Review Article

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

Seong-Hoon Yun , Sang-Heum Han , and Joo-In Park

Department of Biochemistry, Dong-A University College of Medicine, Busan, Republic of Korea

Correspondence should be addressed to Joo-In Park; jjpark@dau.ac.kr

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

1. Introduction

Peroxisome proliferator-activated receptor γ (PPAR γ) 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 PPAR γ 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]. PPAR γ 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 PPAR γ isoforms are known, PPAR γ 1 and PPAR γ 2 [4, 5]. PPAR γ 2, 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 PPAR γ 1. PPAR γ 2 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]. PPAR γ 1 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. PPAR γ 1 is a molecular target of antidiabetic thiazolidinediones [7, 8]. Our previous review summarized the role and action mechanisms of PPAR γ in colorectal cancer [8], but the role of PPAR γ in cancer is still debated. Thus, this review updates the progress in understanding the role and molecular mechanisms of PPAR γ in cancer.

The PPAR γ coactivator-1 (PGC-1) family is composed of PGC-1 α , PGC-1 β , and PGC-1-related coactivator (PRC). PGC-1 α was initially identified as a transcriptional coactivator involved in mitochondrial function and thermogenesis in brown fat [9]. PGC-1 β 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-1 α and PGC-1 β . 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 PPAR γ (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-1 α has a Ser/Arg-rich domain and RNA binding motif that plays an important role in mRNA splicing [14, 15]. Because PGC-1 α was described initially as a PPAR γ interacting protein, some investigators recently studied the expression and clinical significance of PGC-1 α in cancer [16, 17]. However, the expression and the roles of PGC-1 α in cancer were not significantly related to the expression of PPAR γ . In addition, controversies still exist whether PGC-1 α acts as a tumor promoter or a tumor suppressor in cancer. This review focuses on the expression and actions of PGC-1 α in order to understand the clinical significance of PGC-1 α expression in cancer.

2. The Role and Action Mechanisms of PPAR γ in Cancer

PPAR γ is expressed in various malignant tissues, including bladder, colon, prostate, and breast cancer [18–22]. Natural ligands that activate PPAR γ include long-chain polyunsaturated fatty acids, eicosanoids, components of oxidized low density lipoproteins (oxLDLs), and 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-PGJ₂) [23]. Synthetic ligands include the antidiabetic thiazolidinedione (TZD) class of drugs [23]. An increasing number of studies have focused on the effect of PPAR γ in cancer using natural and synthetic ligands for PPAR γ and overexpression experiments. However, the role of PPAR γ in cancer is still debated. Thus, this review updates the role and action mechanisms of PPAR γ in cancer since our review published in 2012.

2.1. PPAR γ as a Tumor Suppressor in Cancer. Our previous review summarized that PPAR γ 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- κ B and glycogen synthase kinase (GSK)-3 β , 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 PPAR γ -related tumor suppression since 2012 (Table 1, Figure 2).

Understanding the role of PPAR γ in cancer was improved by developing new synthetic and natural ligands of PPAR γ and performing overexpression and knockdown experiments. PPAR γ agonist troglitazone inhibits colon cancer cell growth through the inactivation of NF- κ B by suppressing GSK-3 β activity [24]. Emerging data suggest that PPAR γ acts as a tumor suppressor by inactivating NF- κ B through different mechanisms. For example, Lee et al. demonstrated that 4-O-methylhonokiol (MH), a PPAR γ agonist, has anti-tumor activity in prostate cancer through increased PPAR γ activity and p21-mediated suppression of NF- κ B activity as observed by the loss of MH-induced growth inhibition and NF- κ B inhibition in a p21 siRNA knockdown experiment [25]. In addition, overexpression of PPAR γ was shown to inhibit cell proliferation and tumor growth via degradation of NF- κ B by acting as an E3 ligase [26]. Hou et al. demonstrated that PPAR γ 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 I κ B kinase, NF- κ B/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 PPAR γ agonist, has been reported to inhibit esophageal squamous cell

TABLE 1: The role and action mechanisms of PPAR γ as a tumor suppressor.

Modification	Experimental system Cell type	Role and action mechanisms	References
Troglitazone treatment (PPAR γ ligand)	Human colon cancer SW620, HCT116 cells	Inhibition of cell proliferation; induction of apoptosis; inactivation of NF- κ B by suppression of GSK-3 β	[24]
PPAR γ 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- κ B activity	[25]
PPAR γ overexpression	Human colon cancer HT-29 cells	Inhibition of cell proliferation and tumor growth; ubiquitination and degradation of NF- κ B by PPAR γ	[26]
PPAR γ overexpression	Human colon cancer HT-29 cells	Inhibition of cell proliferation; ubiquitination and degradation of MUC1-C by PPAR γ	[27]
PPAR γ activation by efatutazone treatment (third-generation PPAR γ 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 (PPAR γ 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 (PPAR γ ligand)	Chronic myeloid leukemia cells, leukemia stem cell (LSC)	Inhibition of cancer stem cell survival; decreased expression of STAT5 and HIF-1 α	[30]
PPAR γ overexpression by PPAR γ 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]
PPAR γ activation by troglitazone, PPAR γ siRNA transfection	Human breast cancer cell lines (MCF-7, MDA-MB-231)	Inhibition of cell proliferation; upregulation of tumor suppressor <i>Cyld</i>	[32]
PPAR γ activation by rosiglitazone, PPAR γ 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 PPAR γ as a tumor suppressor. NF- κ B, nuclear factor- κ B; GSK-3 β , glycogen synthase kinase 3- β ; MUC1-C, mucin 1-C; TERT, telomerase reverse transcriptase; STAT5, signal transducer and activator of transcription factor 5; HIF-2 α , hypoxia inducible factor-2 α ; 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 PPAR γ agonists inhibit the survival of cancer stem cells (CSCs) [29, 30, 53–55]. PPAR γ 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 PPAR γ agonist, eradicates CSCs via the decreased expression of STAT5 and HIF-2 α 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 PPAR γ 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 PPAR γ activation has a tumor suppressive effect by upregulating the expression of tumor suppressor *Cyld*, as the *Cyld* promoter has PPAR γ 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- κ B, JNK, p38, Wnt, Akt, and Notch pathways [65].

Rovito et al. demonstrated that PPAR γ activation down-regulates CXCR4 gene expression through recruitment of the silencing mediator of retinoid and thyroid hormone

FIGURE 3: Action mechanisms of PPAR γ as a tumor promoter. ACLY, ATP citrate lyase; MIG12, midline-1-interacting G12-like protein; FASN, fatty acid synthase; NR1D1, Rev-ErbA α ; 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-1 α (SDF-1 α), has been shown to be expressed in human breast cancer cells, and activation of the SDF-1 α /CXCR4 axis is important in breast cancer migration and metastasis [66, 67].

2.2. PPAR γ as a Tumor Promoter in Cancer. Our previous review described that PPAR γ 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 PPAR γ as a tumor promoter (Figure 3).

Recently, increasing evidence has indicated that PPAR γ acts as a tumor promoter [68–74]. Downregulation of PPAR γ by siRNA knockdown or treatment with PPAR γ antagonist GW9662 has been shown to inhibit the growth of cancer cells, suggesting a tumor-promoting effect for PPAR γ in these cells [68–70]. PPAR γ was shown to protect ErbB2-positive breast cancer cells from palmitate-induced toxicity [75]. In addition, PPAR γ was demonstrated to play a crucial role in the maintenance of stemness in ErbB2-positive breast cancer cells; PPAR γ 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 PPAR γ 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 PPAR γ siRNA showed that PPAR γ suppression inhibits cell proliferation, colony formation, and tumorigenicity *in vivo* [73]. In addition, PPAR γ upregulated VEGF expression through the binding of PPAR γ in the promoter region of *VEGF* in prostate cancer cells [73]. Patitucci et al. demonstrated that PPAR γ activation is involved in steatosis-associated liver cancer and provided evidence supporting the pharmacological modulation of hepatic PPAR γ activity as a therapeutically relevant strategy in hepatic malignancy associated with activated Akt2 and PPAR γ signaling [74].

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

Many studies have examined the role of PGC-1 α in cancer by observing its expression in several cancers and performing PGC-1 α overexpression and siRNA knockdown experiments. PGC-1 α 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-1 α expression is increased in cancer [17, 90]. Even though many studies have been published, the role of PGC-1 α in cancer is still controversial. Therefore, this review describes the role and action mechanisms of PGC-1 α in cancer (Table 2).

3.1. Tumor-Promoting Functions of PGC-1 α . As described above, PGC-1 α is a regulator of PPAR γ activity. Thus, the abnormalities in PGC-1 α expression may affect PPAR γ function. However, there was little report supporting that PGC-1 α expression directs PPAR γ activity in cancer. Thus, this review focuses on the role of PGC-1 α , independent of the role of PPAR γ in cancer. Literature works supporting the tumor-promoting functions of PGC-1 α have increased [17, 34–40, 42, 91–93]. Shiota et al. showed that PGC-1 α promotes cell growth through the activation of androgen receptor in prostate cancer cells by observing cell growth inhibition with PGC-1 α knockdown experiments [17]. In addition, PGC-1 α 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-1 α promotes carcinogenesis and tumor growth through the induction of lipogenic enzymes (acetyl-CoA carboxylase and fatty acid synthase) using genetically modified PGC-1 α mice [35]. That study demonstrated that PGC-1 α knockout mice had decreased chemically induced liver and colon carcinogenesis, suggesting that PGC-1 α may stimulate carcinogenesis [35]. Similarly, Shin et al. first demonstrated that overexpression of PGC-1 α enhances cell proliferation and tumorigenesis via the upregulation of Sp1 and acyl-CoA binding protein [36]. It was also reported that PGC-1 α overexpression leads to increased antioxidant enzymes (catalase, superoxide dismutase) and decreased ROS-induced apoptosis [36]. Similarly, PGC-1 α knockdown significantly decreased cell number and induced apoptosis in PGC-1 α positive melanoma cell lines, suggesting that PGC-1 α is crucial in the survival of PGC-1 α positive melanoma cells [37]. In addition, superoxide dismutase 2 protein levels were decreased in PGC-1 α depleted melanoma cells. Moreover, ectopic expression of PGC-1 α in melanoma cells increased the expression of ROS detoxifying genes. These data support the hypothesis that PGC-1 α 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-1 α depleted cells, implying PGC-1 α 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-1 α /ERR α complex directly regulates the expression of glutamine metabolism enzymes, leading to the provision of glutamine carbons to de novo fatty acid synthesis [38]. PGC-1 α overexpression, or ERR α activation, confers growth

advantages of breast cancer cells even under limited nutrients, supporting the correlative clinical data that high expression of PGC-1 α is associated with poor prognosis, possibly related to the activation of its downstream glutamine pathway target genes [38]. It was reported that PGC-1 α expression is affected by various transcriptional pathways. One example is that melanocyte-lineage transcription master regulator and oncogene MITF activated PGC-1 α 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-1 α -depleted melanoma cell lines, suggesting that intrinsic apoptotic pathway is activated in PGC-1 α -depleted melanoma cells [37]. Another example is that the androgen receptor-AMP-activated protein kinase (AMPK) signaling axis increased expression of PGC-1 α to drive growth advantages in prostate cancers [39]. It was also shown that PGC-1 α expression was significantly higher in lung adenocarcinomas with wild type p53 than in tumors with mutant p53 [40]. Cell proliferation was inhibited by PGC-1 α siRNA knockdown experiments in H1944 lung adenocarcinoma cells [40]. In metabolic stress conditions, PGC-1 α 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-1 α knockdown cells resulted in p53-induced apoptosis [96]. In turn, it was also shown that increased expression of PGC-1 α 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-1 α on angiogenesis. PGC-1 α has been reported to activate the production of VEGF through the estrogen-related receptor α - (ERR α -) dependent pathway [98]. PGC-1 α was shown to regulate HIF-1 α activity. Increased PGC-1 α expression enhances oxygen consumption, resulting in decreased local oxygen tension and increased HIF-1 α stability [99]. In addition, HIF-2 α is a transcriptional target of PGC-1 α , even though the involved transcriptional mechanism is not clear [100]. ERR α is overexpressed in many cancers and its inhibition reduces cell proliferation. Recent studies suggest an important role for the interaction between PGC-1 α and ERR α 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-1 α and ERR α [92]. Interestingly, recent study shows that PGC-1 α plays an important role in the metastatic switch. LeBleu et al. demonstrated that circulating mammary epithelial cancer cells exhibit increased PGC-1 α expression, enhanced mitochondrial biogenesis, and oxidative phosphorylation, which may contribute to distant metastasis and poor patient outcome [93]. In addition, PGC-1 α 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-1 α in cancer.

Modification	Experimental system	Cell type	Role and action mechanisms	References
<i>Tumor-promoting functions of PGC-1α</i>				
PGC-1 α knockdown		Human prostate cancer PC3, LNCap cells	Stimulation of cell proliferation; activation of androgen receptor	[17]
Increased PGC-1 α expression in arsenic-induced skin cancer		Skin cancer	Stimulation of cell proliferation; enhanced mitochondrial biogenesis	[34]
<i>Pgc-1α</i> knockout and knockdown by lentivirus-based PGC-1 α shRNA		Human colorectal cancer cell line (Colo205)	Stimulation of carcinogenesis and tumor growth; induction of lipogenic enzymes	[35]
PGC-1 α overexpression by PGC-1 α 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-1 α shRNA knockdown		Human melanoma PGC-1 α -positive A375 cells, xenograft model	Inhibition of apoptosis; decreased ROS production, induction of ROS detoxifying enzymes	[37]
Increased PGC-1 α expression in breast cancer cell		Breast cancer cell	Stimulation of cell proliferation; enhanced glutamine-mediated lipid biosynthesis	[38]
<i>Pgc-1α</i> shRNA knockdown		Human prostate cancer cell line (C4-2 cells)	Stimulation of cell proliferation; increased mitochondrial biogenesis	[39]
PGC-1 α shRNA knockdown and PGC-1 α overexpression		Human breast cancer cell, human melanoma cells	Stimulation of cell proliferation, increased invasion; increased mitochondrial biogenesis and oxidative phosphorylation	[40]
<i>Anticancer functions of PGC-1α</i>				
PGC-1 α overexpression by adenovirus infection		Human ovarian cancer cell line (Ho-8910)	Induction of apoptosis; downregulation of Bcl-2 and upregulation of Bax	[41]
PGC-1 α overexpression by adenovirus infection		Human hepatoma cell line (HepG2)	Inhibition of cell motility; upregulation of E-cadherin	[42]
PGC-1 α overexpression		Human colorectal cancer cell lines (HT29 and HCT116)	Induction of apoptosis; ROS accumulation	[43]
Increased expression of PGC-1 α by bezafibrate (PPAR panagonist)		Human cancer cell lines (HeLa, 143B, MDA-MB-231)	Inhibition of cell proliferation and invasion; increased mitochondrial biogenesis	[44]
PGC-1 α overexpression		Human prostate cancer cell	Inhibition of cell proliferation and inhibition of metastasis; activation of ERR α -dependent transcriptional program; induction of catabolic state	[45]
PGC-1 α overexpression by adenovirus infection, CRISPR-mediated PGC-1 α 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-1 α 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-1 α . As opposed to the tumor-promoting role of PGC-1 α described above, several studies have shown that PGC-1 α has anticancer effects. As described above, PGC-1 α is decreased in colon [88], breast [89], and ovarian cancer cells [41], and PGC-1 α 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-1 α may be a contributor to the inhibition of tumor growth [41]. Lee et al. found that PPAR γ activation and PGC-1 α overexpression by adenovirus infection in HepG2 human hepatoma cells induced E-cadherin upregulation and inhibited cell motility [42]. One report showed that PGC-1 α overexpression induced apoptosis via ROS accumulation in HT29 and HCT116 colorectal cancer cells. In addition, PGC-1 α overexpression reduced tumor growth in an HT29 xenograft model, suggesting a role of PGC-1 α as a tumor suppressor [43]. Zhang et al. reported that von Hippel-Lindau- (VHL-) deficient clear cell renal carcinomas exhibited higher levels of HIF-1 α and enhanced glycolysis [101]. HIF-1 α is known to induce the expression of transcriptional repressor Dec1, which leads to the suppression of PGC-1 α expression and the inhibition of mitochondrial respiration [102]. However, the enforced PGC-1 α 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-1 α levels with worse patient outcome [102]. It was shown that PGC-1 α attenuates stress responses necessary for cancer cell survival, by interacting with heat-shock factor 1 [104]. Wang and Moraes revealed that increased PGC-1 α 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-1 α downregulation by miRNA-217 led to the promotion of cancer cell proliferation in breast cancer cells, suggesting a role of PGC-1 α as a tumor suppressor [105]. Recently, Torrano et al. showed that PGC-1 α suppresses metastasis of prostate carcinoma through an ERR α -dependent transcriptional program [45]. Highly metastatic melanoma cells expressed lower levels of PGC-1 α [46, 106]. In turn, these PGC-1 α -low cells expressed higher levels of integrin, TGF β , and Wnt signaling components involved in metastasis. It was shown that genetic depletion of PGC-1 α increased metastasis in poorly invasive melanoma cells [46]. In contrast, PGC-1 α 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-1 α in tumor progression. However, it is still not sure if PGC-1 α 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

PPAR γ and PGC-1 α are emerging proteins involved in tumorigenesis and attractive topics to study for further understanding of cancer biology. Originally, PGC-1 α was identified as a PPAR γ interacting protein. However, most of the reported actions of PGC-1 α in cancer were not related to the expression of PPAR γ . Despite the fact that PPAR γ and PGC-1 α 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 PPAR γ and PGC-1 α with other transcriptional partners needs to be further investigated to understand the role of PPAR γ and PGC-1 α in cancer.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

- [1] D. J. Mangelsdorf, C. Thummel, M. Beato et al., "The nuclear receptor super-family: the second decade," *Cell*, vol. 83, no. 6, pp. 835–839, 1995.
- [2] K. Schoonjans, B. Staels, and J. Auwerx, "The peroxisome proliferator activated receptors (PPARs) and their effects on lipid metabolism and adipocyte differentiation," *Biochimica et Biophysica Acta—Lipids and Lipid Metabolism*, vol. 1302, no. 2, pp. 93–109, 1996.
- [3] T. M. Willson, P. J. Brown, D. D. Sternbach, and B. R. Henke, "The PPARs: from orphan receptors to drug discovery," *Journal of Medicinal Chemistry*, vol. 43, no. 4, pp. 527–550, 2000.
- [4] P. Tontonoz, E. Hu, R. A. Graves, A. I. Budavari, and B. M. Spiegelman, "mPPAR γ 2: tissue-specific regulator of an adipocyte enhancer," *Genes & Development*, vol. 8, no. 10, pp. 1224–1234, 1994.
- [5] L. Fajas, D. Auboeuf, E. Raspé et al., "The organization, promoter analysis, and expression of the human PPAR γ gene," *The Journal of Biological Chemistry*, vol. 272, no. 30, pp. 18779–18789, 1997.
- [6] P. Tontonoz, E. Hu, and B. M. Spiegelman, "Stimulation of adipogenesis in fibroblasts by PPAR γ 2, a lipid-activated transcription factor," *Cell*, vol. 79, no. 7, pp. 1147–1156, 1994.

- [7] J. I. Park, "The role of 15d-PGJ₂, a natural ligand for peroxisome proliferator-activated receptor γ (PPAR γ), in cancer," *Cellular and Genetic Practices for Translational Medicine*, pp. 169–195, 2011.
- [8] J.-I. Park and J.-Y. Kwak, "The role of peroxisome proliferator-activated receptors in colorectal cancer," *PPAR Research*, vol. 2012, Article ID 876418, 12 pages, 2012.
- [9] P. Puigserver, Z. Wu, C. W. Park, R. Graves, M. Wright, and B. M. Spiegelman, "A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis," *Cell*, vol. 92, no. 6, pp. 829–839, 1998.
- [10] J. Lin, P. T. Tarr, R. Yang et al., "PGC-1 β in the regulation of hepatic glucose and energy metabolism," *The Journal of Biological Chemistry*, vol. 278, no. 33, pp. 30843–30848, 2003.
- [11] D. Kressler, S. N. Schreiber, D. Knutti, and A. Kralli, "The PGC-1-related protein PERC is a selective coactivator of estrogen receptor α ," *The Journal of Biological Chemistry*, vol. 277, no. 16, pp. 13918–13925, 2002.
- [12] U. Andersson and R. C. Scarpulla, "PGC-1-related coactivator, a novel, serum-inducible coactivator of nuclear respiratory factor 1-dependent transcription in mammalian cells," *Molecular and Cellular Biology*, vol. 21, no. 11, pp. 3738–3749, 2001.
- [13] J. Lin, P. Puigserver, J. Donovan, P. Tarr, and B. M. Spiegelman, "Peroxisome proliferator-activated receptor γ coactivator 1 β (PGC-1 β), a novel PGC-1-related transcription coactivator associated with host cell factor," *The Journal of Biological Chemistry*, vol. 277, no. 3, pp. 1645–1648, 2002.
- [14] M. Monsalve, Z. Wu, G. Adelmant, P. Puigserver, M. Fan, and B. M. Spiegelman, "Direct coupling of transcription and mRNA processing through the thermogenic coactivator PGC-1," *Molecular Cell*, vol. 6, no. 2, pp. 307–316, 2000.
- [15] G. D. Girnun, "The diverse role of the PPAR γ coactivator 1 family of transcriptional coactivators in cancer," *Seminars in Cell & Developmental Biology*, vol. 23, no. 4, pp. 381–388, 2012.
- [16] H. Yu and Y. Xin, "Down-regulated expressions of PPAR γ and its coactivator PGC-1 are related to gastric carcinogenesis and Lauren's classification in gastric carcinoma," *Chinese Journal of Cancer Research*, vol. 25, no. 6, pp. 704–714, 2013.
- [17] M. Shiota, A. Yokomizo, Y. Tada et al., "Peroxisome proliferator-activated receptor γ coactivator-1 α interacts with the androgen receptor (AR) and promotes prostate cancer cell growth by activating the AR," *Molecular Endocrinology*, vol. 24, no. 1, pp. 114–127, 2010.
- [18] J. J. Mansure, R. Nassim, and W. Kassouf, "Peroxisome proliferator-activated receptor γ in bladder cancer: A promising therapeutic target," *Cancer Biology & Therapy*, vol. 8, no. 7, pp. 6–15, 2009.
- [19] R. N. DuBois, R. Gupta, J. Brockman, B. S. Reddy, S. L. Krakow, and M. A. Lazar, "The nuclear eicosanoid receptor, PPAR γ , is aberrantly expressed in colonic cancers," *Carcinogenesis*, vol. 19, no. 1, pp. 49–53, 1998.
- [20] P. Sarraf, E. Mueller, D. Jones et al., "Differentiation and reversal of malignant changes in colon cancer through PPAR γ ," *Nature Medicine*, vol. 4, no. 9, pp. 1046–1052, 1998.
- [21] E. Mueller, P. Sarraf, P. Tontonoz et al., "Terminal differentiation of human breast cancer through PPAR γ ," *Molecular Cell*, vol. 1, no. 3, pp. 465–470, 1998.
- [22] T. Kubota, K. Koshizuka, E. A. Williamson et al., "Ligand for peroxisome proliferator-activated receptor gamma (Troglitazone) has potent antitumor effect against human prostate cancer both in vitro and in vivo," *Cancer Research*, vol. 58, no. 15, pp. 3344–3352, 1998.
- [23] T. Wang, J. Xu, X. Yu, R. Yang, and Z. C. Han, "Peroxisome proliferator-activated receptor γ in malignant diseases," *Critical Reviews in Oncology/Hematology*, vol. 58, no. 1, pp. 1–14, 2006.
- [24] J. O. Ban, D. H. Kwak, J. H. Oh et al., "Suppression of NF- κ B and GSK-3 β is involved in colon cancer cell growth inhibition by the PPAR agonist troglitazone," *Chemico-Biological Interactions*, vol. 188, no. 1, pp. 75–85, 2010.
- [25] N. J. Lee, J. H. Oh, J. O. Ban et al., "4-O-methylhonokiol, a PPAR γ agonist, inhibits prostate tumour growth: P21-mediated suppression of NF- κ B activity," *British Journal of Pharmacology*, vol. 168, no. 5, pp. 1133–1145, 2013.
- [26] Y. Hou, F. Moreau, and K. Chadee, "PPAR γ is an E3 ligase that induces the degradation of NF κ B/p65," *Nature Communications*, vol. 3, article 1300, 2012.
- [27] Y. Hou, J. Gao, H. Xu et al., "PPAR γ E3 ubiquitin ligase regulates MUC1-C oncoprotein stability," *Oncogene*, vol. 33, no. 49, pp. 5619–5625, 2014.
- [28] H. Sawayama, T. Ishimoto, M. Watanabe et al., "Small molecule agonists of PPAR- γ exert therapeutic effects in esophageal cancer," *Cancer Research*, vol. 74, no. 2, pp. 575–585, 2014.
- [29] A. Papi, S. De Carolis, S. Bertoni et al., "PPAR γ and RXR ligands disrupt the inflammatory cross-talk in the hypoxic breast cancer stem cells niche," *Journal of Cellular Physiology*, vol. 229, no. 11, pp. 1595–1606, 2014.
- [30] S. Prost, F. Relouzat, M. Spentchian et al., "Erosion of the chronic myeloid leukaemia stem cell pool by PPAR γ agonists," *Nature*, vol. 525, no. 7569, pp. 380–383, 2015.
- [31] F. Guo, X. Ren, Y. Dong et al., "Constitutive expression of PPAR γ inhibits proliferation and migration of gastric cancer cells and down-regulates Wnt/ β -catenin signaling pathway downstream target genes TERT and ENAH," *Gene*, vol. 584, no. 1, pp. 31–37, 2016.
- [32] A. Pseftogas, C. Gonidas, and G. Mosialos, "Activation of peroxisome proliferator-activated receptor gamma in mammary epithelial cells upregulates the expression of tumor suppressor Cyld to mediate growth inhibition and anti-inflammatory effects," *The International Journal of Biochemistry & Cell Biology*, vol. 82, pp. 49–56, 2017.
- [33] D. Rovito, G. Gionfriddo, I. Barone et al., "Ligand-activated PPAR γ downregulates CXCR4 gene expression through a novel identified PPAR response element and inhibits breast cancer progression," *Oncotarget*, vol. 7, no. 40, pp. 65109–65124, 2016.
- [34] C. Lee, S. Wu, C. Hong et al., "Aberrant cell proliferation by enhanced mitochondrial biogenesis via mtTFA in arsenical skin cancers," *The American Journal of Pathology*, vol. 178, no. 5, pp. 2066–2076, 2011.
- [35] K. Bhalla, B. J. Hwang, R. E. Dewi et al., "PGC1 α promotes tumor growth by inducing gene expression programs supporting lipogenesis," *Cancer Research*, vol. 71, no. 21, pp. 6888–6898, 2011.
- [36] S.-W. Shin, S.-H. Yun, E.-S. Park, J.-S. Jeong, J.-Y. Kwak, and J.-I. Park, "Overexpression of PGC-1 α enhances cell proliferation and tumorigenesis of HEK293 cells through the upregulation of Sp1 and Acyl-CoA binding protein," *International Journal of Oncology*, vol. 46, no. 3, pp. 1328–1342, 2015.
- [37] F. Vazquez, J.-H. Lim, H. Chim et al., "PGC1 α expression defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress," *Cancer Cell*, vol. 23, no. 3, pp. 287–301, 2013.
- [38] S. McGuirk, S. Gravel, G. Deblouis et al., "PGC-1 α supports glutamine metabolism in breast cancer," *Cancer & Metabolism*, vol. 5, no. 1, p. 22, 2013.

- [39] J. B. Tennakoon, Y. Shi, J. J. Han et al., "Androgens regulate prostate cancer cell growth via an AMPK-PGC-1 α -mediated metabolic switch," *Oncogene*, vol. 33, no. 45, pp. 5251–5261, 2014.
- [40] A. Taguchi, O. Delgado, M. Çeliktas et al., "Proteomic signatures associated with p53 mutational status in lung adenocarcinoma," *Proteomics*, vol. 14, no. 23–24, pp. 2750–2759, 2014.
- [41] Y. Zhang, Y. Ba, C. Liu et al., "PGC-1 α induces apoptosis in human epithelial ovarian cancer cells through a PPAR γ -dependent pathway," *Cell Research*, vol. 17, no. 4, pp. 363–373, 2007.
- [42] H. J. Lee, Y. Su, P. H. Yin, H. C. Lee, and C. W. Chi, "PPAR γ /PGC-1 α pathway in E-cadherin expression and motility of HepG2 cells," *Anticancer Research*, vol. 29, no. 12, pp. 5057–5063, 2009.
- [43] I. D'Errico, L. Salvatore, S. Murzilli et al., "Peroxisome proliferator-activated receptor- γ coactivator 1- α (PGC1 α) is a metabolic regulator of intestinal epithelial cell fate," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 16, pp. 6603–6608, 2011.
- [44] X. Wang and C. T. Moraes, "Increases in mitochondrial biogenesis impair carcinogenesis at multiple levels," *Molecular Oncology*, vol. 5, no. 5, pp. 399–409, 2011.
- [45] V. Torrano, L. Valcarcel-Jimenez, A. R. Cortazar et al., "The metabolic co-regulator PGC1 α suppresses prostate cancer metastasis," *Nature Cell Biology*, vol. 18, no. 6, pp. 645–656, 2016.
- [46] C. Luo, J.-H. Lim, Y. Lee et al., "A PGC1 α -mediated transcriptional axis suppresses melanoma metastasis," *Nature*, vol. 537, no. 7620, pp. 422–426, 2016.
- [47] R. Ahmad, D. Raina, V. Trivedi et al., "MUC1 oncoprotein activates the I κ B kinase β complex and constitutive NF- κ B signalling," *Nature Cell Biology*, vol. 9, no. 12, pp. 1419–1427, 2007.
- [48] S. Cascio, L. Zhang, and O. J. Finn, "MUC1 protein expression in tumor cells regulates transcription of proinflammatory cytokines by forming a complex with nuclear factor- κ B p65 and binding to cytokine promoters: Importance of extracellular domain," *The Journal of Biological Chemistry*, vol. 286, no. 49, pp. 42248–42256, 2011.
- [49] R. Ahmad, D. Raina, M. D. Joshi et al., "MUC1-C oncoprotein functions as a direct activator of the nuclear factor- κ B p65 transcription factor," *Cancer Research*, vol. 69, no. 17, pp. 7013–7021, 2009.
- [50] R. Ahmad, H. Rajabi, M. Kosugi et al., "MUC1-C oncoprotein promotes STAT3 activation in an autoinductive regulatory loop," *Science Signaling*, vol. 4, no. 160, article no. ra9, 2011.
- [51] X. Wei, H. Xu, and D. Kufe, "Human MUC1 oncoprotein regulates p53-responsive gene transcription in the genotoxic stress response," *Cancer Cell*, vol. 7, no. 2, pp. 167–178, 2005.
- [52] R. Ahmad, M. Alam, H. Rajabi, and D. Kufe, "The MUC1-C oncoprotein binds to the BH3 domain of the pro-apoptotic BAX protein and blocks BAX function," *The Journal of Biological Chemistry*, vol. 287, no. 25, pp. 20866–20875, 2012.
- [53] B. Apsel Winger and N. P. Shah, "PPAR γ : Welcoming the New Kid on the CML Stem Cell Block," *Cancer Cell*, vol. 28, no. 4, article no. 2152, pp. 409–411, 2015.
- [54] J. M. Egan, "Targeting stem cells in chronic myeloid leukemia with a PPAR- γ agonist," *The New England Journal of Medicine*, vol. 373, no. 20, pp. 1973–1975, 2015.
- [55] Y. Wang, H. Tan, D. Xu et al., "The combinatory effects of PPAR- γ agonist and survivin inhibition on the cancer stem-like phenotype and cell proliferation in bladder cancer cells," *International Journal of Molecular Medicine*, vol. 34, no. 1, pp. 262–268, 2014.
- [56] H. Clevers and R. Nusse, "Wnt/ β -catenin signaling and disease," *Cell*, vol. 149, no. 6, pp. 1192–1205, 2012.
- [57] X. Song, N. Xin, W. Wang, and C. Zhao, "Wnt/ β -catenin, an oncogenic pathway targeted by *H. pylori* in gastric carcinogenesis," *Oncotarget*, vol. 6, no. 34, pp. 35579–35588, 2015.
- [58] A. V. Kwiatkowski, F. B. Gertler, and J. J. Loureiro, "Function and regulation of Ena/VASP proteins," *Trends in Cell Biology*, vol. 13, no. 7, pp. 386–392, 2003.
- [59] K. Hoffmeyer, A. Raggioli, S. Rudloff et al., "Wnt/ β -catenin signaling regulates telomerase in stem cells and cancer cells," *Science*, vol. 336, no. 6088, pp. 1549–1554, 2012.
- [60] A. Najafov, T. Şeker, I. Even et al., "MENA is a transcriptional target of the Wnt/beta-catenin pathway," *PLoS ONE*, vol. 7, no. 5, Article ID e37013, 2012.
- [61] K. T. Pate, C. Stringari, S. Sprowl-Tanio et al., "Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer," *EMBO Journal*, vol. 33, no. 13, pp. 1454–1473, 2014.
- [62] Y. Lecarpentier, V. Claes, A. Vallée, and J. Hébert, "Interactions between PPAR Gamma and the Canonical Wnt/Beta-Catenin Pathway in Type 2 Diabetes and Colon Cancer," *PPAR Research*, vol. 2017, pp. 1–9, 2017.
- [63] G. R. Bignell, W. Warren, S. Seal et al., "Identification of the familial cylindromatosis tumor-suppressor gene," *Nature Genetics*, vol. 25, no. 2, pp. 160–165, 2000.
- [64] D. Komander, F. Reyes-Turcu, J. D. F. Licchesi, P. Odenwaelder, K. D. Wilkinson, and D. Barford, "Molecular discrimination of structurally equivalent Lys 63-linked and linear polyubiquitin chains," *EMBO Reports*, vol. 10, no. 5, pp. 466–473, 2009.
- [65] N. Rajan and A. Ashworth, "Inherited cylindromas: Lessons from a rare tumour," *The Lancet Oncology*, vol. 16, no. 9, article no. 213, pp. e460–e469, 2015.
- [66] A. Müller, B. Homey, H. Soto et al., "Involvement of chemokine receptors in breast cancer metastasis," *Nature*, vol. 410, no. 6824, pp. 50–56, 2001.
- [67] S. Hassan, C. Ferrario, U. Saragovi et al., "The influence of tumor-host interactions in the stromal cell-derived factor-1/CXCR4 ligand/receptor axis in determining metastatic risk in breast cancer," *The American Journal of Pathology*, vol. 175, no. 1, pp. 66–73, 2009.
- [68] J.-J. Lee, A. Drakaki, D. Iliopoulos, and K. Struhl, "MiR-27b targets PPAR γ to inhibit growth, tumor progression and the inflammatory response in neuroblastoma cells," *Oncogene*, vol. 31, no. 33, pp. 3818–3825, 2012.
- [69] K. L. Schaefer, K. Wada, H. Takahashi et al., "Peroxisome proliferator-activated receptor γ inhibition prevents adhesion to the extracellular matrix and induces anoikis in hepatocellular carcinoma cells," *Cancer Research*, vol. 65, no. 6, pp. 2251–2259, 2005.
- [70] Y. Y. Zaytseva, X. Wang, R. C. Southard, N. K. Wallis, and M. W. Kilgore, "Down-regulation of PPAR γ suppresses cell growth and induces apoptosis in MCF-7 breast cancer cells," *Molecular Cancer*, vol. 7, article no. 90, 2008.
- [71] X. Wang, Y. Sun, J. Wong, and D. S. Conklin, "PPAR γ maintains ERBB2-positive breast cancer stem cells," *Oncogene*, vol. 32, no. 49, pp. 5512–5521, 2013.
- [72] D. Kesanakurti, D. Maddirela, Y. K. Banasavadi-Siddegowda et al., "A novel interaction of PAK4 with PPAR γ to regulate Nox1 and radiation-induced epithelial-to-mesenchymal transition in glioma," *Oncogene*, vol. 36, no. 37, pp. 5309–5320, 2017.
- [73] F. S. Forootan, S. S. Forootan, X. Gou et al., "Fatty acid activated PPAR γ promotes tumorigenicity of prostate cancer cells by up

- regulating VEGF via PPAR responsive elements of the promoter," *Oncotarget*, vol. 7, no. 8, pp. 9322–9339, 2016.
- [74] C. Patitucci, G. Couchy, A. Bagattin et al., "Hepatocyte nuclear factor 1 α suppresses steatosis-associated liver cancer by inhibiting PPAR γ transcription," *The Journal of Clinical Investigation*, vol. 127, no. 5, pp. 1873–1888, 2017.
- [75] A. Kourtidis, R. Srinivasaiah, R. D. Carkner, M. J. Brosnan, and D. S. Conklin, "Peroxisome proliferator-activated receptor- γ protects ERBB2-positive breast cancer cells from palmitate toxicity," *Breast Cancer Research*, vol. 11, no. 2, article R16, 2009.
- [76] T. Lapidot, C. Sirard, J. Vormoor et al., "A cell initiating human acute myeloid leukaemia after transplantation into SCID mice," *Nature*, vol. 367, no. 6464, pp. 645–648, 1994.
- [77] M. Al-Hajj, M. S. Wicha, A. Benito-Hernandez, S. J. Morrison, and M. F. Clarke, "Prospective identification of tumorigenic breast cancer cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 7, pp. 3983–3988, 2003.
- [78] M. Smalley and A. Ashworth, "Stem cells and breast cancer: a field in transit," *Nature Reviews Cancer*, vol. 3, no. 11, pp. 832–844, 2003.
- [79] B. D. Craene and G. Berx, "Regulatory networks defining EMT during cancer initiation and progression," *Nature Reviews Cancer*, vol. 13, no. 2, pp. 97–110, 2013.
- [80] H. Zheng, M. Shen, Y.-L. Zha et al., "PKD1 phosphorylation-dependent degradation of SNAIL by SCF-FBXO11 regulates epithelial-mesenchymal transition and metastasis," *Cancer Cell*, vol. 26, no. 3, pp. 358–373, 2014.
- [81] S. Lamouille, J. Xu, and R. Derynck, "Molecular mechanisms of epithelial-mesenchymal transition," *Nature Reviews Molecular Cell Biology*, vol. 15, no. 3, pp. 178–196, 2014.
- [82] F. A. Siebzehnrbul, D. J. Silver, B. Tugertimur et al., "The ZEB1 pathway links glioblastoma initiation, invasion and chemoresistance," *EMBO Molecular Medicine*, vol. 5, no. 8, pp. 1196–1212, 2013.
- [83] B. Dummmler, K. Ohshiro, R. Kumar, and J. Field, "Pak protein kinases and their role in cancer," *Cancer Metastasis Reviews*, vol. 28, no. 1-2, pp. 51–63, 2009.
- [84] M. Radu, G. Semenova, R. Kosoff, and J. Chernoff, "PAK signalling during the development and progression of cancer," *Nature Reviews Cancer*, vol. 14, no. 1, pp. 13–25, 2014.
- [85] D. Kesanakurti, C. Chetty, D. Rajasekhar Maddirela, M. Gujrati, and J. S. Rao, "Functional cooperativity by direct interaction between PAK4 and MMP-2 in the regulation of anoikis resistance, migration and invasion in glioma," *Cell Death & Disease*, vol. 3, article e445, 2012.
- [86] M. K. Y. Siu, H. Y. Chan, D. S. H. Kong et al., "p21-activated kinase 4 regulates ovarian cancer cell proliferation, migration, and invasion and contributes to poor prognosis in patients," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 43, pp. 18622–18627, 2010.
- [87] A. D. Whale, A. Dart, M. Holt, G. E. Jones, and C. M. Wells, "PAK4 kinase activity and somatic mutation promote carcinoma cell motility and influence inhibitor sensitivity," *Oncogene*, vol. 32, no. 16, pp. 2114–2120, 2013.
- [88] J. Feilchenfeldt, M.-A. Bründler, C. Soravia, M. Tötsch, and C. A. Meier, "Peroxisome proliferator-activated receptors (PPARs) and associated transcription factors in colon cancer: Reduced expression of PPAR γ -coactivator 1 (PGC-1)," *Cancer Letters*, vol. 203, no. 1, pp. 25–33, 2014.
- [89] G. Watkins, A. Douglas-Jones, R. Mansel, and W. Jiang, "The localisation and reduction of nuclear staining of PPAR γ and PGC-1 in human breast cancer," *Oncology Reports*, vol. 12, no. 2, pp. 483–488, 2004.
- [90] S. Srivastava, J. N. Barrett, and C. T. Moraes, "PGC-1 α / β upregulation is associated with improved oxidative phosphorylation in cells harboring nonsense mtDNA mutations," *Human Molecular Genetics*, vol. 16, no. 8, pp. 993–1005, 2007.
- [91] R. Haq, J. Shoag, P. Andreu-Perez et al., "Oncogenic BRAF regulates oxidative metabolism via PGC1 α and MITF," *Cancer Cell*, vol. 23, no. 3, pp. 302–315, 2013.
- [92] K. W. Fisher, B. Das, R. L. Kortum, O. V. Chaika, and R. E. Lewis, "Kinase suppressor of ras 1 (KSR1) regulates PGC1 α and estrogen-related receptor α to promote oncogenic ras-dependent anchorage-independent growth," *Molecular and Cellular Biology*, vol. 31, no. 12, pp. 2453–2461, 2011.
- [93] V. S. LeBleu, J. T. O'Connell, K. N. G. Herrera et al., "PGC-1 α mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis," *Nature Cell Biology*, vol. 16, no. 10, pp. 992–1003, 2014.
- [94] R. J. DeBerardinis, N. Sayed, D. Ditsworth, and C. B. Thompson, "Brick by brick: metabolism and tumor cell growth," *Current Opinion in Genetics & Development*, vol. 18, no. 1, pp. 54–61, 2008.
- [95] C. T. Hensley, A. T. Wasti, and R. J. DeBerardinis, "Glutamine and cancer: cell biology, physiology, and clinical opportunities," *The Journal of Clinical Investigation*, vol. 123, no. 9, pp. 3678–3684, 2013.
- [96] N. Sen, Y. K. Satija, and S. Das, "PGC-1 α , a key modulator of p53, promotes cell survival upon metabolic stress," *Molecular Cell*, vol. 44, no. 4, pp. 621–634, 2011.
- [97] W. Chen, Q. Wang, L. Bai et al., "RIP1 maintains DNA integrity and cell proliferation by regulating PGC-1 α -mediated mitochondrial oxidative phosphorylation and glycolysis," *Cell Death & Differentiation*, vol. 21, no. 7, pp. 1061–1070, 2014.
- [98] Z. Arany, S.-Y. Foo, Y. Ma et al., "HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1 α ," *Nature*, vol. 451, no. 7181, pp. 1008–1012, 2008.
- [99] K. A. O'Hagan, S. Cocchiglia, A. V. Zhdanov et al., "PGC-1 α is coupled to HIF-1 α -dependent gene expression by increasing mitochondrial oxygen consumption in skeletal muscle cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 7, pp. 2188–2193, 2009.
- [100] K. A. Rasbach, R. K. Gupta, J. L. Ruas et al., "PGC-1 α regulates a HIF2 α -dependent switch in skeletal muscle fiber types," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 50, pp. 21866–21871, 2010.
- [101] H. Zhang, P. Gao, R. Fukuda et al., "HIF-1 inhibits mitochondrial biogenesis and cellular respiration in VHL-deficient renal cell carcinoma by repression of C-MYC activity," *Cancer Cell*, vol. 11, no. 5, pp. 407–420, 2007.
- [102] E. LaGory, C. Wu, C. Taniguchi et al., "Suppression of PGC-1 α is critical for reprogramming oxidative metabolism in renal cell carcinoma," *Cell Reports*, vol. 12, no. 1, pp. 116–127, 2015.
- [103] H. Simonnet, N. Alazard, K. Pfeiffer et al., "Low mitochondrial respiratory chain content correlates with tumor aggressiveness in renal cell carcinoma," *Carcinogenesis*, vol. 23, no. 5, pp. 759–768, 2002.
- [104] N. Minsky and R. G. Roeder, "Direct link between metabolic regulation and the heat-shock response through the transcriptional regulator PGC-1 α ," *Proceedings of the National Academy*

of Sciences of the United States of America, vol. 112, no. 42, pp. E5669–E5678, 2015.

- [105] S. Zhang, X. Liu, J. Liu, H. Guo, H. Xu, and G. Zhang, “PGC-1 α interacts with microRNA-217 to functionally regulate breast cancer cell proliferation,” *Biomedicine & Pharmacotherapy*, pp. 541–548, 2017.
- [106] E. Piskounova, M. Agathocleous, M. M. Murphy et al., “Oxidative stress inhibits distant metastasis by human melanoma cells,” *Nature*, vol. 527, no. 7577, pp. 186–191, 2015.
- [107] C. Luo, H. R. Widlund, and P. Puigserver, “PGC-1 Coactivators: Shepherd the Mitochondrial Biogenesis of Tumors,” *Trends in Cancer*, vol. 2, no. 10, pp. 619–631, 2016.