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Review Article

Peroxisome Proliferator-Activated Receptor γ and PGC-1α in Cancer: Dual Actions as Tumor Promoter and Suppressor

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Peroxisome proliferator-activated receptor γ (PPARγ) is part of a nuclear receptor superfamily that regulates gene expression involved in cell differentiation, proliferation, immune/inflammation response, and lipid metabolism. PPARγ coactivator-1α (PGC-1α), initially identified as a PPARγ-interacting protein, is an important regulator of diverse metabolic pathways, such as oxidative metabolism and energy homeostasis. The role of PGC-1α in diabetes, neurodegeneration, and cardiovascular disease is particularly well known. PGC-1α is also now known to play important roles in cancer, independent of the role of PPARγ in cancer. Though many researchers have studied the expression and clinical implications of PPARγ and PGC-1α in cancer, there are still many controversies about the role of PPARγ and PGC-1α in cancer. This review examines and summarizes some recent data on the role and action mechanisms of PPARγ and PGC-1α in cancer, respectively, particularly the recent progress in understanding the role of PPARγ in several cancers since our review was published in 2012.

1. Introduction

Peroxisome proliferator-activated receptor γ (PPARγ) belongs to a nuclear hormone receptor superfamily that regulates the expression of genes involved in cell differentiation, proliferation, the immune/inflammation response, and lipid metabolism [1]. Ligand binding and activation of PPARγ result in heterodimer formation with the retinoid X receptor (RXR) and binding to a PPAR response element (PPRE) to regulate the transcription of numerous target genes [2, 3]. PPARγ consists of a ligand-independent transcriptional activation domain, DNA binding domain (DBD), hinge region for cofactor docking, and ligand binding domain (LBD) (Figure 1(a)). Two PPARγ isoforms are known, PPARγ1 and PPARγ2 [4, 5]. PPARγ2, which is generated by alternative splicing, contains an additional 28 amino acids in mice and 30 amino acids in humans, at the N-terminus compared to PPARγ1. PPARγ2 is expressed selectively in adipose tissue and plays an important role in adipocyte differentiation, lipid storage in white adipose tissue, and energy dissipation in brown adipose tissue [4, 6]. PPARγ1 is expressed in the colon, immune system, and hematopoietic cells and plays an important role in the control of inflammation, macrophage maturation, and embryo implantation. PPARγ1 is a molecular target of antidiabetic thiazolidinediones [7, 8]. Our previous review summarized the role and action mechanisms of PPARγ in colorectal cancer [8], but the role of PPARγ in cancer is still debated. Thus, this review updates the progress in understanding the role and molecular mechanisms of PPARγ in cancer.

The PPARγ coactivator-1 (PGC-1) family is composed of PGC-1α, PGC-1β, and PGC-1-related coactivator (PRC). PGC-1α was initially identified as a transcriptional coactivator involved in mitochondrial function and thermogenesis in brown fat [9]. PGC-1β and PRC were discovered in sequence homology searches [10–13]. The PGC-1 family members have similar activity to increase mitochondrial function when overexpressed and have a related modular structure (Figure 1(b)). The most common functional domains are shared between PGC-1α and PGC-1β. The N-terminal activation domain interacts with several transcriptional coactivators, including p300 and steroid receptor coactivator-1 (SRC-1). A domain involved in inhibition of PGC-1 activity

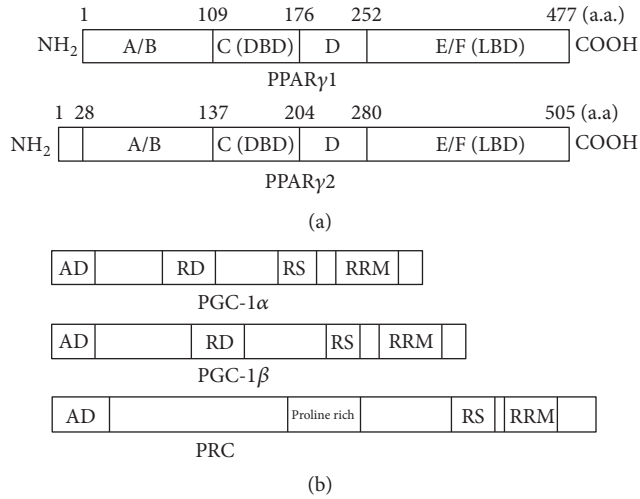

Figure 1: Structure of PPARγ (a) and the PGC-1 family (b). (a) A/B, transcriptional activation domain; C, DNA binding domain (DBD); D, hinge region; E/F, ligand binding domain (LBD). (b) AD, transcriptional activation domain; RD, transcriptional repression domain; RS, arginine/serine rich domain; RRM, RNA binding domain.

is located adjacent to the N-terminal region. Through several LXXLL motifs, the N-terminal half of PGC-1 interacts with many transcription factors, whereas the C-terminal end of PGC-1 interacts with the TRAP/DRIP/Mediator complex. PGC-1α has a Ser/Arg-rich domain and RNA binding motif that plays an important role in mRNA splicing [14, 15]. Because PGC-1α was described initially as a PPARγ interacting protein, some investigators recently studied the expression and clinical significance of PGC-1α in cancer [16, 17]. However, the expression and the roles of PGC-1α in cancer were not significantly related to the expression of PPARγ. In addition, controversies still exist whether PGC-1α acts as a tumor promoter or a tumor suppressor in cancer. This review focuses on the expression and actions of PGC-1α in order to understand the clinical significance of PGC-1α expression in cancer.

2. The Role and Action Mechanisms of PPARγ in Cancer

PPARγ is expressed in various malignant tissues, including bladder, colon, prostate, and breast cancer [18–22]. Natural ligands that activate PPARγ include long-chain polyunsaturated fatty acids, eicosanoids, components of oxidized low density lipoproteins (oxLDLs), and 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) [23]. Synthetic ligands include the antidiabetic thiazolidinedione (TZD) class of drugs [23]. An increasing number of studies have focused on the effect of PPARγ in cancer using natural and synthetic ligands for PPARγ and overexpression experiments. However, the role of PPARγ in cancer is still debated. Thus, this review updates the role and action mechanisms of PPARγ in cancer since our review published in 2012.

2.1. PPARγ as a Tumor Suppressor in Cancer. Our previous review summarized that PPARγ inhibits cell proliferation and induces apoptosis through the upregulation of Phosphatase and Tensin Homolog (PTEN), downregulation of survivin, downregulation of X-linked inhibitor of apoptosis (XIAP), suppression of NF-κB and glycogen synthase kinase (GSK)-3β, upregulation of cyclin-dependent kinase (CDK) inhibitors, downregulation of CDK and cyclin D1, downregulation of COX-2, upregulation of Krüppel-Like Factor 4 (KLF4), upregulation of Bax, downregulation of Bcl-2, and inhibition of telomerase activity and hTERT expression through modulation of the Myc/Mad/Max network [8]. This review briefly describes and summarizes new molecular mechanisms of PPARγ-related tumor suppression since 2012 (Table 1, Figure 2).

Understanding the role of PPARγ in cancer was improved by developing new synthetic and natural ligands of PPARγ and performing overexpression and knockdown experiments. PPARγ agonist troglitazone inhibits colon cancer cell growth through the inactivation of NF-κB by suppressing GSK-3β activity [24]. Emerging data suggest that PPARγ acts as a tumor suppressor by inactivating NF-κB through different mechanisms. For example, Lee et al. demonstrated that 4-O-methylhonokiol (MH), a PPARγ agonist, has antitumor activity in prostate cancer through increased PPARγ activity and p21-mediated suppression of NF-κB activity as observed by the loss of MH-induced growth inhibition and NF-κB inhibition in a p21 siRNA knockdown experiment [25]. In addition, overexpression of PPARγ was shown to inhibit cell proliferation and tumor growth via degradation of NF-κB by acting as an E3 ligase [26]. Hou et al. demonstrated that PPARγ inhibits mucin 1- (MUC1-) C-mediated cell proliferation via MUC1-C ubiquitination and degradation [27]. MUC1-C is known as an oncoprotein and interacts with IκB kinase, NF-κB/p65, and signal transducer and activator of transcription factor 3 (Stat3), p53, or BAX in order to activate the downstream pathway associated with tumor growth [47–52]. Efatutazone, a third-generation PPARγ agonist, has been reported to inhibit esophageal squamous cell

Table 1: The role and action mechanisms of PPARγ as a tumor suppressor.

Experimental system		Role and action mechanisms	References
Modification	Cell type		
Troglitazone treatment (PPARγ ligand)	Human colon cancer SW620, HCT116 cells	Inhibition of cell proliferation; induction of apoptosis; inactivation of NF-κB by suppression of GSK-3β	[24]
PPARγ activation by 4-O-methylhonokiol treatment	PC3, LNCap prostate cancer cells, PC3 xenografts	Inhibition of cell proliferation and tumor growth; induction of apoptosis; p21-mediated suppression of NF-κB activity	[25]
PPARγ overexpression	Human colon cancer HT-29 cells	Inhibition of cell proliferation and tumor growth; ubiquitination and degradation of NF-κB by PPARγ	[26]
PPARγ overexpression	Human colon cancer HT-29 cells	Inhibition of cell proliferation; ubiquitination and degradation of MUC1-C by PPARγ	[27]
PPARγ activation by efatutazone treatment (third-generation PPARγ agonist)	TE-4, TE-8, TE-11, TE-6 esophageal squamous cell carcinoma (ESCC) cells; TE-4 xenografts	Inhibition of cell proliferation and tumor growth; increased p21 protein levels by inactivation of Akt	[28]
Pioglitazone and 6-OH-11-O-hydroxy phenanthrene (PPARγ and RXR agonist treatment)	Breast cancer MCF-7 cells, breast cancer associated fibroblast	Inhibition of cancer stem cell survival; inhibition of IL-6 promoter and reduced MMP-2, MMP-9 expression and activity	[29]
Pioglitazone treatment (PPARγ ligand)	Chronic myeloid leukemia cells, leukemia stem cell (LSC)	Inhibition of cancer stem cell survival; decreased expression of STAT5 and HIF-1α	[30]
PPARγ overexpression by PPARγ plasmid	Gastric cancer cell lines (MKN-28, SGC-7901, BGC-823)	Inhibition of cell proliferation and migration; downregulation of TERT and ENAH by inhibition of β-catenin	[31]
PPARγ activation by troglitazone, PPARγ siRNA transfection	Human breast cancer cell lines (MCF-7, MDA-MB-231)	Inhibition of cell proliferation; upregulation of tumor suppressor *Cyld*	[32]
PPARγ activation by rosiglitazone, PPARγ inhibition by GW9662	Human breast cancer cell lines (MCF-7, MDA-MB-231)	Inhibition of cell migration and invasion; downregulation of CXCR4 gene expression	[33]

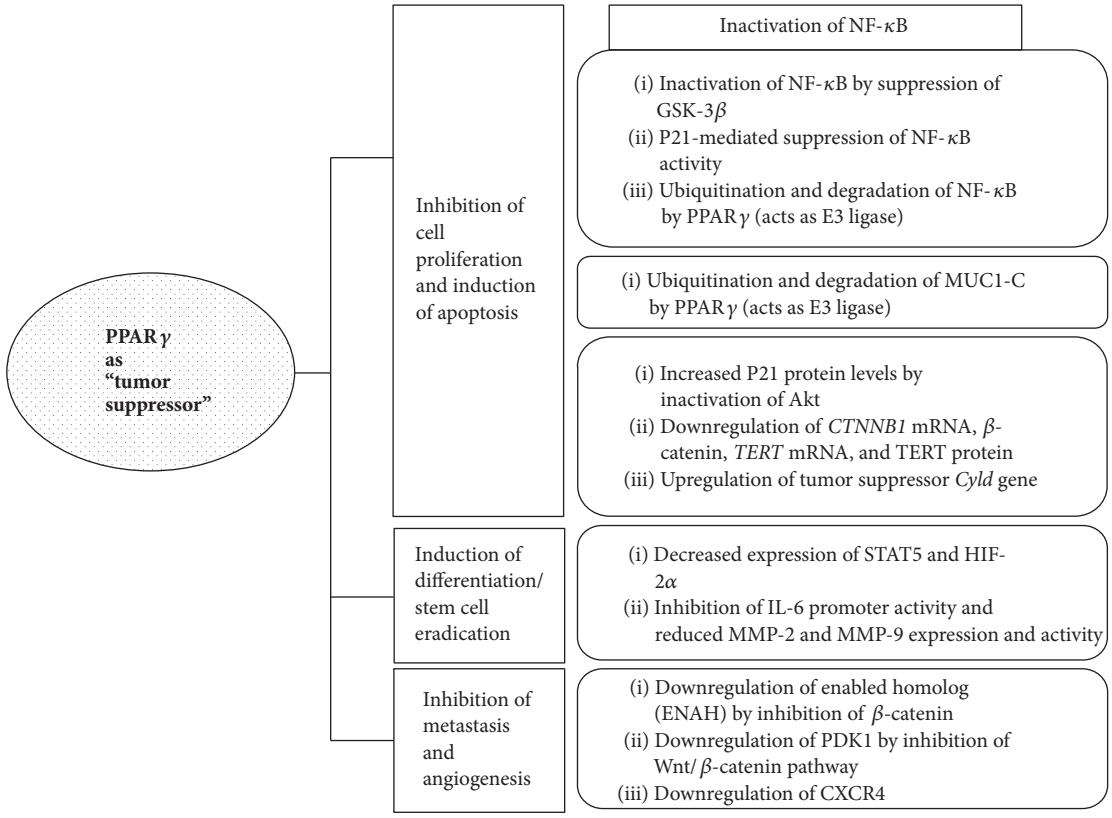

Figure 2: Action mechanisms of PPARγ as a tumor suppressor. NF-κB, nuclear factor-κB; GSK-3β, glycogen synthase kinase 3-β; MUC1-C, mucin 1-C; TERT, telomerase reverse transcriptase; STAT5, signal transducer and activator of transcription factor 5; HIF-2α, hypoxia inducible factor-2α; IL-6, interleukin-6; PDK1, pyruvate dehydrogenase kinase 1.

carcinoma (ESCC) cell proliferation *in vitro* and *in vivo* through increased p21Cip protein levels via inactivation of Akt [28].

Several recent studies have shown that PPARγ agonists inhibit the survival of cancer stem cells (CSCs) [29, 30, 53–55]. PPARγ and RXR agonists were demonstrated to inhibit interleukin-6 (IL-6) promoter activity and reduce MMP-2 and MMP-9 expression and activity in tumor-associated fibroblasts [29]. Prost et al. demonstrated that pioglitazone, a PPARγ agonist, eradicates CSCs via the decreased expression of STAT5 and HIF-2α in chronic myeloid leukemia [30].

The Wnt/β-catenin signaling pathway plays an important role in the occurrence and development of cancer [56, 57]. Guo et al. reported that PPARγ overexpression inhibits the proliferation and migration of gastric cancer cells through downregulation of telomerase reverse transcriptase (TERT) and enabled homolog (ENAH) via inhibition of β-catenin [31]. Mammalian enabled (Mena), encoded by *ENAH*, is an actin-regulatory protein involved in controlling cell motility and cell-cell adhesion, which are important for the development of metastatic potential [58]. *TERT* and *ENAH* are new targets of the Wnt/β-catenin signaling pathway [59, 60]. Recently, activation of canonical Wnt signaling was reported to directly act on aerobic glycolysis and increase vessel formation in colon cancer through the Wnt target gene pyruvate dehydrogenase kinase 1 *(PDK1)* [61]. Via PDK1 activation, pyruvate is converted into acetyl-CoA, which enters the TCA cycle and is converted into citrate, which stimulates protein synthesis. Accumulation of metabolic intermediates (such as aspartate, glycine, serine, and ribose) in cells promotes de novo nucleotide synthesis, contributing to growth and proliferation [62]. In addition, blocking the Wnt pathway decreases PDK1 expression via transcriptional regulation and inhibits *in vivo* tumor growth [61].

Pseftogas et al. reported that PPARγ activation has a tumor suppressive effect by upregulating the expression of tumor suppressor *Cyld*, as the *Cyld* promoter has PPARγ binding sites [32]. *Cyld* was identified as a tumor suppressor gene that is causally associated with the development of inherited cylindromas [63]. The gene encodes a protein (CYLD) possessing a carboxyl-terminal ubiquitin-specific protease domain that selectively hydrolyzes K63- and M1-linked polyubiquitin chains [64]. A number of studies have suggested a role for CYLD in the growth suppression of different types of cancer cells, such as colon, hepatocellular, lung, melanoma, and breast cancer (reviewed in [65]). CYLD can inhibit several growth and antiapoptotic signaling pathways, including the NF-κB, JNK, p38, Wnt, Akt, and Notch pathways [65].

Rovito et al. demonstrated that PPARγ activation downregulates CXCR4 gene expression through recruitment of the silencing mediator of retinoid and thyroid hormone

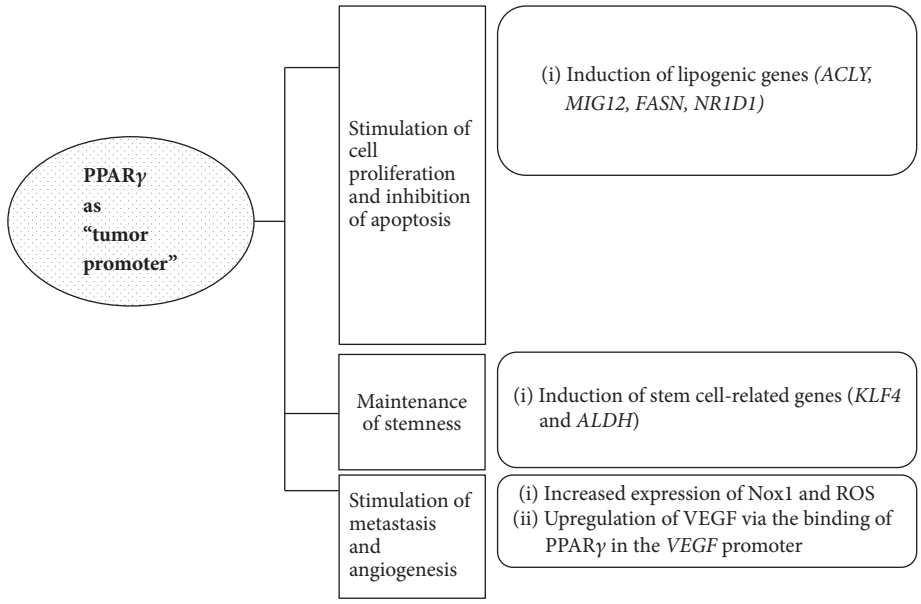

Figure 3: Action mechanisms of PPARγ as a tumor promoter. ACLY, ATP citrate lyase; MIG12, midline-1-interacting G12-like protein; FASN, fatty acid synthase; NR1D1, Rev-ErbAα; KLF4, Krüppel-Like Factor 4; ALDH, aldehyde dehydrogenase; Nox1, NADPH oxidase 1; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

receptor (SMRT) corepressor to PPRE within the CXCR4 promoter and then inhibits breast cancer cell migration and invasion [33]. CXCR4, a seven-transmembrane G-protein-coupled receptor for stromal-cell derived factor-1α (SDF-1α), has been shown to be expressed in human breast cancer cells, and activation of the SDF-1α/CXCR4 axis is important in breast cancer migration and metastasis [66, 67].

2.2. PPARγ as a Tumor Promoter in Cancer. Our previous review described that PPARγ has tumor-promoting activity through the upregulation of β-catenin and c-Myc expression, upregulation of COX-2, upregulation of the expression of vascular endothelial growth factor (VEGF) and VEGF receptors, and upregulation of MMP-1 [8]. This review briefly introduces the action mechanisms of PPARγ as a tumor promoter (Figure 3).

Recently, increasing evidence has indicated that PPARγ acts as a tumor promoter [68–74]. Downregulation of PPARγ by siRNA knockdown or treatment with PPARγ antagonist GW9662 has been shown to inhibit the growth of cancer cells, suggesting a tumor-promoting effect for PPARγ in these cells [68–70]. PPARγ was shown to protect ErbB2-positive breast cancer cells from palmitate-induced toxicity [75]. In addition, PPARγ was demonstrated to play a crucial role in the maintenance of stemness in ErbB2-positive breast cancer cells; PPARγ antagonist GW9662 induces apoptosis and inhibits tumorsphere formation and tumor formation through the inhibition of lipogenic genes *(ACLY, MIG12, FASN,* and *NR1D1)* and stem cell-related genes (*KLF4* and *ALDH*) [71]. CSCs have been identified as subpopulations of cells within tumors that promote tumor growth and recurrence [76–78].

Kesanakurti et al. demonstrated that PPARγ is involved in radiation-induced epithelial-to-mesenchymal transition (EMT) in glioma by interacting with p21-activated kinase 4 (PAK4), resulting in increased Nox1 expression and reactive oxygen species (ROS) [72]. EMT is a developmental transdifferentiation program facilitating the formation of highly motile cells with stem cell characteristics [79, 80]. EMT is also involved in increased metastatic potential and treatment resistance in cancer [81, 82]. The PAKs are a family of serine/threonine kinases involved in embryonic development, cytoskeletal remodeling, cell motility, and cell proliferation [83, 84], and aberrant expression of PAK4 has been shown to promote cancer cell proliferation and invasion [85–87].

A recent study using PPARγ siRNA showed that PPARγ suppression inhibits cell proliferation, colony formation, and tumorigenicity *in vivo* [73]. In addition, PPARγ upregulated VEGF expression through the binding of PPARγ in the promoter region of *VEGF* in prostate cancer cells [73]. Patitucci et al. demonstrated that PPARγ activation is involved in steatosis-associated liver cancer and provided evidence supporting the pharmacological modulation of hepatic PPARγ activity as a therapeutically relevant strategy in hepatic malignancy associated with activated Akt2 and PPARγ signaling [74].

3. The Role and Action Mechanisms of PGC-1α in Cancer

Many studies have examined the role of PGC-1α in cancer by observing its expression in several cancers and performing PGC-1α overexpression and siRNA knockdown experiments. PGC-1α expression has been shown in some studies to be

decreased in some types of cancer, including colon [88], breast [89], and ovarian cancer [41], whereas other studies have shown that PGC-1α expression is increased in cancer [17, 90]. Even though many studies have been published, the role of PGC-1α in cancer is still controversial. Therefore, this review describes the role and action mechanisms of PGC-1α in cancer (Table 2).

3.1. Tumor-Promoting Functions of PGC-1α. As described above, PGC-1α is a regulator of PPARγ activity. Thus, the abnormalities in PGC-1α expression may affect PPARγ function. However, there was little report supporting that PGC-1α expression directs PPARγ activity in cancer. Thus, this review focuses on the role of PGC-1α, independent of the role of PPARγ in cancer. Literature works supporting the tumor-promoting functions of PGC-1α have increased [17, 34–40, 42, 91–93]. Shiota et al. showed that PGC-1α promotes cell growth through the activation of androgen receptor in prostate cancer cells by observing cell growth inhibition with PGC-1α knockdown experiments [17]. In addition, PGC-1α was increased in tumor samples from arsenic-induced skin cancer patients and may be associated with increased cell proliferation and enhanced mitochondrial biogenesis [34]. Bhalla et al. showed that PGC-1α promotes carcinogenesis and tumor growth through the induction of lipogenic enzymes (acetyl-CoA carboxylase and fatty acid synthase) using genetically modified PGC-1α mice [35]. That study demonstrated that PGC-1α knockout mice had decreased chemically induced liver and colon carcinogenesis, suggesting that PGC-1α may stimulate carcinogenesis [35]. Similarly, Shin et al. first demonstrated that overexpression of PGC-1α enhances cell proliferation and tumorigenesis via the upregulation of Sp1 and acyl-CoA binding protein [36]. It was also reported that PGC-1α overexpression leads to increased antioxidant enzymes (catalase, superoxide dismutase) and decreased ROS-induced apoptosis [36]. Similarly, PGC-1α knockdown significantly decreased cell number and induced apoptosis in PGC-1α positive melanoma cell lines, suggesting that PGC-1α is crucial in the survival of PGC-1α positive melanoma cells [37]. In addition, superoxide dismutase 2 protein levels were decreased in PGC-1α depleted melanoma cells. Moreover, ectopic expression of PGC-1α in melanoma cells increased the expression of ROS detoxifying genes. These data support the hypothesis that PGC-1α plays an important role in activating the ROS detoxification gene program to maintain melanoma cell survival [37]. Vazquez et al. also demonstrated that there was a significant reduction in tumor size in PGC-1α depleted cells, implying PGC-1α may be important in tumor progression [37]. De novo lipogenesis is a distinctive anabolic feature of malignant cells [94]. Carbons from glucose and glutamine supply cytoplasmic citrate for fatty acid synthesis with the help of lipogenic enzymes [94]. Glutamine can serve as an anaplerotic mitochondrial fuel and seems to be important for tumor survival [95]. In ErbB2-positive breast cancer cells, the PGC-1α/ERRα complex directly regulates the expression of glutamine metabolism enzymes, leading to the provision of glutamine carbons to de novo fatty acid synthesis [38]. PGC-1α overexpression, or ERRα activation, confers growth advantages of breast cancer cells even under limited nutrients, supporting the correlative clinical data that high expression of PGC-1α is associated with poor prognosis, possibly related to the activation of its downstream glutamine pathway target genes [38]. It was reported that PGC-1α expression is affected by various transcriptional pathways. One example is that melanocyte-lineage transcription master regulator and oncogene MITF activated PGC-1α expression in melanoma [37, 91]. The decrease in mitochondrial membrane potential and increased ROS production with a decrease in glutathione, cystathionine, and 5-adenosylhomocysteine were observed in PGC-1α-depleted melanoma cell lines, suggesting that intrinsic apoptotic pathway is activated in PGC-1α-depleted melanoma cells [37]. Another example is that the androgen receptor-AMP-activated protein kinase (AMPK) signaling axis increased expression of PGC-1α to drive growth advantages in prostate cancers [39]. It was also shown that PGC-1α expression was significantly higher in lung adenocarcinomas with wild type p53 than in tumors with mutant p53 [40]. Cell proliferation was inhibited by PGC-1α siRNA knockdown experiments in H1944 lung adenocarcinoma cells [40]. In metabolic stress conditions, PGC-1α was shown, in complex with p53, to coactivate the transcription of cell cycle inhibitors, while it was also shown to promote the expression of genes related to mitochondrial biogenesis. These two functions are cooperative processes that promote cell survival. Moreover, oxidative stress in PGC-1α knockdown cells resulted in p53-induced apoptosis [96]. In turn, it was also shown that increased expression of PGC-1α might prevent p53-induced cell death by maintaining an adequate balance between oxidative phosphorylation and glycolysis [97].

Some studies have examined the effect of PGC-1α on angiogenesis. PGC-1α has been reported to activate the production of VEGF through the estrogen-related receptor α-(ERRα-) dependent pathway [98]. PGC-1α was shown to regulate HIF-1α activity. Increased PGC-1α expression enhances oxygen consumption, resulting in decreased local oxygen tension and increased HIF-1α stability [99]. In addition, HIF-2α is a transcriptional target of PGC-1α, even though the involved transcriptional mechanism is not clear [100]. ERRα is overexpressed in many cancers and its inhibition reduces cell proliferation. Recent studies suggest an important role for the interaction between PGC-1α and ERRα in cancer (reviewed in [15]). Kinase suppressor of ras 1 (KSR1), a molecular scaffold of the Raf/MEK/extracellular signal-regulated kinase (ERK) cascade, has been demonstrated to promote oncogenic Ras-dependent anchorage-independent growth through the activation of PGC-1α and ERRα [92]. Interestingly, recent study shows that PGC-1α plays an important role in the metastatic switch. LeBleu et al. demonstrated that circulating mammary epithelial cancer cells exhibit increased PGC-1α expression, enhanced mitochondrial biogenesis, and oxidative phosphorylation, which may contribute to distant metastasis and poor patient outcome [93]. In addition, PGC-1α knockdown decreased ATP production, reduced actin cytoskeleton remodeling, lowered anchorage-independent survival, and decreased intra-/extravasation, which are all checkpoints that prevent metastasis in MDA-MB-231 breast cancer and B16F10 melanoma cells [93]. LeBleu et al. also

Table 2: The role and action mechanisms of PGC-1α in cancer.

Experimental system		Role and action mechanisms	References
Modification	Cell type		
Tumor-promoting functions of PGC-1α			
PGC-1α knockdown	Human prostate cancer PC3, LNCap cells	Stimulation of cell proliferation; activation of androgen receptor	[17]
Increased PGC-1α expression in arsenic-induced skin cancer	Skin cancer	Stimulation of cell proliferation; enhanced mitochondrial biogenesis	[34]
Pgc-1α knockout and knockdown by lentivirus-based PGC-1α shRNA	Human colorectal cancer cell line (Colo205)	Stimulation of carcinogenesis and tumor growth; induction of lipogenic enzymes	[35]
PGC-1α overexpression by PGC-1α plasmid	Human embryonic kidney cells, human colorectal cancer SNU-C4 cells, xenograft model	Stimulation of cell proliferation and tumorigenesis; upregulation of Sp1 and ACBP; upregulation of antioxidant enzyme (catalase, SOD)	[36]
PGC-1α shRNA knockdown	Human melanoma PGC-1α-positive A375 cells, xenograft model	Inhibition of apoptosis; decreased ROS production, induction of ROS detoxifying enzymes	[37]
Increased PGC-1α expression in breast cancer cell	Breast cancer cell	Stimulation of cell proliferation; enhanced glutamine-mediated lipid biosynthesis	[38]
Pgc-1α shRNA knockdown	Human prostate cancer cell line (C4-2 cells)	Stimulation of cell proliferation; increased mitochondrial biogenesis	[39]
PGC-1α shRNA knockdown and PGC-1α overexpression	Human breast cancer cell, human melanoma cells	Stimulation of cell proliferation, increased invasion; increased mitochondrial biogenesis and oxidative phosphorylation	[40]
Anticancer functions of PGC-1α			
PGC-1α overexpression by adenovirus infection	Human ovarian cancer cell line (Ho-8910)	Induction of apoptosis; downregulation of Bcl-2 and upregulation of Bax	[41]
PGC-1α overexpression by adenovirus infection	Human hepatoma cell line (HepG2)	Inhibition of cell motility; upregulation of E-cadherin	[42]
PGC-1α overexpression	Human colorectal cancer cell lines (HT29 and HCT116)	Induction of apoptosis; ROS accumulation	[43]
Increased expression of PGC-1α by bezafibrate (PPAR panagonist)	Human cancer cell lines (HeLa, 143B, MDA-MB-231)	Inhibition of cell proliferation and invasion; increased mitochondrial biogenesis	[44]
PGC-1α overexpression	Human prostate cancer cell	Inhibition of cell proliferation and inhibition of metastasis; activation of ERRα-dependent transcriptional program; induction of catabolic state	[45]
PGC-1α overexpression by adenovirus infection, CRISPR-mediated PGC-1α depletion	Human melanoma cell	Inhibition of metastasis; inhibition of inhibitor of DNA binding protein 2 (ID2) and TCF-mediated gene transcription	[46]

showed that PGC-1α expression in invasive cancer cells was significantly associated with the formation of distant metastases in a clinical analysis of human invasive breast cancers [93].

3.2. Anticancer Functions of PGC-1α. As opposed to the tumor-promoting role of PGC-1α described above, several studies have shown that PGC-1α has anticancer effects. As described above, PGC-1α is decreased in colon [88], breast [89], and ovarian cancer cells [41], and PGC-1α overexpression in human ovarian cancer cell line Ho-8910 has been shown to induce apoptosis via downregulation of Bcl-1 and upregulation of Bax, suggesting that PGC-1α may be a contributor to the inhibition of tumor growth [41]. Lee et al. found that PPARγ activation and PGC-1α overexpression by adenovirus infection in HepG2 human hepatoma cells induced E-cadherin upregulation and inhibited cell motility [42]. One report showed that PGC-1α overexpression induced apoptosis via ROS accumulation in HT29 and HCT116 colorectal cancer cells. In addition, PGC-1α overexpression reduced tumor growth in an HT29 xenograft model, suggesting a role of PGC-1α as a tumor suppressor [43]. Zhang et al. reported that von Hippel-Lindau- (VHL-) deficient clear cell renal carcinomas exhibited higher levels of HIF-1α and enhanced glycolysis [101]. HIF-1α is known to induce the expression of transcriptional repressor Dec1, which leads to the suppression of PGC-1α expression and the inhibition of mitochondrial respiration [102]. However, the enforced PGC-1α expression in VHL-deficient cells, despite the restoration of mitochondrial function, did not block the inhibition of cell growth and enhanced sensitivity to cytotoxic therapies in oxidative stress conditions [102]. This is in line with clinical clear cell carcinoma data that showed the correlation of higher mitochondrial mass with reduced tumor aggressiveness [103], and the association of lower PGC-1α levels with worse patient outcome [102]. It was shown that PGC-1α attenuates stress responses necessary for cancer cell survival, by interacting with heat-shock factor 1 [104]. Wang and Moraes revealed that increased PGC-1α expression due to treatment with PPAR panagonist (bezafibrate) increased mitochondrial biogenesis, resulting in an inhibition of cancer cell proliferation under glycolytic conditions and inhibition of invasion [44]. In addition, PGC-1α downregulation by miRNA-217 led to the promotion of cancer cell proliferation in breast cancer cells, suggesting a role of PGC-1α as a tumor suppressor [105]. Recently, Torrano et al. showed that PGC-1α suppresses metastasis of prostate carcinoma through an ERRα-dependent transcriptional program [45]. Highly metastatic melanoma cells expressed lower levels of PGC-1α [46, 106]. In turn, these PGC-1α-low cells expressed higher levels of integrin, TGFβ, and Wnt signaling components involved in metastasis. It was shown that genetic depletion of PGC-1α increased metastasis in poorly invasive melanoma cells [46]. In contrast, PGC-1α overexpression in melanoma cells by ectopic expression or exposure to $BRAF^{V600E}$ inhibitor vemurafenib suppressed metastasis through the direct regulation of inhibitor of DNA binding protein 2 (ID2) and inhibition of TCF-mediated gene transcription [46].

As described above, there have been many studies of the role of PGC-1α in tumor progression. However, it is still not sure if PGC-1α acts as a tumor promoter or tumor suppressor, and to date it is thought that its effect on tumor varies depending on the tissue context and tumor type (reviewed in [107]).

4. Conclusions

PPARγ and PGC-1α are emerging proteins involved in tumorigenesis and attractive topics to study for further understanding of cancer biology. Originally, PGC-1α was identified as a PPARγ interacting protein. However, most of the reported actions of PGC-1α in cancer were not related to the expression of PPARγ. Despite the fact that PPARγ and PGC-1α can each act as both tumor promoter and tumor suppressor, there is no clearly defined mechanism that can explain the contradictory dual effects. However, their dual actions can be explained, in part, by their cell type-specific effects and variable interacting proteins. Therefore, each of the molecular interactions of PPARγ and PGC-1α with other transcriptional partners needs to be further investigated to understand the role of PPARγ and PGC-1α in cancer.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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