNA-binding domain (DBD) and a moderately conserved ligand-binding domain (LBD), respectively. The amino-terminal A/B domain contains the AF1 domain which is implicated in ligand-independent activation. F region contains a ligand-dependent activation domain, AF2. The D domain harbors a variable hinge region and acts as docking site for co-factors. PPAR-γ binds to its response elements (PPRE) in the promoter region of target genes through its DBD [24]. LBD is responsible for ligand specificity and activation of PPAR-γ binding to PPRE. Recruitment of co-factors occurs on AF2, located in the F region. The E/F domain also includes a region involved in dimerization with the partner nuclear receptor, RXR [25].

Similar to other members of the nuclear hormone receptor superfamily, PPAR-γ functions as a heterodimer with the retinoid X receptor (RXR). PPAR binds to 5′repeat unit of PPRE as a heterodimer with RXR bound to the 3′ repeat. PPRE contain repeats of the sequence AGGTCA separated by one or two nucleotides (known as DR-1 or DR-2 response elements, respectively) and has been found in the promoter regions of most PPAR-γ target genes [26]. In the absence of ligand activation PPAR/RXR bind to various transcription co-repressors (nuclear receptor co-repressor/silencing mediator for retinoid and thyroid hormone receptors, NCoR/SMRT) and histone deacetylases (HDACs), preventing the binding of PPAR-γ/RXR to DNA [26]. After ligand binding PPARs undergo conformational change, recruit certain co-activator complexes (p300/CBP, p160, etc.) to displace co-repressors and the heterodimer binds to DNA on PPRE of the target genes. This results in the recruitment of additional factors (TRAP, DRIP, etc.), disruption of nucleosomes, and chromatin reorganization, facilitating the entry of general transcriptional machinery such as RNA Pol II to promote transcription [27].

PPAR-γ can also negatively regulate expression of some pro-inflammatory genes by a mechanism that does not involve PPAR-γ binding to its response elements, which is termed as transrepression [28–30]. No unifying model was established to account for transrepression activity of PPARs. The proposed models include direct protein – protein interactions with other transcription factors, competing for co-activators, interacting with co-repressors and regulation by kinase activity [26]. Specific examples and the proposed mechanisms will be discussed in the subsequent sections of the review.

## Regulation of PPAR-γ Function by Growth Factor Signaling

Several studies have implicated a role for growth factor induced mitogen-activated protein kinase (MAPK) activation in the regulation of PPAR-γ function. It was shown that ERK, JNK and p38 MAPKs phosphorylate a consensus-MAPK motif (PXSPP) located in N-terminal AF-1 domain of PPAR-γ and thereby significantly inhibit its ligand-independent and ligand-dependent transcriptional activation [31–33]. Growth factor activated MAPKs phosphorylate Ser84 (Ser 82 in mouse) on PPAR-γ1 or Ser114 (Ser 112 in mouse) on PPAR-γ2 in humans [34,35]. Consistently, mutating Ser84 or Ser112 prevents PPAR-γ phosphorylation as well as the growth factor-mediated transcriptional repression [32]. Furthermore, deletion of consensus MAPK phosphorylation motif in PPAR-γ confers enhanced transcriptional activity [36]. It was also shown that N-terminal phosphorylation results in reduced ligand-binding affinity through inter domain communication between the phosphorylated AF-1 domain and the ligand-binding pocket, resulting in the negative

regulation of PPAR-γ activity [37]. Apart from this-on mitogenic stimulation, phospho-MEK directly interacts with PPAR-γ. This leads to rapid export of PPAR-γ-MEK complex from nucleus to cytoplasm through the Nuclear Export Signal (NES) of MEK, thus reducing transcriptional activity of PPAR-γ. MEK does not significantly phosphorylate PPAR-γ [35,36].

Various *in vivo* studies have established that growth factor activated MAPK cascades regulate PPAR-γ function to control the balance between proliferation and differentiation in certain cell types. During adipogenic differentiation of mesenchymal stem cells, co-operation between PPAR-γ and MEK1 facilitates the adipogenic program by MEK1-dependent induction of the C/EBP*α* gene [38]. Consistently, inhibition of MEK attenuates high glucose enhanced adipogenesis and PPAR-γ expression in bone marrow-derived mesenchymal stem cells [39]. Mice with the knocked-in S82/112A mutant allele of PPAR-γ exhibit resistance to diet-induced obesity. Furthermore PPAR-γ phosphorylation on Ser 112 by ERK in Dok1 knockout embryonic fibroblasts exhibit defective adipogenic differentiation [40]. Interestingly, MAPK signaling can also modulate PPAR-γ functions by regulating the expression of co-factors needed for PPAR-γ transcriptional activation [41]. From the above examples, though the significance of PPAR-γ regulation by MAPKs is evident in normal physiology, its role in the cancer cell survival is not well understood. In cancer cells where MAPK signaling is elevated due to enhanced growth factor signaling, it is assumed that differentiation promoting functions of PPAR-γ are attenuated. Therefore, reactivation of PPAR-γ, by its ligands was used as a therapeutic approach to promote differentiation and growth inhibition of cancer cells. However, in certain instances MAPK activation is known to co-operate in mediating the biological effects of PPAR-γ. Troglitazone induced a sustained ERK1/2 activation, concurrent with growth inhibition in lung cancer cells, suggesting that in some cell types, PPAR-γ ligands utilize ERK-pathway to promote growth inhibition [2,42]. Consistently, there are reports demonstrating that sustained ERK activation can induce apoptosis and differentiation in cancer cells [42,43].

## Inhibition of Pro-inflammatory Pathways by PPAR-γ Activation

Anti-inflammatory activity is one of the first non-diabetic functions attributed to PPAR-γ and its ligands. PPAR-γ agonists rosiglitazone, troglitazone and 15d-$PGJ_2$ were shown to abrogate the expression of pro-inflammatory genes such as nitric oxide synthase (iNOS), matrix metalloproteinase 9 (MMP-9), and scavenger receptor A in murine macrophages [44] and TNF-α, IL-1β, and IL-6 in human monocytes [45]. Anti-inflammatory actions of PPAR-γ are dependent on its ability to antagonize the transcriptional regulation of NF-κB, AP-1 and STAT [44,46]. However, rather than having a broader effect, PPAR-γ lignads were reported to selectively inhibit only a subset of genes driven by above transcription factors. For example, rosiglitazone inhibits LPS-induced MMP-9 expression, but not the LPS-induced IL-8 expression [47]. In another mechanism, PPAR-γ is proposed to mediate transrepression of a subset of LPS induced inflammatory genes in macrophages by preventing the clearance of co-repressor complexes from their promoters. Under basal conditions, iNOS gene promoter is occupied with NCoR/HDAC3/TBL/TAB2 complexes [48] and following LPS stimulation the NCoR and HDAC3 components is cleared from iNOS promoter by ubiquitin ligases. Interestingly, on agonist binding SUMOylated PPAR-γ was shown to localize to NCoR complexes on the iNOS promoter and prevents its removal by ubiquitination-dependent mechanism. Mutataion of K365 SUMOylation site on PPAR-γ prevents its ability to repress iNOS promoter [30]. Similar results were obtained for additional endogenous LPS-target genes including Ccl3, Ccl7, Cxcl10 and Tgtp, indicating that this mechanism of transrepression is not specific for the iNOS promoter. In addition, repression of only a subset of LPS-target genes by NCoR complexes indicates a PPAR-γ-specific repression rather than a general repression of all LPS target genes [30].

NF-κB is the master regulator of inflammatory responses. PPAR-γ is able to attenuate NF-κB function either by directly interfering with the transcription activating capacity of the NF-κB complex [49] or indirectly, by regulating proteins that suppress activation of NF-κB or by competing for the proteins that are essential for NF-κB function through a process known as squelching [50,51]. Ciglitazone block LPS-induced IL-12 production in murine macrophages and promote apoptosis in HT-29 cells by inhibiting the activity of NF-κB through direct protein-protein interaction between NF-κB subunits and PPAR-γ [49,52]. In another mechanism, PPAR-γ was shown to prevent the up regulation of p53 as well as its effector p21 in MCF-7 cells by replacing the NF-κB from its binding sites on the p53 promoter [53]. Alternatively, PPAR-γ inhibits NF-κB activity indirectly either by inducing the expression of IκBα [54], an inhibitor of NF-κB or inhibiting the IKK activity, which prevents IκBα degradation [55,56]. Even though regulation of IκBα by PPAR-γ was not demonstrated, activation of PPAR-α in human smooth muscle cells was shown to increase IκBα levels by transcriptional activation [57]. The other common indirect mechanism of inhibition employed by PPARs, is competing for the limited pool of transcriptional co-activators such as p300, CREB-binding protein, C/EBPb and GRIP-1/TIF-2) [58,59]. However, in many cases the role of co-regulators in transrepression by PPAR-γ were deduced from studies utilizing over-expression systems and transient transfections experiments, which do not necessarily reflect the actual scenario of transrepression observed at naturally occurring levels of coregulators. Therefore, there is a need to address these issues using appropriate experimental model systems. Similarly, direct and indirect mechanisms are implicated in PPAR-γ-mediated inhibition of other pro-inflammatory transcription factors including AP-1, C-JUN, STATs, and NFAT [58].

## Activation of PPAR-γ Antagonizes TGF-β Signaling

Transforming growth factor (TGF-β) is a multifunctional cytokine involved in the regulation of cell proliferation, differentiation and extracellular matrix production. Upon TGF-β binding, the type II (TGFβRII) receptor heterodimerizes with type I (TGFβRI) TGF-β receptor at the cell surface and that results in phosphorylation of R-Smads (Smad2 and Smad3). R-Smads heterodimerize with Smad4, and translocate into the nucleus to induce transcription of target genes [60,61]. During early stages when response to TGF-β in cells is normal, it inhibits tumorogenesis. Whereas, in later stages of tumor progression when genetic or epigenetic alterations in multiple pathways overcome the tumor suppressor activity, resulting in the pleiotropic tumor promoting roles for TGF-β [62]. Although the exact mechanism remains to be defined, mutual interference between PPAR-γ and TGF-β signaling pathways has been reported at multiple levels including phosphorylation of PPAR-γ, repression of PPAR-γ gene expression, and the interaction of PPAR-γ and Smad3 [63].

In hepatobiliary cells PPAR-γ activation inhibits the tumor suppressive activity of TGF-β by inhibiting Smad transcriptional activity. In these cells, TGF-β treatment simultaneously activates Smad-mediated gene transcription and phosphorylation of cPLA2α, wherein phosphorylation of cPLA2α initiates two signaling pathways that counteract Smad-mediated growth inhibition, including activation of its G-protein-coupled receptor $EP_1$ through PGE2 and activation of PPAR-γ. Antisense inhibition of cPLA2α or siRNA-mediated depletion of PPAR-γ enhances TGF-β-mediated Smad activation and partially restores the growth inhibition by TGF-β [64]. On the other hand, PPAR-γ activity was inhibited by TGF-β, during adipogenic differentiation, by decreasing the expression of both C/EBPα and C/EBPβ, which are important co-regulators of PPAR-γ [65]. The basis for such a mutually antagonistic affect between PPAR-γ and TGF-β is not clear. Recently it has been demonstrated that Cited2 (CREB-binding protein/p300-interacting transactivator with ED-rich tail 2) protein functions as a transcriptional co-activator for both TGF-β [66] and PPAR-γ [67] and competing for the shared common transcriptional co-activator may result in

mutual antagonism. Contrary to above examples, in vascular smooth muscle cells (VSMCs) PPAR-γ activation by pioglitazone was reported to exert direct anti-atherosclerotic and anti-restenotic effects by inducing apoptosis through increased TGF-β levels and translocation of phospho-Smad2 into nucleus. This effect was blocked either by using PPAR-γ antagonist GW9662 or anti-TGF-β1 antibody or activin receptor-like kinase inhibitor (SB-431442), demonstrating the TGF-β-dependent regulation of PPAR-γ signaling [68].

Accumulating evidence suggests that the activation of PPAR-γ can also interfere with the TGF-β signaling in the tumor microenvironment. In advanced stages of cancer, TGF-β is known to induce activation of fibroblasts to myofibroblasts [69]. Myofibroblasts serve as major stromal source of extracellular matrix proteins, especially fibrillar collagens, fibronectin, proteoglycans, MMPs, cytokines and chemokines that are involved in chemoresistance, angiogenesis, tumor migration, invasion and metastasis. Myofibroblasts affect the cancer progression by secreting and organizing altered ECM within the tumor stroma [70]. Both natural and synthetic PPAR-γ agonists are reported to suppress the activation of fibroblasts into myofibroblasts [71]. PPAR-γ ligands 15d-$PGJ_2$, ciglitazone and rosiglitazone inhibited TGF-β-driven myofibroblast differentiation as well as type I collagen production in human lung fibroblasts without affecting their viability [71]. Pioglitazone attenuates the induction of fibronectin and its spliced variant $EDA^+FN$ by TGF-β in human mesangial cells [72]. Similarly pioglitazone counteracts fibronectin activated invasion of breast carcinoma through the suppression of TGF-β signaling. TGF-β is also a potent inducer of the process known as EMT which is implicated in the dissemination of individual cancer cells to distant organs for metastasis [69,73]. Activation of PPAR-γ was shown to inhibit EMT at least in the context of fibrosis [74]. We have recently shown that activation of PPAR-γ inhibits tumor metastasis in lung cancer cells by antagonizing Smad3-mediated EMT [63].

## Implications for Lung Cancer Therapy

Several independent studies including ours, demonstrated that various ligands of PPAR-γ induce differentiation of lung cancer cells and inhibit their growth. Transcriptional activation of PPAR-γ by ciglitazone or PGJ2 was shown to induce general (gelsolin, PPAR-γ, Mad, and p21) as well as lineage specific (MUC1, SP-A, CC10, and $HTI_{56}$) differentiation markers in lung cancer cells making them less tumorigenic [75]. Interestingly, this differentiation response was observed only in the presence of serum in the culture medium where PPAR-γ ligands inhibited cell growth to promote differentiation. In the absence of serum, the same ligands induced apoptosis in the lung cancer cells, at a 5-fold lesser concentration than what is required for inducing differentiation in the presence of serum [4]. Consistently, using two different TZDs we showed inhibition of tumor cell growth both in-vitro and in-vivo, by promoting differentiation but did not induce apoptosis. In addition, we demonstrated that sustained Erk1/2 activation mediated troglitazone-induced differentiation of lung cancer cells [2].

PPAR-γ ligands inhibit growth and induce apoptosis of lung cancer cells by different mechanisms depending on the growth conditions and the ligands used. Ciglitazone and PGJ2 were shown to induce p21 expression transcriptionally by enhancing the binding of transcriptional factors SP1 and C/EBP-α to the promoter of p21 gene. [76]. Similarly, troglitazone treatment can activate the promoter activity of DNA damage inducible gene, GADD153 and inhibit growth and induce apoptosis in NSCLC cells [77]. Rosiglitazone was shown to effect lung cancer growth by modulating mTOR signaling [78]. In addition pathways such as cPLA2, Cox2, PGE2, 15-PGDH, and Wnt7a were also implicated in the PPAR-γ ligands induced growth inhibition of lung cancer cells [79] [80] [81]. In another interesting study, overexpression of PPAR-γ cDNA alone was sufficient to inhibit tumor

growth in-vivo, cellular migration and invasion in-vitro in lung cancer cells [82]. This study clearly demonstrates the direct anti-neoplastic affects of PPAR-γ and suggests potential presence of an endogenous PPAR-γ ligand.

In addition to affecting cancer cells, PPAR-γ ligands also influence tumor progression by modulating various aspects of tumor microenviroment as described above in lung cancers, including angiogenesis, ECM components, immune cell function, and fibroblast activation. Rosiglitazone was shown to inhibit mouse lung tumor cell growth and metastasis in-vivo through direct and indirect anti-angiogenic effects [83]. Similarly, A549 cell xenografts from SCID mice that were treated with pioglitazone or troglitazone showed significant reduction in blood vessel density. Consistently, treatment of A549 cells, in-vitro with troglitazone or transfected with a constitutively active PPAR-γ blocked the production of angiogenic chemokines IL-8, ENA-78, and Gro-α by inhibiting NF-κB transcriptional activity that regulates their expression [84]. Among the ECM components, PPAR-γ ligands were shown to inhibit fibronectin expression by antagonizing transcription factors that regulate its expression. In addition, these ligands were also reported to inhibit the expression of α5 integrin resulting in the reduction of a fibronectin receptor, α5β1. Together, these results suggest that by inhibiting fibronectin and its receptor, PPAR-γ ligands disrupt tumor cell and ECM interactions essential for tumor cell proliferation [85,86]. With respect to the effects on immune cell functions in tumor microenvironment, PPAR-γ ligands reverse the antitumor cytotoxic T-lymphocyte suppressive activity and the M2 phenotype of tumor associated macrophages [87]. PPAR-γ ligands are also known to inhibit the expression of several cytokines and chemokines produced by most of the major immune cell types present in the tumor microenvironment. As described earlier these ligands can inhibit activation of lung fibroblasts into myofibroblasts, a phenotype similar to that of tumor-associated fibroblasts [71]. Together, these observations suggest that PPAR-γ might be an important target for modulating lung tumor microenvironment.

PPAR-γ ligands, apart from their direct activity, also demonstrate a synergistic interaction with other cytotoxic as well as targeted anti-cancer agents. Combining platinum based chemo therapeutic drugs including cisplatin and carboplatin with PPAR-γ ligands such as rosiglitazone and GW1929, demonstrate a potent synergistic activity against lung cancer cells in-vitro and in-vivo [88,89]. Further analysis revealed that PPAR-γ ligands induce a downregulation of metallothionins which sequester platinum drugs and prevent their cytotoxicity [89]. We observed a similar synergistic interaction between PPAR-γ ligands (troglitazone and pioglitazone) and chemotherapeutic drugs cisplatin and paclitaxel, in spite of their two different modes of action. Interestingly, this synergy was observed only when the treatment of PPAR-γ ligands is preceded by the treatment with cisplatin or paclitaxel. This sequence specific synergy was suggested to be due to induction of PPAR-γ expression by cisplatin and paclitaxel [90]. Among the targeted agents, PPAR-γ ligands facilitated the antiproliferative effects of gefitinib (rosiglitazone), an inhibitor of the epidermal growth factor receptor signaling [91], potentiated the effect of the HDAC inhibitor, phenyl butyrate ( Ciglitazone) [75], and demonstrated synergy with lovastatin (troglitazone) [92].

In summary, despite such a wide range of potential anti-tumor affects and overwhelming amount of preclinical data, demonstrating the efficacy of PPAR-γ ligands, so far there are no clinical trials testing the efficacy of these ligands in oncology, with the exception of one ongoing clinical trial in lung cancer. Though less relevant to oncology use, recent findings of potential liver and cardio toxicities associated with PPAR-γ ligands has partly tempered the enthusiasm. However, a retrospective analysis of more than 80,000 individuals revealed a 33% reduction in lung cancer risk among TZD users compared to nonusers after adjusting for confounding variables [93]. This observation, together with the relatively low toxicity

profile of TZDs that are currently in clinic justify prospective, randomized, clinical studies to determine the true effect of PPAR-γ ligands, at least in lung cancer.

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## Abbreviations

| | |
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| **EGFR** | Epidermal growth factor receptor |
| **HDAC** | Histone deacetylases |
| **IKK** | IκB kinase |
| **IL-1β** | Interleukin 1 β |
| **MAPK** | Mitogen activated protein kinase |
| **MMP** | Matrix metallo protease |
| **NES** | Nuclear export signal |
| **PGC1α** | PPARγ coactivator-1 |
| **PGJ2** | Prostaglandin J2 |
| **PGE** | Prostaglandin E |
| **PPAR** | Peroxisome Proliferators-Activated Receptors |
| **PPRE** | Peroxisome proliferators' response elements |
| **RXR** | Retinoid X receptor |
| **SRC-1** | Steroid receptor coactivator 1 |
| **TGF-β** | Transforming growth factor β |
| **TNF-α** | Tumor necrosis factor α |
| **TZD** | Thiazolidinediones |

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**Figure 1.**
Mutual cross-regulation of PPAR-γ and other signaling pathways and its implications