Biological Actions of PPAR-γ in Health and Disease

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Abstract
Peroxisome proliferator-activated receptors (PPARs) are ligand activated transcription factors that modulate target gene expression in response to endogenous and exogenous ligands. Peroxisome proliferator-activated receptors are expressed in many tissues, including adipocytes, hepatocytes, muscles and endothelial cells. The PPARs, a family of nuclear receptors (NRs), are a set of three receptor sub-types encoded by distinct genes. The discovery of PPAR-specific ligands has led to a significant advancement in our understanding of the structure of these receptor proteins and molecular mechanisms of their ligand dependent activation. The nuclear receptor peroxisome proliferator-activated receptor (PPAR)-γ is a crucial cellular and metabolic switch that regulates many physiologic and disease processes.

Keywords: PPAR-gamma; inflammation; adipose tissue; insulin sensitivity; cancer.

Introduction
The peroxisome proliferator activated receptors (PPARs) are ligand-inducible transcription factors belonging to superfamily of nuclear hormone receptor (NHR) containing 48 members (1). These receptors are identified in the 1990 in rodents. These receptors are named because of its property of peroxisome proliferation. NHR also includes other members such as retinoic acid receptors (RARs), the thyroid hormone receptors (TRs) and the steroid receptors (1, 2). But, these agents are associated with no proliferation in the humans. Structurally, PPARs are similar to steroid or thyroid hormone receptor and are stimulated in response to small lipophilic ligands.

Isoforms of PPARs: Three subtypes of PPARs, classified as PPAR-α (NR1C1), PPAR-β/δ (NR1C2) and PPAR-γ (NR1C3), encoded by separate genes, were cloned from a Xenopus cDNA library in 1992. PPAR-γ is further of three type’s i.e PPAR-γ1, PPAR-γ2, PPAR-γ3 that differs at their 5' end and is generated by alternative promoter usage and splicing. Proteins produced from PPAR-γ1 and PPAR-γ3 mRNAs are identical, whereas, PPAR-γ2 protein contains an additional N-terminal region composed of 28 amino acids.

Structural features of PPARs: All three PPAR isoforms possess similar structural and functional features. Principally, four functional domains have been identified, called A/B, C, D and E/F (Fig. 1). The N-terminal A/B domain contains a ligand-independent activation function 1 (AF-1) (4), responsible for the phosphorylation of PPAR. The DNA binding domain (DBD) or C domain promotes the binding of PPAR to the peroxisome proliferator response element (PPRE) in the promoter region of target genes (5). The D site is a docking domain for cofactors. The E domain or ligand-binding domain (LBD) is responsible for ligand specificity and activation of PPAR binding to the PPRE, which increases the expression of targeted genes. Recruitment of PPAR co-factors to assist the gene transcription processes is carried out by the ligand-dependent activation function 2 (AF-2), which is located in the E/F domain (6).
PPARs are composed of four distinct functional regions. The A/B domain located at N-terminal with AF-1 is responsible for phosphorylation, the domain C is implicated in DNA binding, domain D is the docking region for cofactors and domain E/ F is the ligand specific domain, containing AF-2, which promotes the recruitment of cofactors required for the gene transcription.

**Mechanism of action:** PPARs are the transcription factors i.e. they regulate the transcription of genes in response to ligand binding as shown in figure 2 (7). After ligand binding, PPARs undergo specific conformational changes that allow for the recruitment of one coactivator protein or more. Ligands differ in their ability to interact with coactivators, which explains the various biologic responses observed.

**RXR and heterodimerisation:** Unlike the steroid hormone receptors, which function as homodimers, PPARs form heterodimers with the retinoid X receptor (RXR). Like PPARs, RXR exists as three distinct isoforms: RXRα, β, and γ, all of which are activated by the endogenous agonist 9-cis retinoic acid. No specific roles have yet been elaborated for these different isoforms within the PPAR: RXR complex. However, synthetic RXR agonists can activate the complex and thereby obtain antidiabetic outcomes similar to those seen with PPAR agonists in mouse models of type 2 diabetes. The LBD domain facilitates the heterodimerisation of PPARs with the RXR and the resultant heterodimer subsequently binds to peroxisome proliferator response element (PPRE) with the recruitment of cofactors (1).

PPARs regulate gene transcription by two mechanisms i.e transactivation and transrepression. In transactivation, which is DNA-
dependent mechanism, PPAR forms a heterodimer complex with the retinoid X receptor (RXR) and recognizes specific DNA response elements called PPAR response elements (PPRE) in the promoter region of target genes. This results in transcription of PPARγ target genes which ultimately involved in diverse biological processes such as adipocytes proliferation, glucose and lipid metabolism. In transrepression, PPARs can repress gene transcription by negatively interfering with other signal-transduction pathways, such as the nuclear factor-kB (NF-kB) signaling pathway, in a DNA-binding–independent manner (1).

**Peroxisome proliferator-activated receptor-gamma (PPAR-γ):** Most widely used PPAR-γ ligands are thiazolidinediones (10). First drug in this category is Troglitazone (Rezulin) then rosiglitazone (Avandia) and pioglitazone (Actos). Troglitazone is withdrawn from market due to hepatic toxicity. The PPAR-γ contains three isoforms, named as, PPAR-γ1, PPAR-γ2 and PPAR-γ3.

**Table 1. Expression of PPAR isoforms**

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Tissue Expression</th>
<th>Glucose and Lipid lowering effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>Skeletal muscle, Kidney, Heart, Liver, Monocytes, Macrophages, Vascular and endothelial smooth muscle</td>
<td>decreases acyl-CoA enzyme, thereby decreasing triglyceride concentration, increases uptake and oxidation of free fatty acids</td>
</tr>
<tr>
<td>β/δ</td>
<td>Skeletal muscle, Adipocytes, Macrophages, Lungs, Brain, Skin</td>
<td>enhances glucose tolerance and disposal improves lipid catabolism and fatty acid oxidation</td>
</tr>
<tr>
<td>γ1</td>
<td>Kidney, Spleen, Pancreatic β-cells, Cardiac, skeletal and vascular smooth muscle</td>
<td>improves insulin resistance by producing additional adipocytes to better store the elevated fatty acids induces adipocyte expression and differentiation</td>
</tr>
<tr>
<td>γ2</td>
<td>Adipocytes</td>
<td>decreases hepatic glucose production</td>
</tr>
<tr>
<td>γ3</td>
<td>Colon, Macrophages, Adipocytes</td>
<td>redistributes lipids from visceral areas into subcutaneous fat decreases TNF and 11-b hydroxysteroid dehydrogenase 1 increases adiponectin, which increases insulin sensitivity in liver and skeletal muscle</td>
</tr>
</tbody>
</table>

**PPAR-ligands:** Although the nature of true endogenous PPAR ligands is still not known, PPARs can be activated by wide variety of endogenous or pharmacological ligands as shown in table 2. PPAR-α activators include variety of endogenously present fatty acids, LTB4 and hydroxyeicosatetraenoic acids (HETEs), and clinically used drugs, such as fibrates, a class of first-line drugs in the treatment of dyslipidemia. Similarly, PPAR-γ can be activated by a number of ligands, including docosahexaenoic acid, linoleic acid, the anti-diabetic glitazones, used as insulin sensitizers, and a number of lipids, including oxidized.

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LDL, azoyle-PAF, and eicosanoids, such as 5, 8, 11, 14-eicosatetraynoic acid and the prostanoids PGA1, PGA2, PGD2, and its dehydration products of the PGJ series of cyclopentanones (e.g., 15 deoxy-Δ12,14-PGJ2). PPARβ/δ activators include fatty acids and prostacyclin and synthetic compounds L-165,041, GW501516, compound F and L-783,483.

Table 2. PPAR Ligands

<table>
<thead>
<tr>
<th>Endogenous ligand</th>
<th>Biological effect</th>
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<tbody>
<tr>
<td><strong>PPAR-α</strong></td>
<td><strong>PPAR-β</strong></td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>Docaehaxanoic acid</td>
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<tr>
<td>Stearic acid</td>
<td>Arachidonic acid</td>
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<tr>
<td>Palmitoleic acid</td>
<td>Linoleic acid</td>
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<td>Oleic acid</td>
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<tr>
<td>Linoleic acid</td>
<td></td>
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<tr>
<td>Arachidonic acid</td>
<td></td>
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<tr>
<td>Eicosapentaenoic acid</td>
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<tr>
<th>Exogenous ligand</th>
<th><strong>PPAR-β</strong></th>
<th><strong>PPAR-γ</strong></th>
<th>Implication</th>
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<tbody>
<tr>
<td><strong>PPAR-α</strong></td>
<td><strong>Agonists</strong></td>
<td><strong>Agonists</strong></td>
<td><strong>PPAR-α agonists</strong></td>
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<td>Gemfibrozil</td>
<td>L-165041</td>
<td>Thiazolidinediones</td>
<td>Atherosclerosis,</td>
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<td>Clofibrate</td>
<td>GW501516</td>
<td>JTT-501</td>
<td>Inflammation</td>
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<td>Fenofibrate</td>
<td>GW0742</td>
<td>KRP-297</td>
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<td>NC-2100</td>
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<td>Ciprofibrate</td>
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<td>MCC-555</td>
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<td>GW 9578</td>
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<td>Nafenopin</td>
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<td><strong>Antagonist</strong></td>
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<td><strong>Antagonists</strong></td>
<td><strong>Antagonist</strong></td>
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<tr>
<td>MK-886</td>
<td>Sulindac</td>
<td>GW-0072</td>
<td>Cancer</td>
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<td>BADGE</td>
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<td></td>
<td>Diclofenac</td>
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Seema Thakur and Neha Srivastava
Biological actions of PPAR-\(\gamma\)

**Insulin sensitization:** The mechanism underlying insulin-sensitising effects of TZDs are complex and not completely understood. Activation of PPAR-\(\gamma\) in insulin-resistant animals or humans results in an increase in the sensitivity of both the liver to insulin-mediated suppression of hepatic glucose production and insulin-mediated skeletal muscle glucose uptake. These in vivo effects on insulin signaling are because of combined actions of PPAR-\(\gamma\) ligands on the adipose tissue and on liver and skeletal muscles.

Insulin resistance is one of the principle defects underlying the development of type-2 diabetes and Asian Indians are considered to be more insulin resistant. PPAR-\(\gamma\) has also been associated with several genes that affect insulin action (11, 12). Given that PPAR-\(\gamma\) is expressed predominantly in adipose tissue, the prevailing hypothesis regarding the net in vivo efficacy of PPAR-\(\gamma\) agonists involves direct actions on adipose cells, with secondary effects in key insulin-responsive tissues such as skeletal muscle and liver. PPAR-\(\gamma\) enhances the expression of a number of genes encoding proteins involved in glucose and lipid metabolism.

In adipocytes, PPAR-\(\gamma\) regulates the expression of numerous genes involved in lipid metabolism, including aP2, PEPCK, acyl-CoA synthase, and LPL. PPAR-\(\gamma\) has also been shown to control expression of FATP-1 and CD36, both involved in lipid uptake into adipocytes. These genes have all been shown to possess PPREs within their regulatory regions (13).

In addition to the stimulation of adipocyte differentiation, activation of PPAR-\(\gamma\) also promotes apoptosis in mature lipid-filled adipocytes. This ligand-induced apoptosis in mature cells causes the stimulation of adipogenesis from pre-adipocyte precursors, resulting in an increased number of small, relatively insulin-sensitive adipocytes (14).

**Adipocyte differentiation**

Adipogenesis refers to the process of differentiation of the pre-adipocyte precursor cells into adipocytes that are capable of lipid filling, as well as the expression of hormones and cytokines (adipokines). PPAR-\(\gamma\) is expressed at high levels in adipose tissue and is central regulator of adipocytes gene expression and differentiation. In adipocytes, PPAR-\(\gamma\) regulates the expression of numerous genes involved in lipid metabolism, including aP2, PEPCK, acyl-CoA synthase, and LPL. PPAR-\(\gamma\) has also been shown to control expression of FATP-1 and CD36, both involved in lipid uptake into adipocytes. These genes have all been shown to possess PPREs within their regulatory regions (13).

**Atherosclerosis**

Expression of PPAR-\(\gamma\) in endothelial cells, vascular smooth muscle cells (VSMCs) has raised questions regarding its effects on lipid metabolism. This has prompted research on its anti-inflammatory properties. Subsequently, its role in chronic inflammatory disorders such as atherosclerosis, arthritis and inflammatory bowel syndrome were also studied. PPAR-\(\gamma\) agonists were shown to have antiatherosclerotic effects in different animal models. Several mechanisms have been reported which counteracted the pro-
atherogenic activity of PPAR-γ. In endothelial cells, PPAR-γ activators inhibited the VCAM-1 and ICAM-1 expression, resulting in the reduction of monocyte accumulation in the arterial intima and also decreases the inflammatory cell recruitment by inhibiting the chemokines IL-8 and MCP-1 (15, 16, 17). In human monocyte derived macrophages, PPAR-γ agonists inhibited MMP-9 gelatinolytic activity, an enzyme responsible for plaque rupture. The role of VSMCs in the progression of atherosclerosis is paramount and recent studies showed that they were key targets of PPAR-γ agonists. TZDs inhibited VSMC proliferation by decreasing phosphorylation of retinoblastoma protein and increasing levels of cyclin dependent inhibitor p27. In addition, PPAR-γ ligands inhibited the expression and activity of MMP-9 and VSMC migration, thus offsetting the PPAR-γ pro-atherogenic activity. Furthermore, PPAR-γ agonists inhibited angiotensin II type 1 receptor in vascular smooth muscle cells; this down-regulation is beneficial in atherosclerosis and hypertension. PPAR-γ agonists also play an important role in macrophage lipid homeostasis by inducing expression of several key genes including ABCA1, ABCG1, apolipoprotein E (apoE) and CLA-1/SR-BI. Therefore the metabolic syndrome which is clustering of cardiovascular risk factors with insulin resistance is characterised by simultaneous presence of one or more of metabolic disorder such as glucose intolerance, hyperinsulemia, dyslipidemia, coagulation disturbances and hypertension can be effectively modulated by PPAR-γ agonists (1, 15, 18, 19).

Inflammation

Inflammation is a complex and dynamic process initiated by the body in response to tissue injury or infection. PPAR-γ agonists have been shown to be effective in number of inflammatory models such as ulcerative colitis, rheumatoid arthritis (20, 21), asthma (22, 23), allergic encephalomyelitis (24, 25, 26) and pulmonary inflammation (27, 28). Pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 and production of nitric oxide by inducible nitric oxide synthase (iNOS) plays a key role in all these inflammatory conditions. In animal model of asthma, activation of PPAR-γ induces a selective inhibition of eosinophil and lymphocyte influx, without affecting the neutrophil influx (29, 30). Various invitro and invivo studies have shown the efficacy of PPAR-γ agonists in acute and chronic inflammation (31, 32, 33, 34, 35). In vitro reports find PPAR-γ inhibition of monocyte chemoattractant protein-1 directed chemotaxis. PPAR-γ agonists also inhibit chemokines (interleukin-8) in epithelial cells, leading to the suggestion of their use in inflammatory bowel diseases (36). Several lines of evidence suggest that PPAR-γ may exert anti-inflammatory effects by negatively regulating the expression of these pro-inflammatory genes that become induced during macrophage activation. PPAR-γ is expressed in monocytes, and particularly up-regulated upon activation (37). PPAR-γ ligands inhibit the induction of inducible nitric oxide synthase (iNOS), MMP-9, an scavenger receptor A gene transcription (37) and the production of TNF, IL-1β, and IL-6 (38, 39). Furthermore, PPAR-γ activation inhibits the transcriptional activity of cytokine induced pro-inflammatory transcription factors AP-1, NF-κB, and STAT1 transcription factors (37). In addition to effects on activation, PPAR-γ ligands induce apoptosis in old macrophages (40).

Immunoregulation

Various in vivo and in vitro studies have shown that PPAR-γ ligands are also capable of down-regulating most cells of the innate and adaptive immune system (40, 41, 42). This immunoregulatory effect of PPAR-γ ligands has led to numerous studies demonstrating the efficacy of PPAR-γ ligands in treating animal models of autoimmunity including experimental allergic encephalomyelitis, asthma, arthritis, colitis, and diabetes and leads to the excitement about the potential use of PPAR-γ ligands as therapeutic agents in human autoimmune diseases. PPAR-γ enhances the regulatory T-cells through PPAR-γ dependent and –independent mechanisms (43). This immunoregulatory effects of PPAR-γ ligands are believed to be mediated through down-regulation of antigen-presenting
cells and pathogenic T-cell function (44, 45, 46, 47, 48, 49).

**Cardiovascular diseases**: Peroxisome proliferator-activated receptor-γ (PPAR-γ), an essential transcriptional mediator of adipogenesis, lipid metabolism, insulin sensitivity, and glucose homeostasis, also recognized as a key player in inflammatory cells and in cardiovascular diseases (CVD) such as hypertension, cardiac hypertrophy, congestive heart failure, and atherosclerosis (7, 50, 51, 52). PPAR-γ agonists can lower blood pressure and this effect may be at least partially independent of their insulin-sensitizing effects (53, 54, 55, 56). PPAR-γ agonists have also been shown to inhibit hypertrophy of cultured neonatal rat ventricular cardiomyocytes induced by mechanical stress or angiotensin II, and cardiac hypertrophy induced by aortic constriction in rats and mice. The inhibition on hypertrophy was accompanied by the inhibition on expression of embryonic genes, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), skeletal α-Actin, as well as that of endothelin-1 that can induce cardiac hypertrophy (55, 56).

Cardiac remodeling after ischemic injury is one of the major causes that lead to heart failure. This remodeling process is characterized by myocyte hypertrophy and cardiac fibrosis. PPAR-γ agonists attenuate this remodeling process after ischemia in experimental animals (57, 58). Pioglitazone reduces cell growth, synthesis of collagen type I, and expression of matrix metalloproteinase-1 in cardiac fibroblasts undergone anoxia-reoxygenation or treated with angiotensin II, likely through inhibition of reactive oxygen species generation and NF-κB activation. So various evidences suggest that PPAR-γ activators impact the cardiovascular system through not only their lipid- and carbohydrate-lowering effects but also their anti-inflammatory and antioxidant actions (59-63).

**Immune Response**

PPARs are expressed in immune cells (48, 64) where they modulate the expression of cytokines and costimulatory molecules. In dendritic cells (DC), the major antigen-presenting cells capable of inducing T-cell-mediated immune responses against a wide range of antigens, PPAR-γ activators reduce the secretion of IL-12, a proinflammatory cytokine playing a key role in atherogenesis and the polarization of the immune response toward Th1. PPAR-γ activation also affects playing a key role in atherogenesis and the polarization of the immune response toward Th1 (65). PPAR-γ activation also affects the surface expression of costimulatory molecules, such as CD80 and CD86, and the synthesis of chemokines involved in the recruitment of TH1 cells, including RANTES and IP-10. In addition, PPAR-γ ligands reduce IL-10 secretion and inhibit the expression of the chemokine EB1 ligand and CCR7, both playing a pivotal role in DC migration to the lymph nodes. These effects are accompanied by downregulation of LPS-induced nuclear localization of the RelB protein, a transcription factor of the NF-κB family controlling DC differentiation and function. These effects of PPAR-γ ligands in DCs can drive the local immune response by favoring the differentiation of TH2 cells, thus orienting the immune response toward a cytokines, including IFN-γ and TNF-α, and exert antiproliferative effects. PPAR-γ activation leads to decreased effects. PPAR-γ activation leads to a decreased production of IL-2 by negatively interfering with the T-cell specific transcription factor NFAT (66). Inhibition of inflammatory cytokine production and proliferation in T-cells is correlated with the suppression of activated transcription factor AP-1 and NF-κB. Moreover, PPAR-γ ligands can also control major histocompatibility complex class-(MHC) II mediated T-cell activation by inhibiting IFN-γ induced MHC-II expression in vascular cells (67-68).

**Neurodegenerative diseases**

PPAR-γ agonists are shown to be effective in number of neurodegenerative disorders such as Alzheimer disease (AD), Parkinson disease (PD), Amyotrophic lateral sclerosis (ALS), Multiple sclerosis (MS) and Experimental allergic
encephalomyelitis (EAE). These neurodegenerative and neuro-immunological diseases occurs mainly due to activation of non-neuronal cells particularly the microglia and astrocytes (69, 70, 71, 72, 73). PPAR-γ receptors have been found to be expressed on the surface of microglia and PPAR-γ activation has been reported to inhibit the microglial activation (74, 75). The major hallmark of AD is the formation of amyloid plaques which are populated by abundant activated microglia and astrocytes along with increased expression of inflammatory enzymes such as inducible nitric oxide synthase (iNOS). Invitro and invivo studies have shown that the activation of PPAR-γ in microglial cells suppressed the inflammatory cytokine expression, iNOS and COX-2 expression. These effects results from the capacity of PPAR-γ to suppress proinflammatory genes through antagonism of transcription factor nuclear factor κB (NFκB), and, to a lesser extent, activator protein 1. PPAR-γ agonists also suppress the amyloid-β (Aβ)-mediated activation of microgla invitro thereby preventing the cortical or hippocampal neuronal cell death (38, 39, 74, 74).

PPAR-γ agonists are also effective in pathogenesis of PD. The pathological hallmark of idiopathic PD is the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Excitotoxicity, oxidative phosphorylation, generation of reative oxygen species are all thought to contribute to neuronal cell death. Pioglitazone decreased microglial and astrocyte activation, and also reduce the number of iNOS-positive cells in the striatum and SNpc (74, 75, 76). In ALS, pioglitazone is effective in transgenic animal model. Oral treatment of pioglitazone extended the survival of motor neurons in SOD-G93A transgenic mice and also delays the onset of disease. Number of activated microglia were also markedly reduced at the site of neurodegeneration by Pioglitazone (77, 78).

Proinflammatory cytokines plays a key role in the pathogenesis of MS and EAE, an established animal model of MS. PPAR-γ agonists exerts profound and long lasting anti-inflammatory effects in peripheral immune cells (37, 38, 39, 79) and in models of autoimmune disorders (24, 25, 27, 54) suggesting the use of these drugs in invitro and invivo models of MS. Moreover it has been demonstrated that expression of PPAR-γ increases in microglia and astrocyte during EAE, supporting a role this receptor in modulating inflammatory response in MS.

Cancer: The interest in studying the effects of PPAR-γ activation is derived from previous results suggesting that PPAR-γ ligands inhibited cell proliferation when inducing adipocytes differentiation. PPARγ is highly expressed in several human cancer cell lines, including liposarcoma, breasts (81, 82), colon (83, 84), lungs (85, 86), prostate (87, 88), bladder and gastric (89, 90). The PPARγ agonists such as TZDs and 15d-prostaglandin J2 (15d-PGJ-2) have demonstrated not only apoptosis and growth inhibition of numerous cancer cell lines in vitro, but have also shown tumour growth suppression in vivo rodent carcinoma models. PPAR-γ not only controls the expression of genes involved in differentiation but also negatively regulates the cell cycle. One possible mechanism is upregulation of tumor suppressor PTEN by PPAR gamma agonists (91, 92). PPAR-γ ligands were also shown to inhibit growth and at least for breast and prostate cancer cells to induce apoptosis. These observations suggest that induction of terminal differentiation by PPAR-γ agonists may represent a promising therapeutic approach to certain human malignancies (93-95).

Systemic sclerosis: Fibrosis is recognized as an important feature of many chronic diseases, such as systemic sclerosis (SSc), an autoimmune disease of unknown etiology, characterized by immune dysregulation and vascular injury, followed by progressive fibrosis affecting the skin and multiple internal organs. SSc has a poor prognosis because no therapy has been shown to reverse or arrest the progression of fibrosis, representing a major unmet medical need. Recently, antifibrotic effects of PPAR5-γ ligands have been studied in vitro and in vivo and some theories have emerged leading to
new insights. Aberrant PPAR-γ function seems to be implicated in pathological fibrosis in the skin and lungs. This antifibrotic effect is mainly related to the inhibition of TGF-β Smad signal transduction but other pathways can be involved (96, 97).

**Risk associated with PPAR-γ**: PPAR-γ agonists have been responsible for various therapeutic effects as well as side effects as shown in figure 3. The withdrawal of troglitazone has led to concerns of the other thiazolidinediones also increasing the incidence of hepatitis and potential liver failure, an approximately 1 in 20,000 individual occurrence with troglitazone. Because of this, the FDA recommends two to three month checks of liver enzymes for the first year of thiazolidinedione therapy to check for this rare but potentially catastrophic complication. The main side effect of all thiazolidinediones is water retention, leading to edema, generally a problem in less than 5% of individuals, but a big problem for some and potentially, with significant water retention, leading to a decompensation of potentially previously unrecognized heart failure. Therefore, thiazolidinediones should be prescribed with both caution and patient warnings about the potential for water retention/weight gain, especially in patients with decreased ventricular function (NYHA grade III or IV heart failure).

Though older studies suggested there may be an increased risk of coronary heart disease and heart attacks with rosiglitazone (98), pioglitazone treatment, in contrast, has shown significant protection from both micro- and macro-vascular cardiovascular events and plaque progression (99, 100). These studies led to a period of Food and Drug Administration advisories (2007 - 2013) that, aided by extensive media coverage, led to a substantial decrease in rosiglitazone use. In November 2013, the FDA

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**Fig. 3. Benefit and risk associated with PPAR-γ**

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announced it would remove the usage restrictions for rosiglitazone in patients with coronary artery disease (101). The new recommendations were largely based on the reasoning that prior meta-analyses leading to the original restrictions were not designed to assess cardiac outcomes and, thus, not uniformly collected or adjudicated. In contrast, one of the largest trials (RECORD trial) that were specifically designed to assess cardiac outcomes found no increased risk of myocardial infarction with rosiglitazone use, even after independent re-evaluation for FDA review (102).

A 2013 meta-analysis concluded that use of pioglitazone is associated with a slightly higher risk of bladder cancer compared to the general population. The authors of the same analysis recommended that other blood sugar lowering agents be considered in people with other risk factors for bladder cancer such as cigarette smoking, family history, or exposure to certain forms of chemotherapy (103).

**Conclusion**

PPARs are critical gene regulators in many metabolically active tissues, yet their functions are not fully established. PPAR gamma agonists convey beneficial effects as therapeutic agents for diabetes and atherosclerosis by lowering blood glucose, improving insulin resistance, inflammation, and lipid metabolism; however, adverse side effects limit their clinical use. Therefore, understanding how the PPAR gamma genes is regulated during disease processes will provide us the opportunity to design effective therapeutic modalities to treat disease by the inactivation, conjugation, and transport of toxic endogenous metabolites. Intensive research on this therapeutic target will likely lead to the development of safer and more effective PPAR agonists in the near future.

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