Review Article

Therapeutic Implications of Targeting Energy Metabolism in Breast Cancer

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PPARs are ligand activated transcription factors. PPARγ agonists have been reported as a new and potentially efficacious treatment of inflammation, diabetes, obesity, cancer, AD, and schizophrenia. Since cancer cells show dysregulation of glycolysis they are potentially manageable through changes in metabolic environment. Interestingly, several of the genes involved in maintaining the metabolic environment and the central energy generation pathway are regulated or predicted to be regulated by PPARγ. The use of synthetic PPARγ ligands as drugs and their recent withdrawal/restricted usage highlight the lack of understanding of the molecular basis of these drugs, their off-target effects, and their network. These data further underscores the complexity of nuclear receptor signalling mechanisms. This paper will discuss the function and role of PPARγ in energy metabolism and cancer biology in general and its emergence as a promising therapeutic target in breast cancer.

1. Introduction

The peroxisome proliferator-activated receptors (PPARs) are ligand activated transcription factors, belonging to the nuclear receptor superfamily, that control the expression of genes involved in organogenesis, inflammation, cell differentiation, proliferation, lipid, and carbohydrate metabolism [1, 2]. PPARs activated by their selected ligands, heterodimerizes and its receptor with the 9-cis-retinoic acid receptor, they then bind to peroxisome proliferator response elements (PPREs), specific sequences in their target genes. The consensus PPRE site consists of a direct repeat of the sequence AGGTCA separated by a single/double nucleotide, which is designated as DR-1 site/DR-2 site [3] (Figure 1). Each major isoforms of PPAR (PPARα, PPARβ/δ, and PPARγ), encoded by a different gene, performs different functions and exhibit different tissue localizations in many parts of the human body [4]. The peroxisome proliferator-activated

receptor γ (PPARγ) is the most extensively studied subtype of the PPARs [5]. PPARγ is expressed in adipose tissue, colon, immune system, hematopoietic cells, and retina involved in lipid anabolism, adipocyte differentiation, control of inflammation, macrophage maturation, embryo implantation, and molecular targets of antidiabetic thiazolidinediones [6]. Its role in cancer development and potential as a target for cancer prevention and treatment strategies has been noted in recent years. Activation of PPARγ could possibly be an approach to induce differentiation in cells thereby inhibiting proliferation of a variety of cancers. This antiproliferative effect has been reported in many different cancer cell lines including breast [7], colon [8], prostate [9], and non-small-cell lung cancer [10]. In particular, breast tissue was found to express PPARγ in amounts greater than those found in normal breast epithelium. Ligand activated PPARγ is reported to inhibit invasion and metastasis of breast cancer cells and induce G1/S arrest by upregulation of p21^{WAF1}/Cip1 or p27^{Kip1},
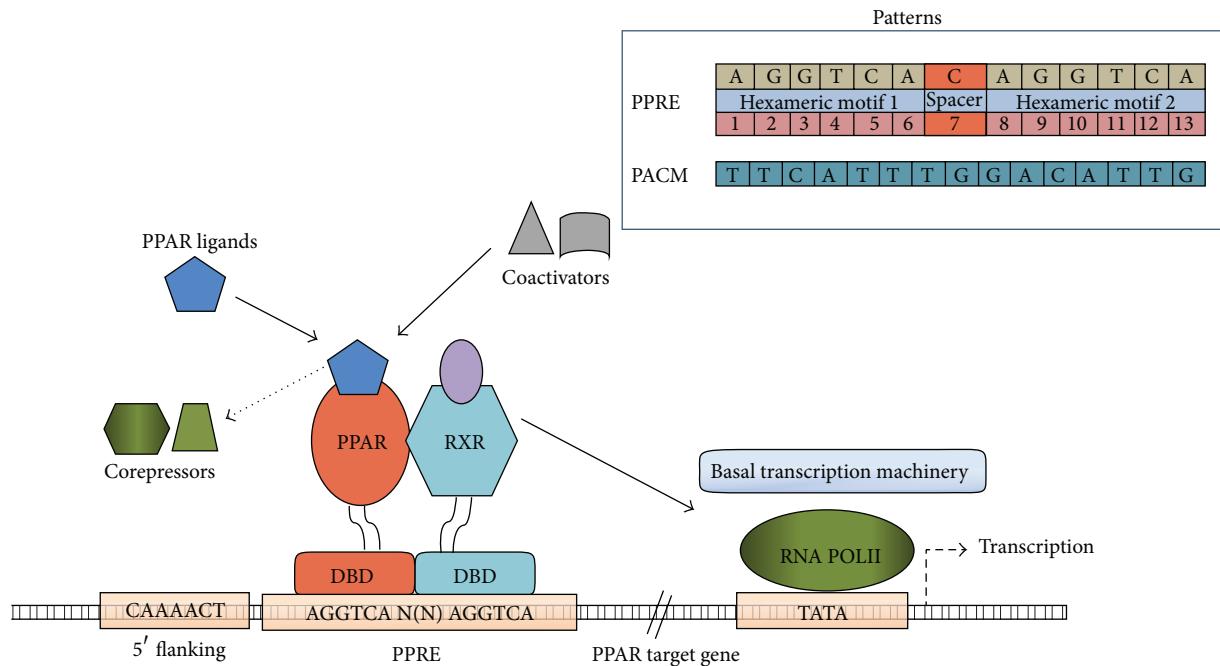
FIGURE 1: PPAR gamma activation mechanism. PPRE and PACM motifs are shown.

and downregulation of cyclin D1 [11–13]. Moreover, PPARγ on activation by specific ligands exerts antitumor activity through growth inhibition and cellular differentiation [14–17]. Imbalances in expression of target genes forms the core of metabolic syndrome and cancer regulation through atherogenic metabolic triad/lipid triad metabolism modulation by PPARs [18]. Despite these promising results, the target genes involved in the anticancer activity of PPARγ ligands and their pathways still remain elusive.

Breast cancer is the fifth most common cancer globally and accounts for the highest morbidity and mortality. It is the second highest occurring cancer in women and one of the leading causes of death [19]. Although antiestrogens have provided an effective endocrine therapy, a significant proportion of patients have acquired resistance to these drugs, others are intrinsically resistant [20]. Hence, there is a requirement for alternative therapeutics to treat breast cancer. Development of selective anticancer agents based on the biological differences between normal and cancer cells is essential to improve therapeutic selectivity, sensitivity, and specificity. A list of genes reported in the literature to be regulated by PPARγ and involved in breast cancer is shown in Figure 2.

Differences in energy metabolism between normal and cancer cells are reported and alterations in cellular bioenergetics are one of the hallmarks of cancer [21]. The general principles of metabolic control analysis can be effective for cancer management as abnormal energy metabolism and biological disorder are characteristics of tumors [22]. In line with this, increased aerobic glycolysis and elevated oxidative stress are two prominent biochemical features frequently observed in cancer cells, as shown by the Warburg hypothesis. This paper will discuss the function and role of PPARγ in energy metabolism and cancer biology in general and its emergence as a promising therapeutic target in breast cancer.

2. Glycolysis and Cancer

Coordinated upregulation of glycolysis pathway proteins has been detected in several different tumor types including breast cancer tumors [23–26]. Amon et al. identified increased levels of glycolysis proteins in plasmas of women with breast cancer [27]. Glycolysis for ATP synthesis rather than oxidative phosphorylation occurs primarily when cells are deprived of oxygen, but the Warburg hypothesis suggests the central role of glycolysis in cancer and tumor cells even in the presence of oxygen [28]. Warburg determined that there is a tenfold increase of glucose consumption in cancer cells as compared to normal cells, and a twofold production of lactic acid as compared to that produced by normal tissue. Cancer cells are provided with several growth advantages like growth of cells in adverse microenvironment, generation of substrates for glycosylation reactions, and supply of precursors for biosynthetic reactions by aerobic glycolysis/enhanced glucose uptake [29, 30]. Recent reports indicate that mTOR activation is a key regulator of the Warburg effect leading to upregulation of glycolytic enzymes [31, 32]. Aerobic glycolysis is disadvantageous and detrimental as compared to oxidative phosphorylation due to the low ATP yield (only 2 mol ATP/mole of glucose while oxidative metabolism of glucose results in about 36 mol ATP/mole of glucose) as compared to investment as well as lactic acidosis that may result from Cori's cycle that follows aerobic glycolysis resulting in release of proteolytic enzymes and therefore local toxicity including cell death and extracellular matrix degradation [33, 34].
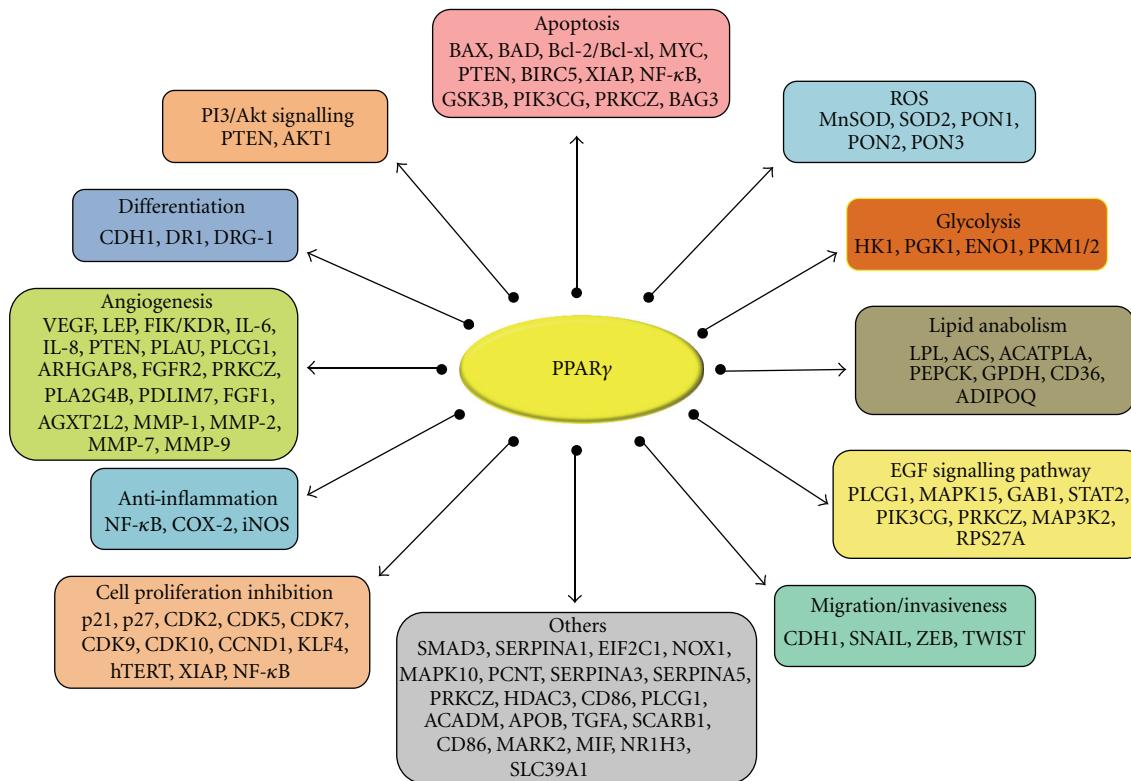
FIGURE 2: PPAR gamma gene targets and their pathways.

A recent report suggests that a relatively minor fraction (<30%) of a cancer cell's aerobic ATP production is derived from glycolysis according to mass balance analyses [35]. Conflicting evidence suggests that hydrogen ions production by glycolysis create the acidic environment responsible for degradation of the extracellular matrix, critical for facilitating tumor invasion into normal host tissue [36]. Adaptive advantages are also conferred by increased glycolysis (or pentose phosphate metabolism) if it allows excess pyruvate to be available for lipid synthesis or providing essential anabolic substrates, such as ribose for nucleic acid synthesis [37]. Glucose consumption through the pentose pathway may also provide essential reducing equivalents (NADPH) to reduce the toxicity of reactive oxygen species conferring resistance to senescence and anabolic substrates such as ribose for nucleic acid synthesis [38]. These evolutionary advantages can explain the remarkable prevalence of the glycolytic phenotype in human cancers and the otherwise puzzling observation that malignant cells remain glycolytic even in the presence of normoxia. This conceptual model of constitutive upregulation of glycolysis has been demonstrated by empirical studies and is consistently observed during the transition from premalignant lesions and invasive cancer [39, 40]. It is interesting to note that several of the glycolytic enzymes have isoforms which are expressed only in malignant cells and thus can be potential targets for therapy (Figure 3). This is important since aerobic glycolysis is an existing metabolic function in all eukaryotic cells and using normal isoforms as target for cancer therapeutics may lead to

cytotoxicity issues. Interestingly, hypoxia-mediated HIF-1 has been suggested to lead to the expression of specific isoforms of glycolytic enzymes and transporters through alternative splicing. Pre-mRNA splicing has been reported to play a core role in "orchestrating" cellular stress phrase to gene-expression profiles [41]. A multiphasic response including increased expression of components of the glycolytic pathways including membrane glucose transporters in a HIF-1-dependent manner is elicited by upregulation of the HIF system [42]. Concurrently, PPARγ activates a number of genes in tissues increasing glucose and lipid uptake and glucose oxidation, simultaneously decreasing free fatty acid concentration and insulin resistance. Hence, targeted therapies may be eventually led by understanding the molecular and physiological causes and consequences of upregulated glycolysis and modulation of these. In line with the above, cancer treatment strategies through the target of energy metabolism of cancer could include glucose deprivation, inhibition of the glycolytic pathway (3-bromopyruvate (3-BrPA)), glucose analogues (2-deoxyglucose (2DG)), inhibition of glucose transport (Imatinib), and exploitation of HIF (PX-478).

Here, it must be mentioned that glycolytic inhibitors in combination with other therapies have proven to be more promising than being alone as tumor cells and tumor microenvironment are very heterogeneous and cells within an invasive cancer may use a range of metabolic pathways including some in which oxidative metabolism of glucose or fatty acids contributes significantly to ATP production [43].
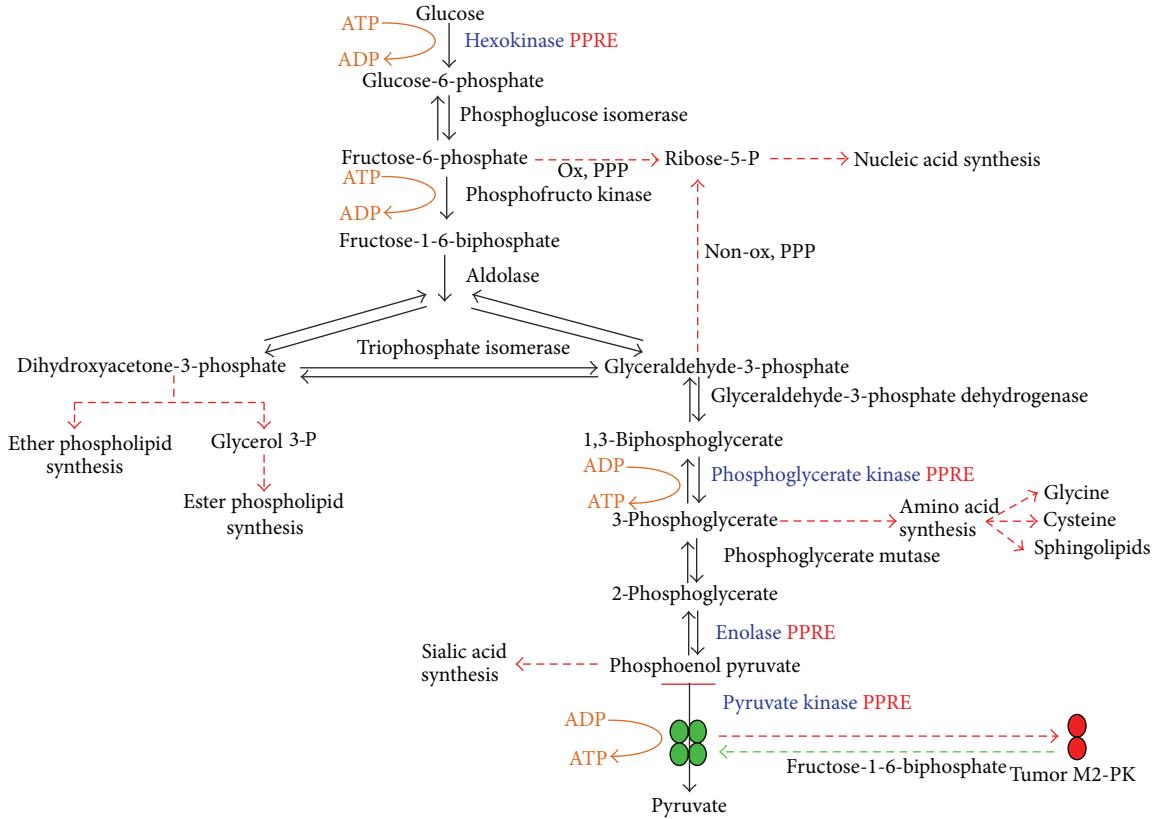
FIGURE 3: Tumor cells have altered glucose metabolism. Many glycolytic enzymes are ubiquitously expressed in cancers. One such glycolytic enzyme is pyruvate kinase type M2 whose levels are found to be elevated in human cancer biopsies, compared to adjacent normal tissues. PKM2 is a key regulator of the metabolic budget system in tumor cells which promotes the Warburg effect and tumor growth. This tumor specific PKM2 can be switched between dimeric and tetrameric forms in cancer cells. Dimeric PKM2 has a higher K_m value for the substrate PEP than the tetrameric form of PKM2 and is inactive at physiological concentrations of PEP. PKM2 is allosterically activated by the glycolytic metabolite fructose-1,6-biphosphate (FBP) and serine. This leads to accumulation of energy rich phospho metabolites upstream of glycolytic pathway which are then channelled to macromolecule biosynthesis via pentose phosphate pathway (PPP). These pathways include pyrimidine, glycerol, and serine/glycine biosynthesis (red arrows) instead of leading to oxidative metabolism for energy production thereby promoting cancer cell proliferation and tumor growth.

Moreover, enhanced glycolysis may be possible via different mechanisms such as gene amplification, increased gene expression, increased translation, posttranslational modification, and regulation by protein-protein interactions in the cytoplasm. Different cancers exploit different mechanisms to achieve increased glucose consumption.

3. Isoforms of Glycolytic Genes and PPARγ

Cancer cells are found to upregulate glucose transport and switch their main energy supply pathway from oxidative phosphorylation to glycolysis depending heavily on glucose as both energy and biosynthesis sources. Thus, cancer cells are more sensitive than normal cells to changes in glucose concentration [44, 45] and it is easier than normal cells to induce death in limited glucose supply and disruption of glycolysis [46]. These molecular and metabolic changes also provide targets for cancer treatment. Inhibiting either various steps of glycolysis or glucose transport, the first rate-limiting step leading to glycolysis, is likely to severely disrupt both

energy supply and biosynthesis processes inside cancer cells, resulting in reduction of proliferation rate and induction of apoptosis of cancer cells. Several glycolytic enzymes are predicted by us to have the PPRE site, suggesting their regulation by PPARγ (Figure 3).

The enzymes in glycolytic pathway and their isoforms are discussed below.

3.1. Hexokinases. They catalyze the first irreversible step of the glycolytic pathway for the phosphorylation of glucose to glucose-6-phosphate with consumption of ATP. Four important mammalian hexokinase isozymes that vary in subcellular locations and kinetics with respect to different substrates and conditions and physiological functions are known and designated as HK1-4 [47]. HK2, the predominant isoform overexpressed in malignant tumors, strategically binds to the outer mitochondrial membrane coupling ATP formation in mitochondria to the phosphorylation of glucose, thus conferring cancer cells with a highly glycolytic phenotype and ample biosynthetic precursor [48, 49]. In addition to its critical

metabolic role, HK2 can also promote cancer by repressing mitochondrial function on cell death, immortalizing cancer cells.

3.2. Fructose-2, 6-Bisphosphatase.

6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 3 (PFKFB3), is a bifunctional enzyme and is central to glycolytic flux. It is downstream to the metabolic stress sensor AMP-activated protein kinase (AMPK) that modulates glycolysis and possibly activates isoforms of PFKFB, specifically PFKFB3 expressed in tumor cells. It has been demonstrated that long-term low pH exposure induces AMPK activation, which results in the upregulation of PFKFB3 and an increase in its serine residue phosphorylation. Pharmacologic activation of AMPK is responsible for increase in PFKFB3 as well as an increase in glucose consumption, whereas inhibition of AMPK results in the downregulation of PFKFB3 and decreased glycolysis [50].

3.3. Pyruvate Kinase (PKM).

It converts phosphoenolpyruvate to pyruvate and regulates the rate-limiting final step of glycolysis. It has two specific isoforms: the adult isoform, PKM1, promotes oxidative phosphorylation and the PKM2 isoform, which promotes aerobic glycolysis and is expressed in embryonic and cancerous cells. The above isoforms are produced as a result of mutually exclusive alternative splicing of the PKM pre-mRNA that corresponds to inclusion of either exon 9 (PKM1) or exon 10 (PKM2) [51, 52]. We have recently shown that PKM2 is downregulated by PPARγ activation by 15d-PGJ$_2$, a PPAR-gamma ligand [53]. Concurrently, PGK1, another important enzyme at ATP generation step in glycolysis, has been reported by us to be downregulated by PPAR gamma upon activation by 15d-PGJ$_2$ [54].

4. pH Regulator NHE1

Cancer cells thrive in an acidic environment and do not survive in normal or more alkaline environment. Lactic acid production due to increased glycolysis by cancer cells makes the environment even more acidic. NHE1 is a ubiquitously expressed membrane phosphoglycoprotein comprising of 10–12 transmembrane segments (N-terminal) and a large cytoplasmic tail. NHE1 is reported to be involved in intracellular pH (pHi) homeostasis and cell volume regulation [55, 56]. Under physiological conditions, the Na$^+$/H$^+$ exchanger NHE1 extrudes one H$^+$ ion in exchange for one extracellular Na$^+$ ion. An alkaline pHi together with an acidic extracellular environment is associated with a transformed or tumorigenic phenotype, suggesting that active proton extrusion capabilities provide a twofold advantage to tumor cells: the alkaline pHi favours metabolic processes associated with cellular proliferation, whereas the acidic extracellular environment, a consequence of H$^+$ extrusion, enhances the invasive capacity of transformed cells [57]. The role of pHi and NHE1 in the regulation of tumorigenic and metastatic properties of tumor cells, however, remains unclear. Since NHE1 is activated upon growth factor stimulation, it has been suggested that NHE1 also plays a role in cellular proliferation [58]. In

addition, tumor cells deficient in NHE1 activity either do not grow or show severely arrested growth when implanted in immunodeficient mice [59, 60].

Interestingly, a recent report implicated the pH regulator, NHE1, in tumor cell growth is arrested by activated PPARγ, an interesting connotation considering that the activation of NHE1 is an oncogenic signal necessary for the development and maintenance of the transformed phenotype [57, 60, 61]. Also, it was recently reported that decrease in NHE1 expression led to tumor cell growth arrest, intracellular acidification, and sensitization to death stimuli [62]. These data support downregulation of NHE1 as a possibility for inducing growth arrest in cancer cells [9]. In light of the increased expression of PPARγ in breast cancer cell lines and its association with acidic intracellular pH, we hypothesized that, in addition to inhibiting NHE1 activity, ligand-induced activation of PPARγ could regulate NHE1 gene expression. Interestingly, our results corroborate with the data which reported that exposure of breast cancer cell lines expressing high levels of PPARγ to natural ligands of PPARγ significantly inhibited NHE1 gene expression compared with noncancerous cells or cancer cell lines expressing low levels of PPARγ [9, 63].

5. MnSOD as a Target for PPARγ

Cancer cells have higher levels of reactive oxygen species (ROS) than normal cells. They exhibit increased intrinsic ROS stress, due to oncogenic stimulation, increased metabolic activity, and mitochondrial malfunction [64]. The increased amounts of ROS in cancer cells may have significant consequences, such as stimulation of cellular proliferation, promotion of mutations and genetic instability, and alterations in cellular sensitivity to anticancer agents. It is logical to speculate that the biochemical and molecular changes caused by ROS may contribute to the development of a heterogeneous cancer cell population and the emergence of drug-resistant cells during disease progression. Cells have evolved several antioxidant defenses, including repair and detoxifying enzymes, and small scavenger molecules, such as glutathione. The intracellular ROS-scavenging system includes superoxide dismutases (SOD), glutathione peroxidase (GPx), peroxiredoxins (PRDXs), glutaredoxins, thioredoxins (TRXs), and catalases. In mitochondria, superoxide anion (O$_2^-$) can be dismutated to hydrogen peroxide (H$_2$O$_2$) by two enzymes, namely, copper-zinc superoxide dismutase (CuZnSOD) and manganese superoxide dismutase (MnSOD), that are present in the mitochondrial matrix and in the intermembrane space, respectively [65]. Once generated, H$_2$O$_2$ can be quenched by GPx in mitochondria, or by catalase in the cytosol. The expression of antioxidant enzymes is regulated by complex mechanisms, oxidative stress being a major factor that induces the adaptive expression of these enzymes [66]. Thus, increased ROS stress in cancer cells is likely to cause increased expression of SOD and other antioxidant enzymes. In fact, analysis of SOD protein expression in primary tissues from adenocarcinomas of the stomach and squamous cell carcinomas of the oesophagus showed a significantly higher MnSOD expression in the cancer cells compared to

normal mucosa cells [67]. The activities of SOD, glutathione peroxidase (GPx), and glutathione-S-transferase (GST) were increased significantly in the mitochondria of colorectal cancer tissues compared to adjacent normal tissues of the same subjects [68]. Increased SOD levels were also observed in breast cancer tissue from 23 patients [69]. Detection of MnSOD using specific antibody showed positive reactions with ovarian carcinomas and malignant brain tumors, but not with the respective normal control tissues [70]. Some studies further demonstrated a significantly increased expression of CuZnSOD (SOD1), MnSOD (SOD2), and catalase in chronic lymphocytic leukemia cells and ovarian cancer cells [71]. Increases in SOD1 and SOD2 have been observed in blood samples from patients with various types of leukemia [72]. Interestingly, leukemia regression was accompanied by a decrease in the serum MnSOD, suggesting that MnSOD in serum may serve as an indicator of disease activity. Analysis of SOD in blood samples from patients with ovarian cancer yielded conflicting results [73]. We reported human MnSOD as a PPARγ target gene and the downregulation of MnSOD gene expression *in vitro* by PPARγ agonists [9].

6. Glycolysis, Diabetes, Obesity, Cancer, and PPARγ

The nuclear transcription factor PPARγ is highly expressed in adipose tissue and plays a central role in adipocyte function, fat storage, and lipid metabolism. PPARγ activators are commonly used to treat patients with type 2 diabetes who share metabolic abnormalities including excessive and inflamed adipose tissue [74], particularly in visceral depots [75], elevated circulating concentrations of nonesterified fatty acids (NEFA), triglycerides, glucose, insulin, and inflammatory mediators and reduced concentrations of adiponectin and high-density lipoprotein cholesterol (HDL-C). On the other hand, key cancer-related oncogenes type I receptor tyrosine kinase HER2- (*erb*B-2-) dependent endogenous fatty acid (FA) constitutive upregulation and biogenesis catalyzed by lipogenic enzymes such as fatty acid synthase (FASN) [76, 77], constitutes an oncogenic stimulus that drives normal epithelial cells progression toward malignancy and has been reported to provide a "lipogenic benefit" in terms of enhanced breast cancer cell proliferation, survival, chemoresistance, and metastasis [78]. This would require a constant supply of precursors, energy, and reducing equivalent required for FASN-driven lipogenesis. Moreover, excess of the end product of *de novo* FA synthesis, namely, palmitate (and other palmitate-like saturated FAs), is toxic to cells because of its ability to generate a variety of apoptotic signals involving either the production of ROS or the synthesis of ceramide. Indeed, disturbance in lipogenic balance caused by the accumulation of FAs and neutral lipids in nonadipose tissue stimulates lipolysis and apoptosis [79, 80]. Moreover, palmitate excess could have feedback to inhibit endogenous FA synthesis [81]. Also, PPARγ, in HER2-positive cancer cells, which produce high levels of endogenous fat, helps to convert FAs to triglycerides, thus allowing these cells to avert the cell death resulting from endogenous palmitate-related lipotoxicity [82]. It must be noted here that PPARγ

has been reported to directly interact with SIRT1 (human silent information regulator type 1-deacetylase protein) and inhibit SIRT1 activity, forming a negative feedback and self-regulation loop. Also, the transcriptional activity of PPARγ is regulated through deacetylation by SIRT1. This association of SIRT1 and PPARγ together with the transcriptional modulation of SIRT1 appears to be important in the senescence/aging process controlled by PPARγ [83].

6.1. Diabetes, Obesity, Cancer, and PPARγ. Epidemiologic evidence suggests that people with diabetes are at significantly higher risk for many forms of cancer [84]. Earlier on, Liao et al. has indicated that diabetes can be considered as a risk factor for breast cancer [85]. Boyle et al. recently investigated the association between occurrence of diabetes and breast cancer risk and observed that the risk of breast cancer in women with type 2 diabetes is increased by 27%, a figure that decreased to 16% after adjustment [86].

Also, obesity has been reported as a risk factor for breast cancer [87]. Interestingly, obesity is also a risk factor for type-2 diabetes [87] may be due to link between diabetes and cancer in metabolic syndrome. However, the physiological mechanism by which these risk factors interact to promote tumorigenesis is not understood. Computational analyses by us and generation of gene-disease network suggests that PPARγ is implicated in pathology of several diseases including cancer, diabetes, and obesity (Figure 4). These results are in accordance with several isolated reports on their involvement in individual disorders.

PPARs are ligand activated transcription factors and the PPARγ receptor can be activated by endogenous ligands, for example, prostaglandin D2 (PGD2), 15-deoxy prostaglandin J2 (15dPGJ2), or 15-hydroxyeicosatetraenoic acid (15-HETE) [88, 89]. Synthetic ligands for PPARγ include insulin sensitizing antidiabetic thiazolidinediones (TZD); troglitazone (TGZ), rosiglitazone (RGZ), ciglitazone (CGZ), or pioglitazone (PGZ) [90–92], and nonsteroidal anti-inflammatory compounds indomethacin, ibuprofen, flufenamic acid, or fenoprofen [24] are commonly known as PPARγ ligands. Although, there is a rationale for the use of TZDs in patients with type 2 diabetes mellitus and they have been seen to be very effective, clinical studies have produced conflicting data, and several important aspects of PPARγ action remain confusing and unresolved. Interestingly, there is no general deficiency in PPARγ function in obesity or insulin-resistant states. Hence, it is not clear why synthetic activation of a receptor should give such dramatic antidiabetic effects. Moreover, variations in ligand binding efficiencies of PPAR gamma ligands do not correlate with potency of the drug (ligand) to be antidiabetic. For example, some ligands with full agonist action, like rosiglitazone, have powerful insulin sensitizing actions, while other compounds with poor agonist activities, such as the benzylindole MRL24, retain very good antidiabetic effects [93].

In addition to acting as insulin sensitizers, PPAR agonists mediate *in vitro* and *in vivo* pleiotropic anticancer effects. The insulin-like growth factor (IGF) system has a role in cancer development and progression and in resistance to drug-induced apoptosis. It is now well established that the
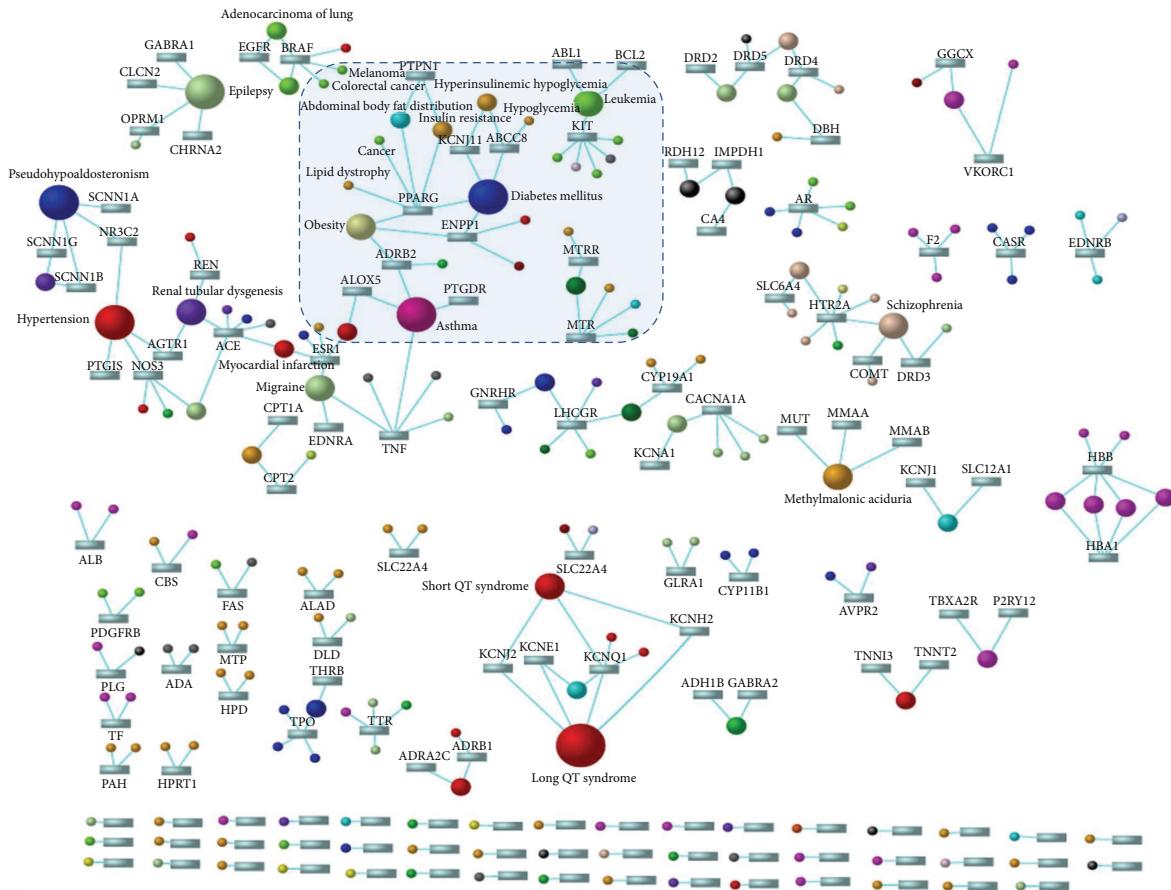
FIGURE 4: PPAR gamma disease gene network. Rectangles represent genes and circles represent diseases. Only genes involved in more than one disease are shown.

IGF system is dysregulated/overactivated (resulting from receptor and ligand abnormal expression) in a variety of human malignancies. It has also been shown that a high level of circulating insulin (hyperinsulinemia) is associated with an increased risk for a number of malignancies [94]. Moreover, hyperinsulinemia is closely associated with obesity and type 2 diabetes [95]. Thiazolidinediones (TZDs) downregulate both the PI3 K and the Ras pathway, which are the two main signalling pathways downstream receptors of the IGF system, and they also ameliorate insulin resistance and lower circulating levels of insulin and free IGF-I [96]. Moreover, TZDs, and other PPAR-agonists, such as the prostanoid 15d-PGJ2 [97], induce a variety of favorable changes (growth arrest, apoptosis, and/or partial redifferentiation) in several malignancies, including liposarcoma, and cancers of the breast, colon, pancreas, and prostate [98–101]. Oxidants and inflammatory mediators such as tumour necrosis factor-alpha (TNF-alpha) activate nuclear factor kappa B (NF-kappaB) and activator protein-1 (AP-1) transcription factors, and enhance the expression of both proinflammatory and protective antioxidant genes in several diseases including cancer and atherosclerosis [102, 103]. NF-kappaB is reported to promote breast cancer cell migration and metastasis by inducing the expression of the chemokine receptor CXCR4 [104]. Also, NF-kappaB regulates the expression of a large number of genes, including growth factors, proinflammatory cytokines (e.g., TNFa, IL-6, and IL-1b), adhesion molecules (e.g., VCAM-1, P-selectin), and others such as iNOS and COX-2 [105]. PPAR activation by agonists is reported to regulate inflammatory responses [106], cell proliferation and differentiation, and apoptosis [107]. PPARγ regulates expression (transcriptional level) of proinflammatory mediators such as inhibitor nuclear factor-κB (NF-kappaB), signal transducers and activators of transcription (STAT)-1, and activating protein-1 (AP-1) activating signals [108]. Since, both PPARγ activator and NF-KappaB are transcription factors, it was proposed that PPARγ likely acts through physical interaction with NF-kappaB, resulting in the inhibition of transcriptional activation [109]. The suppressive action of PPARγ on NF-kappaB was suggested to be related to its competition for limited availability of transcriptional coactivators [110] and it was suggested that due to this limitation of cofactors, neither NF-kappaB nor AP-1 could activate their target genes (e.g., iNOS or TNFa) [111]. Thus, transrepression appears to be one viable mechanism by which PPARγ activators exert their anti-inflammatory effects on age-induced inflammation and oxidative stress via the downregulation of NF-kappaB.

Thus, PPAR gamma agonists have been reported as new and potentially efficacious treatment of inflammation, diabetes, obesity, cancer, AD, and schizophrenia [112]. The use

of synthetic PPARγ ligands as drugs and their recent withdrawal/restricted usage highlight the lack of understanding of the molecular basis of these drugs, their off-target effects, and their network. These data further underscores the complexity of nuclear receptor signalling mechanisms. Thus, there is a need to continue enhancing our understanding of the complexities of nuclear receptor pharmacology and a need to view the functions of this family of transcription factors in detail supported by clinical trials and adverse side effects data as tenable well beyond traditional discreet categories of agonism and antagonism which will open new doors to using PPAR gamma as a target.

Authors' Contribution

M. K. Sakharkar, B. Shashni, and K. R. Sakharkar contributed equally to this paper.

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