



OPEN ACCESS

EDITED BY

Yingkun Xu,
Chongqing Medical University, China

REVIEWED BY

Jindong Xie,
Sun Yat-sen University Cancer Center
(SYSUCC), China
Qi-Dong Xia,
Huazhong University of Science and
Technology, China

*CORRESPONDENCE

Liyan Yu,
✉ yeah80@sina.com
Xueling Qu,
✉ quxuelingmm@sina.com
Tao Huang,
✉ 4133858@qq.com

RECEIVED 12 March 2023

ACCEPTED 05 May 2023

PUBLISHED 12 May 2023

CITATION

Sun J, Yu L, Qu X and Huang T (2023), The
role of peroxisome proliferator-activated
receptors in the tumor
microenvironment, tumor cell
metabolism, and anticancer therapy.
Front. Pharmacol. 14:1184794.
doi: 10.3389/fphar.2023.1184794

COPYRIGHT

© 2023 Sun, Yu, Qu and Huang. This is an
open-access article distributed under the
terms of the [Creative Commons
Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use,
distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication
in this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

The role of peroxisome proliferator-activated receptors in the tumor microenvironment, tumor cell metabolism, and anticancer therapy

Jiaao Sun¹, Liyan Yu^{2*}, Xueling Qu^{3*} and Tao Huang^{1*}

¹Department of Urology, First Affiliated Hospital, Dalian Medical University, Dalian, China, ²Department of Respiratory and Critical Care Medicine, First Affiliated Hospital, Dalian Medical University, Dalian, Liaoning, China, ³Dalian Women and Children's Medical Center(Group), Dalian, Liaoning, China

Peroxisome proliferator-activated receptors (PPARs) have been extensively studied for over 3 decades and consist of three isotypes, including PPAR α , γ , and β/δ , that were originally considered key metabolic regulators controlling energy homeostasis in the body. Cancer has become a leading cause of human mortality worldwide, and the role of peroxisome proliferator-activated receptors in cancer is increasingly being investigated, especially the deep molecular mechanisms and effective cancer therapies. Peroxisome proliferator-activated receptors are an important class of lipid sensors and are involved in the regulation of multiple metabolic pathways and cell fate. They can regulate cancer progression in different tissues by activating endogenous or synthetic compounds. This review emphasizes the significance and knowledge of peroxisome proliferator-activated receptors in the tumor microenvironment, tumor cell metabolism, and anti-cancer treatment by summarizing recent research on peroxisome proliferator-activated receptors. In general, peroxisome proliferator-activated receptors either promote or suppress cancer

Abbreviations: PPAR peroxisome proliferators-activated receptor; TME tumor microenvironment; WT1L wilms tumor inhibitor; ANGPTL4 angiotensin-like protein 4; PPRE peroxisome proliferative response element; PGI2 prostaglandin I2; PDGFR β platelet derived growth factor receptor beta; AKT1 AKT serine/threonine kinase 1; EIF4G1 eukaryotic initiation factor G1; CDK1 cyclin-dependent kinase 1; BTSC brain tumor stem cells; GPx3 glutathione peroxidase 3; NIS sodium iodide cotransporter; CD133 cluster of differentiation 133; ERK extracellular regulated protein kinases; MAPK mitogen-activated protein kinase; NHE1 Na⁺/H⁺ transporter gene; BRCA1 breast cancer susceptibility gene 1; LAMP-1 lysosomal associated membrane protein 1; PTEN phosphatase gene; LXR- α liver X receptor alpha; ABCA1 ATP-binding cassette transporter A1; PERK PKR-like ER kinase; CHOP C/Ebp-Homologous protein; ATF4 activating transcription factor 4; mPGES microsomal PGE synthase; RXR retinoid receptor; MPM malignant pleural mesothelioma; TRAIL tumor necrosis factor-associated apoptosis-inducing ligand; MCL mantle cell lymphoma; TNBC triple-negative breast cancer; PML Promyelocytic leukemia; EET epoxyeicosatrienoic acids; Cyp2c44 cytochrome P450 arachidonic acid epoxygenases; Bad Bcl-2-associated death protein; VEGF vascular endothelial growth factor; AMPK adenosine 5'-monophosphate -activated protein kinase; ERK extracellular regulated protein kinases; Bcl2 B-cell lymphoma-2; VDAC Voltage-dependent anion channel; PTPRZ1 protein tyrosine phosphatase receptor type Z1; Wnt8a Wnt family member 8 A; HNPGL head and neck paraganglioma; GB glioblastoma; ROSI Rosiglitazone; PGZ Pioglitazone; TGZ Troglitazone; CLL chronic lymphocytic leukemia; HMGCS2 3-Hydroxy-3-Methylglutaryl-CoA Synthase 2; GLUT glucosetransportertype; FAS fatty acid synthase; CPTIC carnitine palmitoyltransferase 1C; OXPHOS oxidative phosphorylation; ALDH acetaldehyde dehydrogenase; FASN fatty Acid Synthase; ACLY ATP citrate lyase; Acsc2 acetyl-coA synthetase 2; TSP-1 thrombospondin 1; Ang angiotensin; FGF2 fibroblast growth factor 2; PAI-1 plasminogen activator inhibitor 1

in different types of tumor microenvironments. The emergence of this difference depends on various factors, including peroxisome proliferator-activated receptor type, cancer type, and tumor stage. Simultaneously, the effect of anti-cancer therapy based on drug-targeted PPARs differs or even opposes among the three peroxisome proliferator-activated receptor homotypes and different cancer types. Therefore, the current status and challenges of the use of peroxisome proliferator-activated receptors agonists and antagonists in cancer treatment are further explored in this review.

KEYWORDS

PPARs, cancer, tumor microenvironment, metabolic reprogramming, anti-cancer therapy

1 Introduction

Peroxisome proliferator-activated receptors (PPARs) were first recognized as promoters of peroxisome proliferation more than 40 years ago. PPARs are ligand-induced transcription factors that belong to the nuclear receptor superfamily involved in nutrient and energy metabolism, regulating energy homeostasis throughout the body during lipid and carbohydrate metabolism, cell growth, and cancer development (Hong et al., 2019). In 1990, two researchers from the Central Toxicology Laboratory discovered a steroid hormone receptor in mice that is structurally similar to the steroid hormone receptors that have been described previously, but the two receptors are significantly different. The newly discovered receptor can be activated by different molecules, including fatty acids and fibrin, and mediates peroxisome proliferation; it was subsequently named PPAR α (NR1C1) and found to be expressed in frogs, mice, rabbits, and humans (Issemann and Green, 1990; Göttlicher et al., 1992; Sher et al., 1993; Guan et al., 1997). Later, in 1992, two more members of the PPARs family, PPAR β/δ (NR1C2) and PPAR γ (NR1C3), were discovered in humans and in the *Xenopus* frogs (Dreyer et al., 1992; Schmidt et al., 1992). Since then, due to their role as major regulators of metabolism and body energy homeostasis research on PPARs has grown exponentially. After ligand binding, PPARs bind to peroxisome proliferation reaction elements (PPREs) on DNA and after heterodimerization with retinoid X receptors, translocate to the nucleus to regulate the transcription of target genes (Phua et al., 2018; Tan et al., 2021).

All three types of PPARs share the basic structural characteristics of nuclear receptors, including four functional domains: A/B, C, D, and E/F. The A/B domain is an activated functional domain responsible for PPAR phosphorylation. The C domain consists of two zinc fingers and is responsible for PPARs binding to the peroxisome proliferative response element (PPRE) located in the promoter of the target gene. The D domain is the docking site for various cofactors. Finally, the E/F domain is involved in the recruitment of PPARs cofactors during transcription. The E domain is also called the ligand-binding domain, which enables PPARs to bind endogenous or exogenous ligands (Werman et al., 1997; Kota et al., 2005; Heidari et al., 2019). PPARs activated by different ligands participate in different physiological responses, including metabolism and energy homeostasis. The endogenous ligands of PPARs are mostly fatty acids and their derivatives, which are produced by diet, *de novo* synthesis of fatty acids, and lipolysis (Woller et al., 2016). The three

PPARs subtypes are highly homologous but encoded by different genes, distributed in different tissues, and exhibit different behavioral patterns in biological functions (Berger and Moller, 2002; Bensinger and Tontonoz, 2008; Schupp and Lazar, 2010). PPAR α is mainly expressed in the liver, brown adipose tissue, the heart, kidney, and muscle tissue, is involved in β -oxidation and fatty acid transport, and regulates lipid balance. PPAR β/δ is commonly expressed in skeletal muscle, adipose tissue, the heart, and the gastrointestinal tract and is involved in fatty acid metabolism. PPAR γ is expressed in adipose tissue and immune cells and is mainly responsible for regulating adipocyte differentiation and improving insulin resistance (Gross et al., 2017; Corrales et al., 2018). Based on this, PPARs are used to treat different aspects of the metabolic syndrome. Before PPARs were discovered, fibrin, a PPAR α agonist, was used as a lipid-lowering drug and remains the mainstream treatment for atherosclerotic dyslipidemia and atherosclerosis (Jellinger et al., 2017). The clinical effects of PPARs are not limited to metabolic disorders. So far, PPAR agonists have been tested in many human diseases, including neurodegenerative, psychiatric, autoimmune, inflammatory and malignant diseases, with varying degrees of success (Hong et al., 2018; Cheng et al., 2019).

Previous studies have shown that PPAR β/δ activation is associated with tumor progression, whereas PPAR α and PPAR γ activation is associated with tumor suppression. The role of PPAR in cancer has gradually become a research hot spot because such a generalization seems inappropriate due to the complex regulatory signals of PPARs, and their deep mechanism remains to be explored in detail (Cheng et al., 2019). Most anti-cancer therapies target cancer cells and largely ignore the tumor microenvironment (TME) component. The TME or tumor stromal community, consists of non-malignant host cells and non-cellular components. Over the past few decades, the role of TME in cancer progression and therapeutic efficacy has become apparent, and the function of PPARs in these stromal cells has received increasing attention and affects cancer progression directly and indirectly. The cellular environment of cancer cells is composed of homogeneous cell clusters along with highly dynamic and heterogeneous communities of distinct cell types, including fibroblasts, adipocytes, immune, endothelial, inflammatory, and mesenchymal stem cells, which are collectively termed tumor stromal cells (Balkwill et al., 2012). Cancer development is a complex and dynamic process involving three stages: initiation, progression, and metastasis, and the interaction between tumor stromal cells and cancer cells is critical for each step of tumorigenesis, during which cancer cells exhibit plasticity and resistance to various stressors and physiological signals (Kadosh

et al., 2020). At the same time, the metabolism and bioenergetics of cancer cells are very different from those of normal epithelial cells, and the high basal metabolic rate and abnormal neovascularization in the TME provide cancer cells with greater capacity for self-consumption of energy. The surrounding stromal cells may also play an essential role in this process.

We reviewed the mechanism of action of three subtypes of PPARs in cancer initiation and development, especially the TME energy metabolism and tumor cell mutations, along with the current progress and challenges of targeted PPARs in cancer treatment, to clarify the molecular basis and development direction for early cancer control.

2 The role of PPARs in TME

2.1 PPARs in tumor cells

In hepatocellular carcinoma, ectopic expression of PPAR α in cancer cells significantly inhibits cell proliferation and induces apoptosis. Specifically, the antitumor function of PPAR α is mediated by NF- κ B, as manifested by inhibition of NF- κ B promoter activity, decreased levels of p65, p50, and BCL2, and increased levels of I κ B α protein (Zhang et al., 2014). The deletion of PPAR α in the intestine increases the expression of DNMT1 and PRMT6, which in turn reduce the expression of tumor suppressor genes Cdkn1a (P27) and Cdkn3b (p2) through DNA methylation and histone H1R21 methylation-mediated transcriptional inhibition, respectively, to further promote colon carcinogenesis (Luo et al., 2019).

In addition, most studies support the anti-cancer effects of PPAR γ ; for instance, a 2019 study found that high expression of PPAR γ was associated with a good prognosis in patients with colorectal cancer (Yaghoobzadeh et al., 2020). PPAR γ inhibits colorectal cancer by regulating cell differentiation and the expression of cell cycle regulators (Chen et al., 2005; Drori et al., 2005). In cervical and liver cancer, PPAR γ upregulates the expression of the tumor suppressor gene PTEN, suppresses the PI3K signaling pathway, and reduces the self-renewal and aggressiveness of cancer stem cells (Liu et al., 2013a; Bigoni-Ordóñez et al., 2018). Regarding cancer cell proliferation, multiple cyclins and cyclin-dependent kinases (CDKs) are positive regulators of cell cycle progression, and activated PPAR γ promotes cyclin D1 ablation and induces cell arrest (Motomura et al., 2000; Huang et al., 2005). Similarly, when PPAR γ is activated by ligand binding, it interacts with Sp1 to stimulate p21 gene transcription and thereby induces the G0/G1 phase arrest in human colorectal and gastric cancer cells (Liu et al., 2018). In another *in vivo* study in a rat model of breast cancer, direct upregulation of PTPRF gene expression by PPAR γ had some inhibitory effect on tumor cell proliferation (Xu et al., 2019).

Recently, the dual roles of PPAR β/δ in cancer have been fully explored, most of which are cancer-promoting activities, especially in colorectal cancer (Wagner and Wagner, 2020). First, the IL-6/STAT3 pathway is a key signaling pathway in colitis-associated colorectal cancer. In mouse models of colitis-associated colon cancer, PPAR β/δ increased IL-6 expression and phosphorylation of STAT3, promoting tumorigenesis, while the concomitant 15-

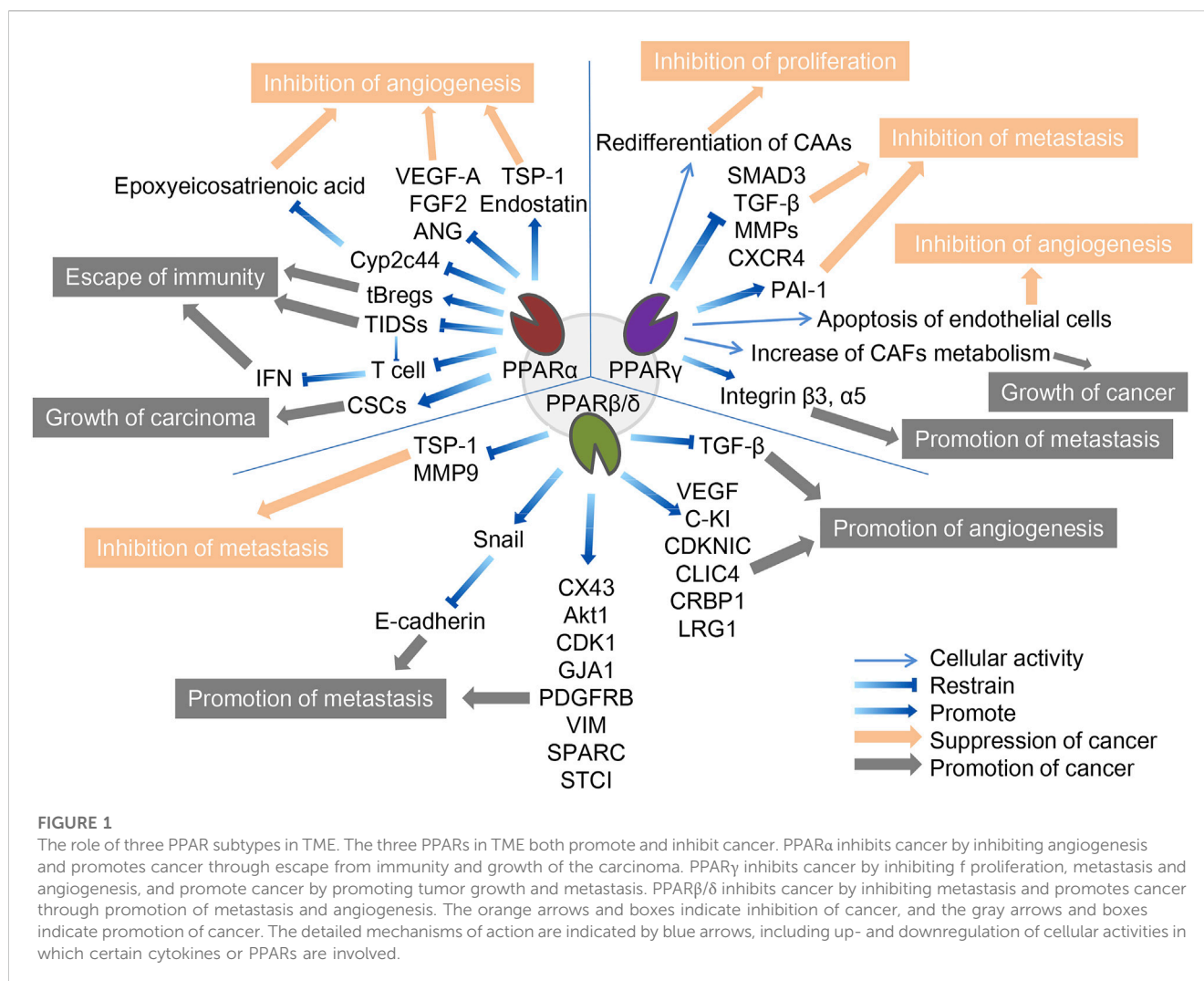
lipoxygenase-1 in colon epithelial cells inhibited these effects by downregulating PPAR β/δ (Mao et al., 2015). In mouse models of skin cancer, ultraviolet light exposure induced PPAR β/δ activity, further stimulated Src expression, increased Src kinase activity, enhanced the EGFR/Erk1/2 signaling pathway, increased EMT markers expression, and increased tumor burden (Montagner et al., 2014). In prostate cancer cells, PPAR β/δ , as a key target of transforming growth factor β 1 (TGF- β 1), activates the cholesterol transporters ABCA1 and cave protein-1 (Cav1), leading TGF- β 1 to induce tumor growth, migration, and invasion (Her et al., 2013).

We believe that the different environment of tumor cells may cause differences in the function of the three PPAR subtypes on cancer cells. Therefore, we will further analyze the mechanism of PPARs in TME (Figure 1).

2.2 The role of PPAR α in TME

Since tumor cells grow rapidly and require adequate nutrients and oxygen supply, they enhance local blood perfusion by releasing angiogenic factors that would otherwise lead to hypoxia and death, a process significantly influenced by PPAR α , which can inhibit angiogenesis to varying degrees (Eales et al., 2016). It is important to mention that functional tumor endothelial cells (TEC), which evolved from endothelial cells lining the vascular system, contribute to the progression of most cancers by supporting tumor metabolism, secreting paracrine factors, and suppressing anti-tumor immune responses (Yang et al., 2021). First, the synthetic PPAR α agonists fenofibrate and Wy-14643 have been shown to inhibit vascular endothelial cell proliferation and tumor xenograft growth, whereas mice with PPAR α deficiency showed a notable ($p < 0.05$) increase in neovascularization (Pozzi et al., 2007; Panigrahy et al., 2008). Mechanistically, PPAR α affects vascular endothelial growth factor (VEGF) and fibroblast growth factor-mediated endothelial cell proliferation and migration by increasing antiangiogenic factors (thrombospondin-1 and endostatin) and decreasing pro-angiogenic factors (VEGF-A and angiopoietin) (Arima et al., 2017). In addition, NOX1 of the NADPH oxidase (NOX) family is a key mediator of angiogenesis, and PPAR- α is also a downstream regulator of NOX1-mediated angiogenesis, whose activity is inhibited by the presence of NOX1, indicating that in NOX1-deficient cells, the upregulated expression of PPAR- α blocks the angiogenic signals required for endothelial cell migration, germination, and angiogenesis (Garrido-Urbani et al., 2011). Finally, in endothelial cells, PPAR α reduced epoxyeicosatrienoic acid production through inhibition of arachidonic acid cyclooxygenase expression and also inhibited angiogenesis (Pozzi et al., 2010).

Unlike its role in angiogenesis, PPAR α 's effect on immune cells in TME is often pessimistic, ultimately leading to immunosuppression or even cancer immune escape. Tumor-infiltrating dendritic cells (TIDCs) are essential for the regulation of anti-tumor immunity, presentation of tumor-associated antigens to effector T cells, and induction of memory T cells to limit tumor cell growth and recurrence (Diamond et al., 2011). TIDCs that migrate to regional lymph nodes initiate antitumor T cell responses, where they are able to cross antigens from phagocytes to naive CD8+T lymphocytes (Hargadon, 2020). Tumor-derived exosomes carrying fatty acids



significantly activate PPAR α in TIDCs, resulting in increased intracellular lipid content and mitochondrial respiration, driving immune dysfunction and cytotoxic T-cell activation. In addition, colon cancer grew more slowly in PPAR α knockout mice than in wild-type mice, and TIDCs from PPAR α knockout mice showed stronger anti-tumor effects than wild-type mice, suggesting that the PPAR α signaling pathway is crucial in the immune function of TIDCs, and is involved in DC cell dysfunction caused by TME (Yin et al., 2020). Similarly, in the biological functions of T cells, the expression of PPAR α is downregulated after T cell activation, and the activated PPAR α can antagonize the F- κ B signaling pathway and cytokine production in lymphocytes, indicating that PPAR α is an endogenous inhibitor of T cell activation (Jones et al., 2002). IFN- γ levels produced by T cells were higher in PPAR α knockout mice than in wild-type mice. The androgens in human T cells increased PPAR α expression, resulting in decreased IFN- α and increased IL-17 production in male CD4⁺ T cells (Dreyer et al., 1992; Zhang et al., 2012). Compared to T cells, the role of PPAR α in B cells has not been well studied. It has been reported that lipid metabolite of leukotriene B₄ produced by breast cancer cells acts as an endogenous PPAR α agonist and induces immunosuppressive regulation of B cells (tBregs), thereby promoting distant metastasis of cancer cells. Inhibition of

PPAR α in B cells can block the production of tBregs, suggesting that targeting PPAR α may be beneficial in the regulation of tBregs-mediated cancer escape (Wejksza et al., 2013). PPAR α has a similar cancer-promoting effect in cancer stem cells. Cancer stem cells (CSCs) are the most self-renewing subpopulation in the TME, and their activity is positively correlated with malignant tumor progression; the higher the number of CSCs, the greater the potential for tumor development. By activating the stearoyl-CoA desaturase 1 pathway, the activated PPAR α was significantly upregulated for the maintenance of CSC stemness in human liver cancer (Ma et al., 2019). 4-Phenylbutyric acid (4-PBA) is a low molecular weight fatty acid that does not induce long-term liver tumors by itself. However, 4-PBA can promote the occurrence of hepatocellular carcinoma by activating the β -catenin signaling pathway to regulate PPAR- α for the initiation of liver cancer stem cells (Chen et al., 2021a).

2.3 Role of PPAR γ in TME

In addition to being important components of the TME, stromal cells such as tumor-associated fibroblasts (CAFs) and tumor-

associated adipocytes (CAAs) provide tumor cells with essential nutrients, including glutamine, L-lactic acid, fatty acids, and ketone bodies. As an important component of tumor stromal cells, CAFs affect the activation of immune cells in TME and the deposition of extracellular matrix (ECM), and its activation is often a key feature of malignant tumors (Chen et al., 2021b; Zheng et al., 2023). These catabolic capacities are mostly secondary to ROS-induced stress responses, mechanistically mediated by HIF1- α and NF- κ B signaling. Among them, PPAR γ regulates several metabolic remodeling processes in CAFs. With the activation of NF κ B and the significant upregulation of COX-2 expression, PPAR γ expression was significantly upregulated in CAFs of cutaneous squamous cell carcinoma and colorectal adenocarcinoma (Vandoros et al., 2006; Chan et al., 2018). Increased glycolysis and L-lactic acid secretion in CAFs overexpressing PPAR γ was also observed, while the growth rate of MDAMD-231 breast cancer cells was significantly accelerated by the implantation of such CAFs (Avena et al., 2013). In addition, under hypoxic conditions, PPAR γ -dependent hypoxia-inducible factor 1 α (HIF-1 α) exacerbated the autophagic phenotype of tumor stromal cells, and the HIF1 α -PPAR γ -UCP2-AMPK pathway significantly affected the mitochondrial biological function of CAFs, resulting in the metabolic reprogramming of CAFs and exacerbating breast cancer growth (Boutoual et al., 2018; Wang et al., 2019). Therefore, PPAR γ turned CAFs into an energy-exporting machine to support tumor growth.

In addition to CAFs, mesenchymal stem cells can differentiate into adipose precursor cells, which further differentiate into CAA after stimulation by PPAR γ , which is called adipogenic differentiation. Normal fat cells are mainly considered energy reservoirs to store surplus fuel, and new evidence suggests that they are also important endocrine cells, capable of producing a variety of hormones and chemokines that influence tumor behavior (Wolins et al., 2006; Deng and Scherer, 2010). In pancreatic cancer, cancer cells initiate de-differentiation of adjacent CAAs while the number of CAFs increases, accompanied by the loss of fat cell markers such as leptin, HSL, and PPAR γ , and the increase of fibroblast markers such as matrix metalloproteinase (MMP) 11 and α -SMA, which further drives the progression of pancreatic tumors (Zoico et al., 2016; Cai et al., 2019). In a mouse model of lip sarcoma, the activation of Notch signaling weakened PPAR γ ligand activity, which induced dedifferentiation of CAAs and aggravated tumor-like manifestations, while PPAR γ agonists effectively promoted adipocyte redifferentiation and delayed tumor progression (Bi et al., 2016). Similarly, in breast cancer, the deletion of specific PPAR γ in CAA downregulates BRCA1 expression and accelerates tumor formation and progression (Skelhorne-Gross et al., 2012). In breast cancer cells *in vitro* and *in vivo*, the activation of PPAR γ induces cancer cells to differentiate into fat cells and induces apoptosis of fat cells through the upregulation of transcription factor C/Ebp β , thereby inhibiting breast cancer cell growth (Li et al., 2015).

Like PPAR α , PPAR γ exhibits antiangiogenic effects. Previous studies have shown that ligand-activated PPAR γ can inhibit human umbilical vein endothelial cell (HUVEC) tube formation and VEGF-induced choroidal neovascularization *in vitro* and *in vivo*, and the ligand 15d-PGJ2 of PPAR γ has been shown to directly induce endothelial apoptosis (Bishop-Bailey and Hla, 1999; Xin et al., 1999).

However, contrary to the CAFs-dependent pro-tumor properties, PPAR γ reduces hepatoma cell metastasis by inhibiting the transcriptional activity of MMPs and smad family member 3 (SMAD3), thereby reducing hepatoma cell metastasis (Reka et al., 2010; Shen et al., 2012). Activation of PPAR- γ inhibits transforming growth factor β (TGF- β)-induced EMT in lung cancer cells and prevents metastasis by antagonizing SMAD3 function (Reka et al., 2010). Plasminogen activator inhibitor-1 (PAI-1), a member of the serine protease inhibitor family of serpins, inactivates urokinase-type plasminogen activators and inhibits extracellular matrix degradation. There is increasing evidence that PAI-1 is involved in cell migration, tumor invasion, and metastasis. In hepatocellular carcinoma, β -estradiol (E2) activates PPAR γ in cancer cells, and activated PPAR γ inhibits cell invasion by upregulating the expression of PAI-1 (Pang et al., 2013). By inhibiting NF- κ B, activated PPAR γ significantly reduced the expression of pro-inflammatory, pro-angiogenic, and pro-transfer signaling molecules in the TME, including IL-6, IL-8, CXCR4, MMP2, and MMP9, which further inhibited the activity of tumor cells in breast cancer (Papi et al., 2014; Rovito et al., 2016). But at the same time, TAM, as one of the most abundant immune cell groups in TME, may contribute to carcinogenesis by mediating neovascularization, immunosuppression and chemical resistance (Wang et al., 2021). Activation of PPAR γ in macrophages leads to lipid retention and PGE2 secretion, favoring their polarization toward anti-inflammatory tumor-associated macrophages (TAM), reducing M1 macrophage biomarkers, and tilting towards the M2 phenotype, thereby altering macrophage fate and reducing the Stat3-mediated pro-inflammatory response (Penas et al., 2015; Souza-Moreira et al., 2019; Gionfriddo et al., 2020; Christofides et al., 2021). The decrease of such proinflammatory macrophages reduces the host's defenses against microorganisms and weakens anti-tumor immunity (Strack et al., 2020). However, in melanoma, activation of PPAR γ enhances the expression of surface integrins, specifically integrin β -3 and integrin α -5, increasing the capacity for distant metastasis and implantation of cancer cells, a process also associated with the inhibition of thioredoxin-interacting protein (Meylan et al., 2021). Therefore, the role of PPAR γ on TME may be diverse, and further research is needed to explore its deeper mechanism.

2.4 Role of PPAR β/δ in TME

Unlike normal fibroblasts, CAFs are paracrine to tumor cells and disrupt the extracellular matrix, often exacerbating cancer spread. However, CAFs-selective PPAR β/δ deficient skin cancer mice showed some remission of metastasis. Similar results were later observed in mouse models of colon cancer (Yoshida et al., 2019; Tan et al., 2020). Mechanistically, the PPAR β/δ knockout CAFs significantly increased the production of reactive oxygen species (ROS) in the neighboring cells, and subsequently activated the RAF/MEK-mediated NRF2, which induced a strong cytoprotective response. Subsequently, the activated NRF2 reduced the phosphorylation of many oncogenes and upregulated the expression of the tumor suppressor gene PTEN. At the same time, it reduced the oncogenic activity of Src and Akt, thereby delaying the tumor process (Tan et al., 2018). In melanoma cell lines

with high metastatic potential, activation of PPAR β/δ causes upregulation of Snail and increased sensitivity to signaling stimuli for migration and invasion, where Snail acts as a transcription factor to inhibit E-cadherin transcription in epithelial cells, a phenomenon that can be reversed by inhibition of PPAR β/δ (Ham et al., 2014). In colon tumor tissues, the overexpression of PPAR β/δ intensified the activation of the adhesion protein β -catenin and several factors involved in cancer cell invasion, such as connexin 43, platelet-derived growth factor receptor β (PDGFR β), Akt1, EIF4G1, and CDK1, all of which promote colorectal cancer progression (Liu et al., 2019a). Similarly, PPAR β/δ also regulates novel metastasis genes such as GJA1, VIM, SPARC, STC1, and SNCG, accelerating the aggressiveness of colon cancer cells (Zuo et al., 2017).

In contrast, the synthetic ligand GW501516 decreased migration and invasion capacity in breast cancer cell lines *in vitro* following activation of PPAR β/δ . Its mechanism is thought to be regulated by platelet-reactive protein-1 (TSP-1) and its degrading proteases, and activated PPAR δ significantly inhibited breast cancer cell migration and TSP-1 expression (Ham et al., 2017). Similarly, after GW501516 activated PPAR β/δ , the expression of MMP9 was downregulated, and the invasion ability of pancreatic cancer cells *in vitro* decreased (Coleman et al., 2013).

Contrary to the inhibition of neovascularization by PPAR α and PPAR γ , PPAR β/δ is a nuclear receptor that promotes angiogenesis. As discovered in 2006, PPAR β/δ accelerates endothelial cell proliferation and enhances tumor cell feeding and metastasis by increasing VEGF, PDGFR, and c-KI biosynthesis (Piqueras et al., 2007; Wagner et al., 2019). Furthermore, the expression of other potential angiogenic mediators including cyclin-dependent kinase inhibitor 1C, IL-8, intracellular chloride channel protein 4, and cellular retinol-binding protein 1 are also affected by PPAR β/δ (Adamkiewicz et al., 2007; Müller-Brüsselbach et al., 2007; Meissner et al., 2010). Leucine-2 glycoprotein 1 (LRG1) is a unique protein produced by tumor tissue, and its inhibition has been shown to normalize blood vessels in tumors (O'Connor et al., 2021). Transforming growth factor β (TGF- β) is a multifunctional cytokine of the transforming growth factor superfamily, that upregulates tumor suppressor genes, induces differentiation, and improves cellular antioxidant properties (Meng et al., 2016). PPAR β/δ upregulates LRG1 expression in CAFs while attenuating the response of epithelial cells to TGF- β (Sng et al., 2018). In patients with colorectal and pancreatic cancer, LRG1 levels tends to be positively correlated with more advanced cancer stages and worse prognosis, and the PPAR β/δ agonist, GW501516, significantly increases LRG1 expression, strongly indicating that LRG1 is a direct target of PPAR β/δ (Zhou et al., 2017; Liu et al., 2019b; Xie et al., 2019). Compared with normal lung tissue, the expression of PPAR β/δ , Cox-2, c-PLA, PGES, and VEGF was increased in human non-small cell lung cancer, and tumor progression was associated with upregulation of PPAR β/δ , increased VEGF levels, and activation of the PI3K/Akt pathway. Specifically, VEGF induction is due to PPAR β/δ binding to the VEGF promoter, and PI3K/Akt pathway activation is due to PPAR β/δ interaction with the PI3K regulatory subunit p85 α , resulting in PI3K activation and Akt phosphorylation (Genini et al., 2012).

PPAR β/δ plays a unique role in combating endothelial apoptosis. As early as 2001, prostacyclin was found to induce apoptosis by activating PPAR β/δ in HEK293 cell lines, while endothelial cells in the cytoplasm expressing prostacyclin receptors are not affected by apoptosis. From this, prostacyclin-mediated activation of PPAR β/δ is seen to promote vascular endothelial apoptosis in cells lacking prostacyclin receptors (Hatae et al., 2001). A subsequent study further demonstrated that PPAR β/δ exerts anti-apoptotic effects and promotes angiogenesis by activating endothelial cell 14-3-3 ϵ protein (Brunelli et al., 2007). Prostacyclin 165,041 and carbonaceous prostacyclin (cPGL2) have a protective effect on H₂O₂-induced apoptosis, and both substances can increase the expression of PPAR β/δ (Liou et al., 2006). There is also evidence that the axis of the COX-2/PPAR β/δ signaling pathway may be important in the development of colorectal cancer by promoting angiogenesis (Yoshinaga et al., 2009). A recent study of the downstream activation targets of PPAR β/δ in angiogenesis demonstrated that blood vessel density increased and tumor growth and metastasis were enhanced in animals with vascular-specific overexpression of PPAR β/δ . Further RNA sequencing was carried out to identify the downstream targets of PPAR β/δ as PDGFR β , platelet-derived growth factor subunit B (PDGFb), and tyrosinase KIT (c-Kit) (Wagner et al., 2019).

In conclusion, the three types of PPARs play vital roles in cancer tissues, affecting the synthesis of neovascularization, the activity of cancer-like stem cells, the secretion of stromal cells, and the anti-tumor immune process. In such a complex regulatory network, it is impossible to conclude that a certain type of PPAR can inhibit or promote a certain type of cancer; rather, they often form a mutual regulatory cycle.

3 PPARs in the energy metabolism of cancer cells

PPARs play a key role in regulating multiple metabolic pathways such as glucose homeostasis, lipoprotein metabolism, fat production, and fatty acid uptake, and the dysregulation of these metabolic processes can lead to the onset of certain metabolic diseases, such as diabetes, nonalcoholic fatty liver disease, and atherosclerosis. In a fasting state, PPAR α accelerates the formation of fatty acids by lipolysis in hepatic adipose tissue by regulating the expression of apolipoprotein, increases the level of plasma high-density lipoprotein cholesterol, and decreases the level of low-density lipoprotein cholesterol (Berthou et al., 1996; Schoonjans et al., 1996; Vu-Dac et al., 2003). PPAR γ decreased the content of free fatty acids in all organs except adipose tissue and circulating blood, thereby increasing the triglyceride storage capacity of adipose tissue (Gross et al., 2017). In contrast, the effects of PPAR β/δ on different nutrient supply states were not significantly different. PPAR β/δ can promote the catabolism of fatty acids in skeletal muscle and inhibit lipogenesis in adipose tissue (Derosa et al., 2018). PPAR α antagonizes the role of insulin in glucose homeostasis, promotes glycolysis and new fatty acid synthesis, and reduces gluconeogenesis, whereas PPAR γ plays opposite roles in glucose homeostasis, including increased insulin sensitization in skeletal muscle, improved glucose-stimulated insulin

secretion in pancreatic beta cells, and increased gluconeogenesis in the liver, and PPAR β/δ is important in promoting glycolysis, glycogen storage, and reducing gluconeogenesis (Finck et al., 2005; Lee et al., 2006; Ahmadian et al., 2013).

Metabolic reprogramming is essential for cancer cells to adapt to changing environments as tumors develop the features of aggressive cancers. In TME, tumor cells exhibit more active metabolic behavior, making their growth possible in this harsh environment. Among these features, increasing glucose uptake and glycolysis, called the Warburg effect, is the first well-known adaptive metabolic event, providing the most direct source of energy for cancer cells, which is essentially glycolysis in the oxygen microenvironment; enhanced glutamine depletion and dissolution provide carbon and amino nitrogen; abnormal lipid metabolism compensates cancer cells for glucose-based energy and biofilm components and regulates proliferation, survival, and metastasis (Altman et al., 2016; Hay, 2016; Luo et al., 2017). While metabolic disorders of cancer cells may directly affect cancer progression, there is early evidence that the activation of PPARs affects tumor metabolism by interfering with the Warburg effect, and the mechanism of action of three PPARs subtypes in cancer cell metabolism will be explored (Grabacka et al., 2013; Han et al., 2017a; Han et al., 2017b) (Figure 2).

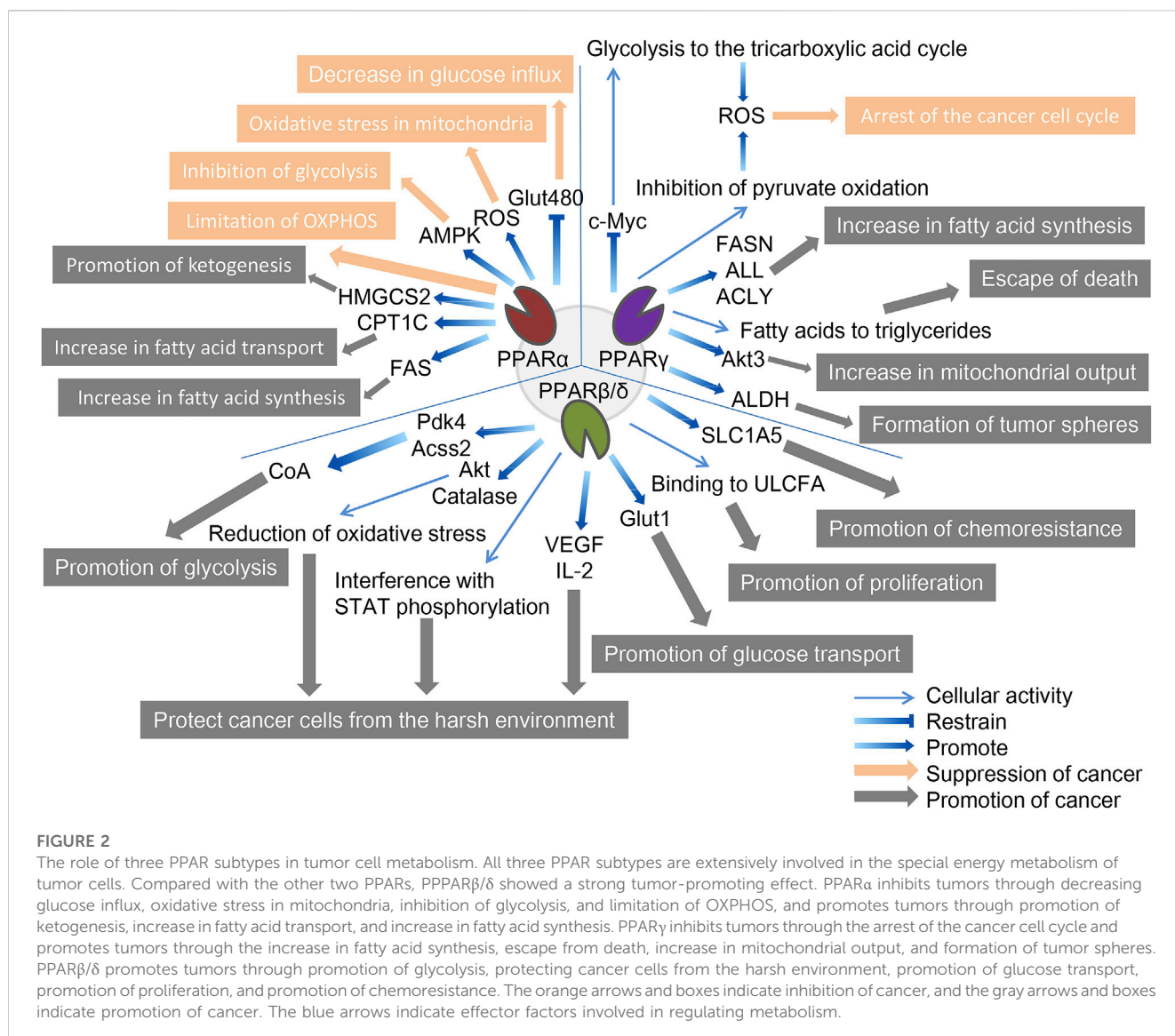
3.1 PPAR α

Activation of PPAR α regulates gene expression of specific proteins involved in mitochondrial and peroxisomal function, which dominate the β -oxidation of fatty acids, glucose metabolism, and fatty acid transport (Feige et al., 2006; Rakhshandehroo et al., 2010). The genes regulated by PPAR α can determine their cancer-promoting or cancer-suppressing effects due to their relationship with tumor metabolism; for example, inhibitory and promoting effects have been reported in melanoma and breast cancer, respectively (Suchanek et al., 2002; Grabacka et al., 2006).

In terms of cancer promotion, CSCs, as the starting cell population of tumor tissue, exhibit similar self-renewal and differentiation characteristics to normal stem cells and significant upregulation of PPAR α , and are important in energy metabolism (Fidoamore et al., 2016). Glioblastoma stem cells are metabolically reprogrammed under hypoxic conditions by upregulating glucose transporters, glucose uptake, and glycogen and lipid storage, in a process that results from the activation of PPAR α by hypoxia-inducible factor-1 (HIF-1). The use of GW6471 to antagonize PPAR α activity was found to improve glucose and lipid tumor metabolism, thereby reducing glioblastoma proliferation (Fidoamore et al., 2017). In another study, two renal cell cancer cell lines (Caki-1 and 786-O cell lines) were cultured using GW6471, and higher levels of PPAR α were observed in high-grade cancer cells than in low-grade cancer cells, requiring high levels of fatty acid oxidation due to their need for more energy, which is regulated upstream by PPAR α signaling (Perroud et al., 2009). Furthermore, blocking PPAR α in renal cell cancer cell lines under the synergistic effect of glycolytic inhibition significantly reduced the levels of the cell cycle-related proteins cyclin D1 and CDK4, and blocked the cell cycle in the G0/G1 phase, thereby reducing cell viability (Shah et al., 2007; Wang et al., 2011). Fatty acid synthase (FAS) is significantly

upregulated in urinary tumors, the metabolic intermediate in the process of fatty acid synthesis is the endogenous ligand of PPAR α . Activated PPAR α further regulates glucose, lipid, and cholesterol metabolism of tumor cells, and inhibition of FAS in mice can lead to PPAR α dysfunction. In addition, PPAR α induces fatty acid synthesis by upregulating FAS, and increased FAS expression may indicate tumor aggressiveness and poor prognosis in renal cell carcinoma (Chakravarthy et al., 2005; Chakravarthy et al., 2007; Horiguchi et al., 2008). Elevated expression of genes involved in fatty acid oxidation and glucose metabolism have also been observed in human hepatocellular carcinoma tissues, including PPAR α , carnitine palmitoyl transferase 1A (CPT1A, an FAO rate-limiting enzyme), glyceraldehyde 3-phosphate dehydrogenase (G3PDH), and cyclin D1 (Kurokawa et al., 2011). Similar to CPT1A, carnitine palmitoyl transferase 1C (CPT1C), an enzyme located in the outer mitochondrial membrane, is involved in fatty acid transport and oxidation and in cell proliferation, a potential driver of cancer cell senescence. The study confirmed that CPT1C is a novel target gene of PPAR α , and that knockout of PPAR α leads to a decrease in CPT1C expression, which inhibits the proliferation of MDA-MB-1 and PANC-1 tumor cell lines in a CPT1C-dependent manner (Chen et al., 2017a). Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2) is a rate-limiting enzyme for ketogenesis that catalyzes the first enzymatic reaction in the ketogenic process, and HMGCS2 expression is associated with clinical prognosis and poor prognosis in patients with colorectal cancer and oral squamous cell carcinoma. Studies have demonstrated that PPAR α and HMGCS2 directly interact, resulting in the activation of the proto-oncogene Src and promoting the growth and invasion of malignant tumors (Saraon et al., 2013; Chen et al., 2017b). PPAR α signaling also improves lipid turnover, which is the rate at which lipids are removed and stored in fat cells, and maintains the high energy requirements of tumor cells to ensure the stemness and self-renewal ability of pancreatic and colorectal cancer stem cells (Kuramoto et al., 2021). Given the interaction between PPAR- α and hormone metabolism, the researchers found that activated PPAR- α increased the expression and activity of CYP1B1 (a subtype of cytochrome P450), further influencing the occurrence and progression of hormone-dependent tumors including breast cancer through the biotransformation of endogenous estrogens and environmental carcinogens (Hwang et al., 2019).

In terms of cancer suppression, studies have demonstrated that, on the one hand, PPAR α limits the process of mitochondrial oxidative phosphorylation (OXPHOS), and non-tumor cells are not affected by it; on the other hand, PPAR α increases the production of ROS, leading to the accumulation of mitochondrial oxidative stress in melanoma cells. At the same time, the activation of PPAR α also promotes the amp-activated protein kinase (AMPK) signaling pathway, which increases the oxidation of fatty acids, while effectively inhibiting the glycolysis of tumor cells, further reducing the production of ATP and resisting the occurrence of oral cancer (Chang and Huang, 2019; Grabacka et al., 2020). In addition, PPAR α in HCT-1, SW1, HeLa, and MCF-116 cancer cell lines reduced levels of the Glut480 (glucose transporter 7) protein. In contrast, silent PPAR α reversed this phenomenon. On further analysis, PPAR α directly targeted the consensus PPRE motif in the Glut1 promoter region, inhibiting Glut1 transcription, which in turn led to a



decrease in glucose inflow in cancer cells (You et al., 2017). The lipid-lowering drug fenofibrate as a PPARα agonist induces metabolic reprogramming in oral cancer, changing the protein expression of hexokinase II (HK II), pyruvate kinase, pyruvate dehydrogenase, and voltage-dependent anion channel, thus delaying tumor development (Jan et al., 2016). In addition, fenofibrate exhibits antitumor activity *in vitro* and *in vivo* through mitochondrial and metabolic reprogramming, altering glucose and lipid metabolism, inhibiting the proliferation of gastric cancer cells, and promoting apoptosis of gastric cancer cells, indicating mitochondrial regulation and normalization of cancer cell metabolism as new therapeutic strategies for cancer (Chen et al., 2020).

3.2 PPARγ

Similarly, although PPARγ has been extensively studied in the metabolic regulation of tumor cells, due to its complex regulatory

network does not allow conclusions to be reduced to simple cancer promotion or suppression. A study in 2009 reported that breast cancer cells positive for ERBB2 (an epidermal growth factor receptor, a marker of poor prognosis) produce large amounts of fat due to the activation of PPARγ, a key pathway for these cells to produce energy and survive. Activated PPARγ enables ERBB2-positive breast cancer cells that produce high levels of fat to convert fatty acids into triglycerides, allowing these cells to avoid cell death caused by lipotoxicity (Kourtidis et al., 2009). After PPARγ was identified as a mature positive regulator of adipogenesis and lipid storage in 2013, inhibition of PPARγ was reported to reduce aldehyde dehydrogenase (ALDH) activity in ERBB2-positive breast cancer cells. The results of an *in vitro* tumor spheroidization assay showed that the PPARγ antagonists GW9662 and T0070907 reduced tumor spheroids formation in ERBB2-positive cells (Wang et al., 2013). A 2014 study showed that activated PPARγ inhibited lung cancer cell proliferation by metabolic changes. Treatment with PPARγ agonist pioglitazone triggers metabolic switches that inhibit pyruvate oxidation and

reduce glutathione levels, and these metabolic changes lead to a significant increase in ROS levels and cell cycle arrest (Srivastava et al., 2014). This was followed in 2015 by the discovery of a link between the induction of PPAR γ activity and concomitant autophagy cell death in chronic myeloid leukemia cell lines (K562 and KCL-22). The anticancer fatty acid derivative AIC-47 binds and activates PPAR γ , indirectly reduces the expression level of oncogene c-Myc, and leads to β -catenin inactivation and increase of the PKM1/PKM2 ratio. Metabolism shifts from glycolysis to the tricarboxylic acid cycle, and at the same time, ROS levels increase, inducing autophagy in cancer cells (Shinohara et al., 2015). The following year, a study based on Sleeping Beauty confirmed that the insertion of mutations in the PPAR γ gene made mice more tumor-aggressive. PPAR γ overexpression determines the upregulation of enzymes involved in *de novo* fatty acid synthesis, and in contrast, this effect is masked by PPAR γ knockout (Ahmad et al., 2016). Similarly, in prostate cancer, overexpression of PPAR γ promotes Akt3 activity, inhibits nuclear output protein CRM1, and enhances nuclear retention of PPAR γ coactivator 1 α (PGC1 α). This activity increases mitochondrial ATP output in cancer cells to meet the high energy demands of EMT and cancer cell metastasis (Galbraith et al., 2021).

In our cancer suppression review, we reported that PPAR γ stimulates adipogenesis in colorectal and breast cancer cells, disrupting the YAP-Hippo signaling pathway, thereby forcing terminal differentiation and inhibiting the proliferation of cancer cells (Sarraf et al., 1998; Basu-Roy et al., 2016). Ornithine decarboxylase 1 (ODC1) is a metabolic enzyme key involved in polyamine biosynthesis, typically upregulated in hepatocellular carcinoma. After siRNA silenced ODC1, the downregulation of ODC1 led to the upregulation of Krüppel-like factor 2 (KLF2), which in turn led to a decrease in PPAR γ levels, inhibition of the expression of important regulators affecting glucose transport and lipid biogenesis in cancer cells, and a significant reduction in lipid droplet accumulation (Banerjee et al., 2003; Choi et al., 2016).

In addition, we found that several typical epithelial cancers share a common feature: disruption of the Wnt/ β -catenin pathway, which often leads to the upregulation of enzymes associated with aerobic glycolysis. In many tissues, PPAR γ activation induces inhibition of the β -catenin pathway, and activation of the typical Wnt/ β -catenin pathway inactivates PPAR γ . The development of most cancers is often accompanied by downregulation of PPAR γ and upregulation of Wnt/ β -catenin pathway (Lecarpentier et al., 2017). Specifically, ligand-activated Wnt ligands trigger nuclear translocations of β -catenin and bind to target genes, including pyruvate dehydrogenase kinase (PDK), monocarboxylic lactate transporter-1 (MCT-1), c-Myc, and COX-2, while downregulation of PPAR γ is associated with upregulation of Wnt/ β -catenin. PDK1 acts as phosphorylating pyruvate dehydrogenase, which is converted to lactate by activating lactate dehydrogenase. Simultaneously, MCT-1 is involved in the secretion of extra cytoplasmic lactic acid. Therefore, PPAR γ inhibits PDK1 and MCT-1 gene transcription, resulting in ineffective activation of the Wnt/ β -catenin pathway (Abbot et al., 2005; Lecarpentier et al., 2014). Activated PPAR γ promotes cell cycle arrest, cell differentiation, and apoptosis, while downregulation of the Wnt/ β -catenin pathway reduces the release of inflammatory factors (TNF- α , TGF- β , IL-6, and IL-8) and oxidative stress. This

pathway inhibits hepatocellular carcinoma metastasis (Vallée and Lecarpentier, 2018; Zuo et al., 2021).

3.3 PPAR β/δ

Compared with that of the other two PPARs, the cancer-promoting effect of PPAR β/δ is more widely recognized. Early studies have shown that PPAR β/δ is a transcription factor associated with metabolic gene regulation and inflammation, which is related to tumor promotion and PDK1 regulation, as a key regulator of the AGC protein kinase family, which includes proto-oncogenes such as Akt and PKB associated with several malignancies, including breast cancer. The PI3K/Akt pathway is known to phosphorylate and activate ATP citrate lyase, the target gene Pdk4 of PPAR β/δ slows the flow of pyruvate to oxidative phosphorylation, and Acss2 (a member of the acyl-CoA synthase short-chain family 2) promotes the conversion of lactate to pyruvate. These three proteins work synergistically to increase the content of acetyl-CoA to promote glycolysis and fatty acid synthesis, while the PPAR β/δ agonist GW501516 improves their prometabolic efficiency and increases cancer cell aggressiveness in cancer model mice (Di-Poi et al., 2002; Pearce et al., 2010; Pollock et al., 2011).

To explore the mechanism whereby PPAR β/δ expression in patients with breast cancer is inversely correlated with survival, human breast cancer cells were cultured under conditions of low glucose and other endoplasmic reticulum stress (such as hypoxia), and cells overexpressing PPAR β/δ had the better potential for multiplication. Conversely, cells that knocked down PPAR β/δ expression had a proliferation rate comparable to that of the control group, and this was associated with elevated levels of catalase and Akt protein. In summary, PPAR β/δ regulates the viability of breast cancer cells in harsh environments by reducing oxidative stress and enhancing metabolic efficiency (Wang et al., 2016). A similar phenomenon has been found in chronic lymphocytic leukemia (CLL) cells: glucocorticoids or synthetic PPAR β/δ agonists are upregulated in depleted tissue culture media (low glucose levels, hypoxia, and exposure to cytotoxic drugs), protecting CLL cells from metabolic stressors (Li et al., 2017). Follow-up studies demonstrated that lipid-activated PPAR β/δ in CLL induces high cholesterol and plasma membrane levels and enhances interferon-dependent STAT phosphorylation (Sun et al., 2018). To further investigate the effect of PPAR β/δ on the survival of cancer cells in harsh environments, Jeong et al. found that the expression of hypoxia-induced tumor-promoting cytokines IL-2 and VEGF was significantly weakened in PPAR δ -deficient HCT116 colon cancer cells; in other words, PPAR δ deletion led to colon cancer cells failing to stimulate endothelial cell angiogenesis and macrophage migration. PPAR β/δ is regulated by PI3K/Akt upstream, but can itself regulate the expression of PI3K and Akt; that is, there may be a closed-loop system between the two (Jeong et al., 2014).

Based on the upstream regulation of promyelocytic leukemia (PML) protein, a PML-PPAR β/δ -fatty acid oxidation pathway maintained hematopoietic stem cell (HSC) activity, and the activation of PPAR β/δ increased the asymmetric cell division of HSCs, which has potential therapeutic significance (Ito et al., 2012). Later, PML was found in breast cancer as a negative regulator of the

acetylation of PPARs co-activator 1 A (PGC1A), and an effective activator of PPARs signaling and fatty acid oxidation (Carracedo et al., 2012). Based on the ability of transmembrane transporters to transport nutrients from the extracellular compartment to the cytoplasm, K-Ras-mediated glucose transporter-1 (Glut1) expression leads to increased glucose uptake and cell survival under low glucose conditions, and PPAR δ directly regulates Glut1 gene transcription, increasing glucose and amino acid uptake, activating mTOR signaling, resulting in tumor progression. Conversely, silencing PPAR δ inhibited this process, and in addition, PPAR δ promoted chemoresistance in cancer cells, which was alleviated by PPAR δ antagonists (Ying et al., 2012; Boroughs and DeBerardinis, 2015; Zhang et al., 2017). Another study reached similar conclusions, where activating PPAR δ significantly increased Glut1 and solute carrier family member 5 (SLC1A5) gene and protein expression in multiple cancer cell lines (HCT-1, SW1, HeLa, and MCF-1), while metformin inhibited this, which was associated with metformin-mediated inhibition of PPAR δ activity (Ding et al., 2019).

Long-chain fatty acids (LCFAs) are energy sources, building blocks of cell membranes, and constituent precursors of signaling molecules. Dietary fatty acids are associated with colon cancer risk, saturated long-chain fatty acids (SLCFAs) are positively correlated with colon cancer risk, and unsaturated long-chain fatty acids (ULCFAs) are negatively correlated. A recent study linking LCFA to PPAR β/δ showed that LCFA binds FABP5 from the cytoplasm to nuclear PPAR β/δ and replaces endogenous ligands and retinoic acid conduction, where SLCFAs inhibit the FABP5-PPAR β/δ pathway to inhibit cancer and ULCFAs activate the FABP5-PPAR β/δ pathway to increase cancer cell proliferation (Hardy et al., 2000; Li et al., 2011; Hodge et al., 2015; Levi et al., 2015).

4 Advances in targeting PPARs in cancer therapy

Due to the potent metabolic regulatory properties and gene targeting of PPARs, PPAR regulators have been widely used in the treatment of several diseases, including obesity, dyslipidemia, type II diabetes, and various metabolic disorders. Strong evidence suggests that PPAR modulators regulate cancer cell proliferation and differentiation, but the results are sometimes unclear or even contradictory, and the relevant progression of each of the three PPAR subtypes in cancer is described below (Heudobler et al., 2018; Cheng et al., 2019) (Table 1–3).

4.1 PPAR α

The synthetic ligands of PPAR α include fenofibrate, clofibrate, and wyeth14643, which are not only particularly effective clinical lipid-lowering drugs but also effective anticancer drugs. Like other fibrates, fenofibrate is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease, and its anti-cancer effects have recently been reported: 1) Inhibition of B-cell lymphoma in mice by regulation of lipid metabolism, specifically, stimulation of the uptake of free fatty acids in the liver, and restoration of the oxidation ability of liver fatty acids, thereby accelerating the clearance of lipids

released by white adipose tissue (Huang et al., 2013). 2) Fenofibrate-mediated IGF-IR inhibition with PPAR α -dependent metabolic induction and the resulting accumulation of ROS helps counteract glioma cell spread; likewise, fenofibrate-induced PPAR α activation inhibits IGF-I-mediated growth and survival responses of medulloblastoma cell lines (Urbanska et al., 2008; Drukala et al., 2010). 3) based on the weakening of MMPs expression, the enhancement of AMPK phosphorylation, and the inhibition of NF- κ B and its DNA-binding activity, fenofibrate resists the invasion and migration activity of Cal27 human oral cancer cells; in addition, fenofibrate activation of PPAR- α may induce a decrease in the migration ability of oral cancer cells *in vitro* by interfering with the Warburg effect, and the mechanism may be to trigger the AMPK signaling pathway to inhibit Akt, downregulate mTOR activity through tsc1/2-dependent signaling pathway, and regulate the mitochondrial oxidative phosphorylation Warburg effect to control the energy-generating pathway (Tsai et al., 2016). 4) Fenofibrate not only alleviates glycolysis and lactic acid production in glioblastoma cells, but also damages the mitochondrial respiration of glioblastoma cells by inhibiting the transcriptional activity of NF- κ B/RelA and destroying its association with hypoxia-inducible factor 1 α (Han et al., 2015). 5) In gastric cancer, fenofibrate induces mitochondrial body mass programming through CPT1 and fatty acid oxidation pathways, as well as activating the AMPK pathway and inhibiting the HK2 pathway, thereby regulating glycolipid metabolism, inhibiting the growth of gastric cancer cells, and causing apoptosis of gastric cancer cells (Chen et al., 2020).

The combination of fenofibrate and tretinoin is a potent inhibitor of the growth of endometrial cancer cells *in vitro*; that of budesonide and fenofibrate has a significant inhibitory effect on A549 lung cancer cells, and its mechanism is related to G1 cell cycle arrest, NF- κ B activity, and ERK signaling pathway. When docetaxel/mitoxantrone is combined with fenofibrate in prostate cancer cell lines, it increases the chemosensitivity of prostate cancer cells by interfering with energy metabolism and damaging drug-resistant cells (Saidi et al., 2006; Liang et al., 2014; Luty et al., 2019).

Clofibrate is a fibroic acid derivative that is clinically used as a lipid-lowering drug; in addition, it shows significant cytotoxicity to breast cancer cells. Specifically, clofibrate inhibits the growth of breast cancer cells by inhibiting the activation of NF- κ B and extracellular regulatory protein kinase 1/2 (ERK1/2), inhibiting the cyclin factor cyclin D1, cyclin A, and cyclin E, leading to cell cycle arrest and inducing pro-apoptotic factor P21 levels (Rakhshandehroo et al., 2010; Chandran et al., 2016). Clofibrate also causes apoptosis in human liver cancer HepG2 cells in a time- and concentration-dependent manner by increasing the expression of protein phosphatase-2A and Bcl-2 pro-apoptotic factor family BAD (Maggiora et al., 2010). For colorectal cancer SW480 cells, clofibrate significantly inhibits tumor proliferation and sensitizes SW480 cells to chemotherapy drugs in a PPAR α -dependent manner, thereby inducing anti-apoptotic Bcl2 protein degradation and promoting autophagy in tumor cells (You et al., 2018). PPAR α activated by clofibrate regulates cell cycle progression and apoptosis in pancreatic cancer cell lines, and the expression of PTPRZ1 and Wnt8a, two core components of the β -catenin pathway, is downregulated by clofibrate, increasing the sensitivity of pancreatic cancer cells to radiation therapy (Xue et al., 2018).

TABLE 1 Summary of the application of PPAR α -targeting drugs in cancer therapy.

Medicine	Manner	Cancer type	Experimental model	Mechanism
Fenofibrate	Excitation	Mantle cell lymphoma	MCL cell line	Downregulate the survival gene TNF- α , reduces the nuclear translocation of NF κ B
	Excitation	Breast cancer	TNBC cell line	Activate the NF- κ B pathway to induce apoptosis of breast cancer cells
	Excitation	Melanoma, breast cancer, Lewis lung cancer	B16-F10, MDA436, LLC cell line	Inhibit endothelial cell proliferation and VEGF production
	Excitation	Lymphoma	C57Bl/6J and PPAR α knock-out mice	Stimulate the liver to the intake of free fatty acids, restore the liver fatty acid oxidation capacity
	Excitation	Liver cancer	Huh7 human hepatoma cell line	Inhibit the proliferation of Huh7 cells by blocking Akt activation
	Excitation	Glioma	LN-229 and T98G glioma cell line	Inhibit IGF-IR and lead to ROS accumulation
	Excitation	Oral cancer	Cal27 human oral cancer cell line	Trigger AMPK pathway inhibits Akt, downregulates mTOR activity
	Excitation	Glioblastoma	U87 and U251 glioblastoma cell line	Impair mitochondrial respiration
	Excitation	Gastric cancer	MGC803 and SGC7901 human gastric cancer cell line	Induce mitochondrial reprogramming
Clofibrate	Excitation	Breast cancer	SUM149PT and SUM1315MO2 breast cancer cell line	Led to cell cycle arrest and inducing the level of pro-apoptotic factor P21
	Excitation	Liver cancer	HepG2 human liver cancer cell line	Induce cell apoptosis
	Excitation	Colorectal cancer	SW480 colorectal cancer cell line	Promote autophagy of tumor cells
	Excitation	Pancreatic cancer	Several pancreatic cancer cell line	Downregulate the expression of PTPRZ1 and Wnt8a
Wy14643	Excitation	Colorectal cancer	Mouse model of DSS induced colitis	Reduced levels of inflammatory cytokines
	Excitation	Non-small cell lung cancer	Wild type and CYP2C44-NULL (Cyp2c44 KO) mice	Downregulate Cyp2c44 expression and circulating EET to inhibit tumor angiogenesis
	Excitation	Colon cancer	SW620 colon carcinoma cell line	Reduce the transcriptional activation of genes involved in inflammatory response
	Excitation	Colorectal cancer	Several colorectal cancer cell line	Inhibits Glut1 transcriptional activity, glucose uptake, and mTOR pathways
GW6471	Inhibition	Breast cancer	MDA-MB-231 Breast cancer cell line	Reduce the viability, proliferation and globular formation of cancer stem cells
	Inhibition	Renal cell carcinoma	VHL (+) and VHL (-) RCC cell line (786-O and Caki-1)	Induce apoptosis and cell cycle arrest at G1/G4
	Inhibition	Head and neck paraganglioma	Primary HNPGL cells from HNPGL patients	Inhibit PI3K/GSK3 β / β -catenin signaling pathway, induce cell apoptosis
NXT629	Inhibition	Chronic lymphocytic leukemia	CLL cells taken from patients and CLL mouse model	Induce CLL cell apoptosis and reduce the tumor burden of CLL cell proliferation <i>in vivo</i>
AA452	Inhibition	Glioblastoma	GB patient-derived GB primary cell	Reduce intracellular cholesterol esters and lipid droplets, restrict cancer cell proliferation
MK866	Inhibition	Chronic lymphocytic leukemia	CLL cells taken from patients	Kill the circulating CLL cells

MCL: mantle cell lymphoma, TNBC: triple-negative breast cancer, EET: epoxyeicosatrienoic acids, Cyp2c44: cytochrome P450 arachidonic acid epoxygenases; Bad: Bcl-2-associated death protein; VEGF: vascular endothelial growth factor; AMPK: adenosine 5'-monophosphate -activated protein kinase; ERK: extracellular regulated protein kinases; Bcl2: B-cell lymphoma-2; PTPRZ1: protein tyrosine phosphatase receptor type Z1; Wnt8a: Wnt family member 8A; HNPGL: head and neck paraganglioma; GB: glioblastoma; CLL: chronic lymphocytic leukemia.

Wy14643 is a commonly used PPAR α agonist in breast cancer. In a DSS-induced mouse model of innate immune-mediated colitis, Wy-14643-activated PPAR α inhibited colorectal cancer by reducing inflammatory factor levels (Azuma et al., 2010). WY14643 attenuates the early stages of colon tumorigenesis by reducing AP-1 (activator-1)-mediated

transcriptional activation of genes involved in the inflammatory response such as Cox-2 and VEGF in a PPAR α -dependent manner (Grau et al., 2006). In addition, WY14643 can increase chemosensitivity by affecting the transcriptional activity of glucose transporter-1, inhibit the mTOR pathway, and lead to apoptosis of cancer cells (Gou et al., 2019).

TABLE 2 Summary of the application of PPAR γ -targeting drugs (Excitation) in cancer therapy.

Targeted medicine	Cancer type	Experimental model	Mechanism
Ciglitazone	Prostate cancer	p53 ^{+/+} and P53 ^{-/-} prostate cancer cell	Inhibit the anti-apoptotic function of Bcl-xL and Bcl-2
	Ovarian cancer	Ovarian cancer cell line	Block the TNF family death receptor signaling pathway
	Brain cancer	T98G and DB29 glioma cell line	Inhibit the proliferation of BTSC
	Breast cancer	MCF-1 breast cancer cell line	Inhibit cyclin D1 and expression of estrogen receptor alpha
	Ovarian cancer	Ovarian cancer implantation mouse model	Decrease the expression of COX-2, mPGES, and EP2, result in decreased angiogenesis and apoptosis
Troglitazone	Breast cancer	MCF-7 breast cancer cell line	Downregulate MMP-9 inhibited MCF-7 cell invasion
	Prostate cancer	PC-3 prostate cancer cell line	Upregulate E-cadherin and GPx3, reduce the growth and invasion of cancer cells
	Colon cancer	Colorectal cancer cell line	Modulate E-cadherin/beta-catenin pathway and Promote cancer cell differentiation
	Thyroid cancer	TPC-1, FTC-133, FTC-236, FTC-238, XTC-1 and ARO82-1 cell line	Downregulate CD133 surface expression and upregulate NIS, induce ant proliferation and redifferentiation of thyroid cancer cell lines
	Breast cancer	MDA-MB-75 and ZR-1-2 cell lines	Upregulate apoptosis signaling pathway
	Breast cancer	MCF-7, BT20, BT474 and other breast cancer cell line	Combined with retinoid receptors, inhibit the proliferation of cancer cells
	Gastric cancer	SGC7901 gastric cancer cell line	In combination with RXR agonists, increased Bax/Bcl-7901 levels were induced to inhibit SGC2 cell proliferation
	MPM	MPM cell line	Induce G1 cell cycle arrest and apoptosis
	Ovarian cancer	HEY cell line	Combined TRAIL overcomes chemical resistance in ovarian cancer
	Cervical cancer	HeLa, Ca Ski, C-33 A cell line	Decreased E6 virus oncoprotein expression, restore TRAIL sensitivity
	Breast cancer	MDA-MB-7 and MCF-7 cell line	Combined with tamoxifen to inhibit cancer cell proliferation
	Lung cancer	CL1-1 and A0 cell line	Downregulated Cdk2, E2F-1 and cyclin B1 to induce cell apoptosis
	thyroid cancer	Mouse xenotransplantation model	Result in G0/G1 phase cell cycle arrest
Pioglitazone	Glioma	Human glioma cell line	Inhibit glioma cell growth and invasion based on β -catenin
	Breast cancer	Human breast cancer cell line	Inhibit expressions of estrogen receptor and aromatase
	Liver cancer	From human primary cancer cell	Block the RAGE signaling to inhibit the growth and invasion of cells
	Lung cancer	NCI-H2347 and NCI-H1993 cell line	Inhibit pyruvate oxidation and increase ROS level
Rosiglitazone	Melanoma	A375 Human melanoma cancer cell line	Inhibit ERK phosphorylation and inhibit MAPK/ERK pathway
	Prostate cancer	PC-3 human prostate carcinoma cell	Inhibit CXCL12/CXCR4 axis, downregulate CxCl12-induced migration and invasion
	Pancreatic cancer	SW1990 pancreatic cancer cell line	Upregulate Bax, inhibit COX-2 and induce apoptosis of pancreatic cancer cells
	Breast cancer	MCF-7, MDA-MB-231 and T47D human breast cancer cells	Bind and inhibit NHE1, lead to sensitization of tumor cells to death
	Breast cancer	MCF-1 breast cancer cell line	Promote BRCA1 to induce cell apoptosis
	Adrenocortical carcinoma	SW13 adrenocortical cancer cells	Increase BECLIN-1 and LAMP-1 expression to promote autophagy
	Hepatocellular carcinoma	BEL-7402 and Huh-7 cell line	Promote the antitumor effect of 5-FU
Efatutazone	Lung adenocarcinoma	Lung adenocarcinoma cell line	Upregulate phosphatase and PTEN and inactivation of Akt pathway
	Lung adenocarcinoma	HCC827-GR and PC9-GR cell lines	Inhibit the expression of LXR- α and ABCA mRNA, and inhibit the proliferation
	Breast cancer	DCIS, MCFDCIS cells	Downregulate Akt phosphorylation and reduce tumor ball formation

(Continued on following page)

TABLE 2 (Continued) Summary of the application of PPAR γ -targeting drugs (Excitation) in cancer therapy.

Targeted medicine	Cancer type	Experimental model	Mechanism
Balaglitazone	Leukemia	K562/DOX human myeloid leukemia cells	Upregulate PTEN expression and reversal of drug resistance
CB13	Non-small cell lung cancer	3T3-L1, A549 and H460 cell line	Induce endoplasmic reticulum stress and cell death

BTSC: brain tumor stem cells; GPx3: glutathione peroxidase 3; NIS: sodium iodide cotransporter; CD133: cluster of differentiation 133; ERK: extracellular regulated protein kinases; MAPK: mitogen-activated protein kinase; NHE1: Na⁺/H⁺ transporter gene; BRCA1: Breast cancer susceptibility gene 1; LAMP-1: Lysosomal Associated Membrane Protein 1; PTEN: phosphatase gene; LXR- α : liver X receptor alpha; ABCA: ATP-binding cassette transporter A1; PERK:PKR-like ER, kinase; CHOP:C/Ebp-Homologous Protein; ATF4: activating transcription factor 4; mPGES: microsomal PG E synthase; RXR: retinoid receptor; MPM: malignant pleural mesothelioma; TRAIL: tumor necrosis factor-associated apoptosis-inducing ligand.

TABLE 3 Summary of the application of PPAR β/δ -targeting drugs in cancer therapy.

Targeted medicine	Cancer type	Experimental model	Mechanism
GW0742	Breast cancer	MDA-MB-231and MCF7 cell line	Inhibit proliferation without promoting apoptosis
	Colorectal cancer	DSS induced mouse model	Remit colorectal cancer progression caused by colitis
	Liver cancer	HBV mouse model	Inhibit steatosis and cell proliferation, enhance hepatocyte apoptosis and regulate anti-inflammatory activity in Kupffer cells
	Colon cancer	PPAR $\beta^{+/+}$ (-/-) mouse model	Reduce chemically-induced colon cancer and reduce intestinal polyps
	Melanoma	A0 and B10F100 cell line	Downregulate the expression of WT1 and inhibit the proliferation of melanoma cells
	Breast cancer	MCF0742 cell line	Upregulate ANGPTL4 to inhibit the proliferation of cancer cells
	Melanoma	UACC501516 cell line	Upregulate ANGPTL4 to inhibit the proliferation of cancer cells
	Melanoma	Melanoma cell lines	Inhibit melanoma cell proliferation by inhibition of WT1
L165041	Lung cancer	A549 lung cancer cell line	Control negative growth of lung cancer cells based on PGI2 signal
		UACC903 cells lines	Upregulate ANGPTL4 to inhibit the spread of cancer cells
GW501560	Breast cancer	MCF-7, MDA-MB-231 breast cancer cell lines	The interaction with c-Myc inhibits tumorigenicity of breast cancer cells
Antagonist GSK3787	Colorectal cancer	Human colorectal cancer organoid cells	Downregulate connexin 43, PDGFR β , AKT1, EIF4G1, and CDK1 to inhibited proliferation

WT1L: wilms tumor inhibitor; ANGPTL4: angiotensin-like protein 4; PGI2: prostaglandin I2; PDGFR β : platelet derived growth factor receptor beta; AKT1: AKT, serine/threonine kinase 1; EIF4G1: eukaryotic initiation factor G1; CDK1: Cyclin-dependent kinase 1; WT: Wilms tumor suppressor 1; ANGPTL4: Angiotensin-like protein 4.

Wy14643 combined with Benazofibrate also significantly inhibited lung cancer cell growth by activating PPAR α (Skrypnik et al., 2014).

Notably, in recent years, the research on synthetic PPAR α antagonists has considerably increased. For example, the antagonist GW6471 has anti-breast cancer cell proliferation and apoptotic effects. It can also induce apoptosis and cell cycle arrest of renal cell cancer cells and inhibit the process of glycolysis, hindering the progression of renal cell carcinoma. Based on the PI3K/GSK3 β / β -catenin pathway, GW6471 is associated with decreased viability and proliferation of head and neck paraganglioma (HNPGL) cells, which interferes with the cell cycle and induces apoptosis, thereby inhibiting the proliferation and migration of HNPGL cells (Abu Aboud et al., 2013; Florio et al., 2017; Castelli et al., 2021). The antagonist AA452 elicited metabolic reprogramming within tumor tissue and was found to increase sensitivity to radiotherapy in human glioblastoma primary cells by reducing intracellular

cholesterol esters and lipid droplets while regulating the mevalonate pathway, thereby limiting cancer cell proliferation and migration (Benedetti et al., 2017).

4.2 PPAR γ

Thiazolidinedione drugs (TZDs) are a class of synthetic ligands for the synthesis of PPAR γ , including rosiglitazone (ROSI), pioglitazone (PGZ), troglitazone (TGZ), and ciglitazone, which are commonly used clinically to lower blood sugar and resist cardiovascular and cerebrovascular diseases. In anti-cancer therapy, this class of drugs is involved in the cell cycle, apoptosis, and hormonal response, and other aspects of regulation, including intracellular Ca²⁺ depletion, proteasome degradation to induce cell cycle arrest and transcriptional inhibition of related hormone receptors, and reduction of macrophage activation, while they

also induce apoptosis to inhibit cancer cell proliferation by participating in reducing the expression of c-Myc, Bcl2, VEGF, and b-FGF (Wei et al., 2009; Zhang et al., 2013; Fröhlich and Wahl, 2015).

Initially, ciglitazone inhibits the cell cycle of cancer cells by partially consuming Ca²⁺ in cells, resulting in the passivation of eukaryotic initiation factor 2 to inhibit translational initiation and exert anticancer activity (Palakurthi et al., 2001). In the apoptotic pathway, ciglitazone can inhibit the anti-apoptotic function of Bcl-xL and Bcl-2 and improve the abnormal intrinsic apoptotic activity of prostate cancer cells (Shiau et al., 2005). By selectively inhibiting the apoptosis inhibitor protein FLIP, blocking early events of the TNF family death receptor signaling pathway, ciglitazone downregulates apoptosis signaling to eliminate tumor cells (Kim et al., 2002). Ciglitazone and another PPAR γ agonist 15d-PGJ2 inhibit the viability and proliferation of brain cancer stem cells by inhibiting SOX2 while enhancing the expression of the NANOG gene (Pestereva et al., 2012).

PGZ-activated PPAR γ targets estrogen receptors (ER) and aromatase, activates the tumor suppressor gene PTEN to inhibit ER expression or induce proteasome-dependent ER degradation, and inhibits aromatase through PGE2 and BRCA1 signaling pathways to prevent breast cancer progression (Margalit et al., 2012). Advanced glycosylated end product (RAGE) receptor is significantly expressed in human hepatocellular carcinoma (HCC), and is closely related to the pathological stage and tumor invasion. After PGZ treatment, PPAR γ expression in hepatoma cells was elevated and the growth and invasion of HCC cells were inhibited by blocking RAGE signaling (Yang et al., 2015). According to Srivastava et al., PGZ activation of PPAR γ induces metabolic switches; PPAR γ inhibits pyruvate oxidation by inhibiting pyruvate dehydrogenase kinase 4 (PDK4) or β -oxidation of fatty acids and reducing glutathione levels, resulting in a significant increase in ROS levels and ultimately inducing cell cycle progression in lung cancer cells (Srivastava et al., 2014).

ROSI is a second-generation thiazolidinedione PPAR γ agonist originally developed as an insulin sensitizer for the treatment of diabetes (Chi et al., 2021). The PI3K/AKT/mTOR and MAPK/ERK pathways are two important cell proliferation signaling pathways, among which PTEN is a natural inhibitor of the PI3K/AKT pathway, and ROSI activates PPAR γ in HCC cell lines to bind to PTEN promoters and increase the expression of PTEN. MAPK/ERK is a signaling pathway from membrane receptors to the nucleus, and PPAR γ activated by ROSI will inhibit phosphorylation of ERK, thereby inhibiting the growth of melanoma and breast cancer cells (Liu et al., 2006; Moon et al., 2010). In terms of cancer metastasis, ROSI activates PPAR γ and inhibits the activation of the PI3K-Akt pathway by inhibiting downregulation of CXCL12-induced migration and invasion on the CXCL12/CXCR4 axis in prostate cancer cell lines. In addition to chemokines, ROSI also inhibits the expression of some migration-related genes, including MMP-7, COX-2, and TIMP-1, thereby reducing tumor metastasis (Miao et al., 2011; Qin et al., 2014). ROSI also plays a certain role in promoting the apoptosis of tumor cells. Overexpression of COX-2 may be native, and inhibition of COX-2 after ROSI activation of PPAR γ has been shown to improve treatment outcomes in colon cancer. The Bcl-2 family is an effective regulator of apoptosis, while ROSI induces apoptosis in pancreatic cancer cells by upregulating

the expression of the Bax acceleration factor (Sun et al., 2009). The Na⁺/H⁺ transporter gene NHE1 is a permeable homeostatic regulator. Decreases in its expression cause tumor cell sensitivity to death, its promoter region has a PPAR γ response element, PPAR γ can bind and inhibit its expression, and histopathological analysis of breast cancer biopsies obtained from patients with type II diabetes treated with ROSI has shown significant inhibition of NHE1 in tumor tissue (Kumar et al., 2009).

In addition, efatutazone is a novel PPAR γ agonist belonging to the third generation of TZDs, and two independent studies reported that efatutazone upregulates PPAR γ , phosphatase, and PTEN protein expression and inactivates the Akt pathway. This inhibits the EGFR-TKI resistance pathway in lung adenocarcinoma, which works synergistically with LXR α , a member of another class of nuclear receptors reported to be a potential target for the prevention and treatment of a variety of cancers (Ni et al., 2017; Ni et al., 2018). In a phase 1 trial, oral efatutazone enhanced the efficacy of paclitaxel in treating thyroid cancer (Smallridge et al., 2013). Balaglitazone, another member of the TZDs family, has shown elevated expression of PPAR γ and PTEN, resulting in a partial reversal of P-glycoprotein-mediated multidrug resistance in doxorubicin-resistant human myeloid leukemia (K562/DOX) cells (Yousefi et al., 2017).

In terms of combined administration, the combination of ciglitazone and the chemotherapy drug cisplatin can improve the anti-cancer efficacy of human ovarian cancer (Yokoyama et al., 2011). Combined use of TGZ and human retinol X receptor RXR α ligand enhances the apoptosis and growth inhibitory effects on gastric and breast cancer cell lines (Elstner et al., 2002; Liu et al., 2013b). In ovarian and breast cancer cell lines that do not respond to conventional therapy, TGZ combined with the cell signaling molecule TNF-associated apoptosis-inducing ligand (TRAIL) showed effective synergistic pro-apoptosis results (Bräutigam et al., 2011; Plissonnier et al., 2017). Resistance to 5-fluorouracil (5-FU) is the main cause of chemotherapy failure in advanced hepatocellular carcinoma, and ROSI activation of PPAR γ increases PTEN expression and decreases COX-2 expression, inducing sensitivity to 5-FU antitumor activity in HCC cell lines (Cao et al., 2009). In addition, other drugs including lovastatin, aspirin, and the estrogen modulator tamoxifen have been reported as synergistic antitumor drugs with TGZ against thyroid, glioblastoma, lung, breast, and cervical cancer (Yao et al., 2006; Yu et al., 2008; Yan et al., 2010; Zhong et al., 2018).

4.3 PPAR β/δ

As early as 1999, Kinzler et al. determined that PPAR δ was the target of the tumor suppressor gene APC by analyzing the overall gene expression profile of human colorectal cancer (CRC) cells. PPAR δ expression is elevated in CRC cells, and APC inhibits its expression by inhibiting β -catenin/Tcf-4 regulatory transcription. Given that nonsteroidal anti-inflammatory drugs (NSAIDs) can inhibit colorectal tumorigenesis and the ability of PPARs to bind to eicosasulfonic acids, PPAR δ may also be a target for NSAIDs. APCs and NSAIDs inhibit the common target PPAR δ , thus providing a link between the genetic alterations behind tumor development and cancer chemoprevention (He et al., 1999).

Similarly, targeted inhibition of PPAR β/δ using aspirin in epithelial ovarian cancer cell lines expressing high levels of PPAR β/δ may reduce epithelial cell proliferation. Mechanistically, as a nonsteroidal anti-inflammatory drug that inhibits COX-1, aspirin impairs PPAR β/δ function and cell growth by inhibiting extracellular signal-regulatory kinase 1/2 (ERK1/2) (Daikoku et al., 2007).

In addition, several specific PPAR β/δ activators, GW0742, GW501516, L165041, and the antagonist GSK3787 play unique roles in cancer. The combination of GW0742 and the COX-2 inhibitor nimesulide can further reduce tumor diversity in wild-type mice (Zhu et al., 2010). In addition, GW0742 can slow the progression of colon cancer in mice and the carcinogenicity of human breast cancer cells, a phenomenon that was not observed in mice with PPAR δ knockout (Ouyang et al., 2006; Yao et al., 2014). In transgenic hepatitis B virus mice, long-term treatment with GW0742 reduced the number of liver tumor foci, based on a decrease in cyclin D1 and c-Myc expression, and activated PPAR δ reduced the proliferation of tumor cells (Balandaram et al., 2016). Another study showed that activation of PPAR β by GW0742 in mice led to increased expression of mRNA-encoding adipocyte differentiation-related proteins, fatty acid binding proteins, and cathepsin E, weakening chemically induced colon carcinogenesis (Marin et al., 2006). Culture of MCF0742 (breast cancer) and UACC501516 (melanoma) cells in the presence of GW0742 caused upregulation of the PPAR β/δ target gene angiopoietin-like protein 4 (ANGPTL4), and the growth of both tumor cell lines was inhibited (Girroir et al., 2008). GW0742-activated PPAR β/δ also inhibits the proliferation of different melanoma cell lines via its inhibition of Wilms tumor suppressor (WT1) promoter and direct transcriptional inhibition of its downstream target genes (Michiels et al., 2010). In addition, Liu et al. found that treatment with the PPAR δ antagonist GSK3787 inhibited colorectal cancer tumorigenesis in mice (Liu et al., 2019a). Agonist L165041 induces apoptosis in lung cancer cell lines when used in combination with the nonsteroidal anti-inflammatory drug indomethacin (Fukumoto et al., 2005).

4.4 Carcinogenic side effects of PPARs-targeted drugs

Carcinogenic side effects of PPAR γ agonists have been gradually discovered in recent years. To investigate the role of PPARs in diet-induced carcinogenesis, mice susceptible to intestinal tumors were treated with a synthetic PPAR γ ligand. The mice developed multiple polyps in the colon, suggesting that PPAR γ activation may provide a molecular link between a high-fat diet and an increased colorectal cancer risk (Saez et al., 1998). Similarly, animals treated with the PPAR δ agonist GW501516 exhibited an accelerated formation of breast cancer tumors, particularly adenocarcinomas and squamous cell carcinomas, and tumors of mice treated with GW501516 exhibited increased levels of PPAR δ and activated PDK1 (Yin et al., 2005). In a new transgenic mouse model, endogenous activation of PPAR δ led to progressive histopathologic changes that resulted in estrogen receptor-positive, progesterone receptor-positive, and ErBB2-negative invasive ductal carcinoma. The incubation period of the mice was 12 months; however, the incubation period of the GW501516 treated mice was reduced to 5 months (Yuan et al., 2013). Another study showed that GW501560 increased VEGF

expression in tumor cell lines in Apc (Min/+) mice, and VEGF directly promoted the survival of colorectal adenoma epithelial cells by activating PI3K-Akt signaling, which was manifested by a significant increase in the number and size of intestinal polyps (Gupta et al., 2004; Wang et al., 2006).

5 Conclusion

Cancer has long been considered the most harmful disease in the world due to its high morbidity and mortality rates. However, it is reassuring that many new therapeutic targets, such as PPARs, have demonstrated great potential in the inhibition of tumor proliferation and metastasis. Our study focused on the profound effects of PPARs on tumor tissue metabolism and TME. Previous studies have implicated PPARs in adipogenesis, lipid metabolism, insulin sensitivity, inflammation, and blood pressure regulation. PPARs-related metabolic disorders, such as obesity and type 2 diabetes, are independent risk factors for carcinogenesis and cancer prognosis predictors (Johnson et al., 2012; Hopkins et al., 2016; Mustafa et al., 2020). Although PPARs affect different aspects of TME and tumor cell metabolism, the three PPARs subtypes cannot be classified as having only pro- or anti-tumor effects because PPARs affect different cancers and cell types differently, and are perturbed by other cell signals. Notably, tumor cells are affected by PPARs while providing endogenous PPARs ligand signals to other cells in the TME, regulating PPARs activity through feedback, forming a more complex permanent closed loop. In conclusion, with the hope of providing valuable insights for better cancer treatment, we have attempted to establish the relationship between PPARs and cancer. However, the significance of PPARs-targeted drugs in cancer treatment has yet to be fully explored. The clinical applicability of PPARs-targeted drugs, the elimination of drug side effects, and the prognosis are the areas that require further research to gain satisfactory insights.

Author contributions

JS is the first author, to collect data, drafting and revising the manuscript. LY, XQ and TH design research direction provide writing guidance and participate in the manuscript revision and supplement. All authors have agreed to the version of the manuscript for this release and have agreed to work on their respective aspects. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Acknowledgments

We thank PubMed for providing publicly available data.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

References

- Abbot, E. L., McCormack, J. G., Reynet, C., Hassall, D. G., Buchan, K. W., and Yeaman, S. J. (2005). Diverging regulation of pyruvate dehydrogenase kinase isoform gene expression in cultured human muscle cells. *Febs J.* 272 (12), 3004–3014. doi:10.1111/j.1742-4658.2005.04713.x
- Abu Aboud, O., Wettersten, H. I., and Weiss, R. H. (2013). Inhibition of PPAR α induces cell cycle arrest and apoptosis, and synergizes with glycolysis inhibition in kidney cancer cells. *PLoS One* 8 (8), e71115. doi:10.1371/journal.pone.0071115
- Adamkiewicz, J., Kaddatz, K., Rieck, M., Wilke, B., Müller-Brüsselbach, S., and Müller, R. (2007). Proteomic profile of mouse fibroblasts with a targeted disruption of the peroxisome proliferator activated receptor-beta/delta gene. *Proteomics* 7 (8), 1208–1216. doi:10.1002/pmic.200601003
- Ahmad, I., Mui, E., Galbraith, L., Patel, R., Tan, E. H., Salji, M., et al. (2016). Sleeping Beauty screen reveals Pparg activation in metastatic prostate cancer. *Proc. Natl. Acad. Sci. U. S. A.* 113 (29), 8290–8295. doi:10.1073/pnas.1601571113
- Ahmadian, M., Suh, J. M., Hah, N., Liddle, C., Atkins, A. R., Downes, M., et al. (2013). PPAR γ signaling and metabolism: The good, the bad and the future. *Nat. Med.* 19 (5), 557–566. doi:10.1038/nm.3159
- Altman, B. J., Stine, Z. E., and Dang, C. V. (2016). From krebs to clinic: Glutamine metabolism to cancer therapy. *Nat. Rev. Cancer* 16 (11), 749. doi:10.1038/nrc.2016.114
- Arima, T., Uchiyama, M., Nakano, Y., Nagasaka, S., Kang, D., Shimizu, A., et al. (2017). Peroxisome proliferator-activated receptor alpha agonist suppresses neovascularization by reducing both vascular endothelial growth factor and angiopoietin-2 in corneal alkali burn. *Sci. Rep.* 7 (1), 17763. doi:10.1038/s41598-017-18113-3
- Avena, P., Anselmo, W., Whitaker-Menezes, D., Wang, C., Pestell, R. G., Lamb, R. S., et al. (2013). Compartment-specific activation of PPAR γ governs breast cancer tumor growth, via metabolic reprogramming and symbiosis. *Cell Cycle* 12 (9), 1360–1370. doi:10.4161/cc.24289
- Azuma, Y. T., Nishiyama, K., Matsuo, Y., Kuwamura, M., Morioka, A., Nakajima, H., et al. (2010). PPAR α contributes to colonic protection in mice with DSS-induced colitis. *Int. Immunopharmacol.* 10 (10), 1261–1267. doi:10.1016/j.intimp.2010.07.007
- Balandaram, G., Kramer, L. R., Kang, B. H., Murray, I. A., Perdew, G. H., Gonzalez, F. J., et al. (2016). Ligand activation of peroxisome proliferator-activated receptor- β/δ suppresses liver tumorigenesis in Hepatitis B transgenic mice. *Toxicology* 363–364, 1–9. doi:10.1016/j.tox.2016.07.010
- Balkwill, F. R., Capasso, M., and Hagemann, T. (2012). The tumor microenvironment at a glance. *J. Cell Sci.* 125 (23), 5591–5596. doi:10.1242/jcs.116392
- Banerjee, S. S., Feinberg, M. W., Watanabe, M., Gray, S., Haspel, R. L., Denking, D. J., et al. (2003). The Krüppel-like factor KLF2 inhibits peroxisome proliferator-activated receptor-gamma expression and adipogenesis. *J. Biol. Chem.* 278 (4), 2581–2584. doi:10.1074/jbc.M210859200
- Basu-Roy, U., Han, E., Rattanakor, K., Gadi, A., Verma, N., Maurizi, G., et al. (2016). PPAR γ agonists promote differentiation of cancer stem cells by restraining YAP transcriptional activity. *Oncotarget* 7 (38), 60954–60970. doi:10.18632/oncotarget.11273
- Benedetti, E., d'Angelo, M., Ammazalorso, A., Gravina, G. L., Laezza, C., Antonosante, A., et al. (2017). PPAR α antagonist AA452 triggers metabolic reprogramming and increases sensitivity to radiation therapy in human glioblastoma primary cells. *J. Cell Physiol.* 232 (6), 1458–1466. doi:10.1002/jcp.25648
- Bensinger, S. J., and Tontonoz, P. (2008). Integration of metabolism and inflammation by lipid-activated nuclear receptors. *Nature* 454 (7203), 470–477. doi:10.1038/nature07202
- Berger, J., and Moller, D. E. (2002). The mechanisms of action of PPARs. *Annu. Rev. Med.* 53, 409–435. doi:10.1146/annurev.med.53.082901.104018
- Berthou, L., Duverger, N., Emmanuel, F., Langouët, S., Auwerx, J., Guillouzo, A., et al. (1996). Opposite regulation of human versus mouse apolipoprotein A-I by fibrates in human apolipoprotein A-I transgenic mice. *J. Clin. Invest.* 97 (11), 2408–2416. doi:10.1172/JCI118687
- Bi, P., Yue, F., Karki, A., Castro, B., Wirbisky, S. E., Wang, C., et al. (2016). Notch activation drives adipocyte dedifferentiation and tumorigenic transformation in mice. *J. Exp. Med.* 213 (10), 2019–2037. doi:10.1084/jem.20160157
- Bigoni-Ordóñez, G. D., Ortiz-Sánchez, E., Rosendo-Chalma, P., Valencia-González, H. A., Aceves, C., and García-Carrancá, A. (2018). Molecular iodine inhibits the expression of stemness markers on cancer stem-like cells of established cell lines derived from cervical cancer. *BMC Cancer* 18 (1), 928. doi:10.1186/s12885-018-4824-5
- Bishop-Bailey, D., and Hla, T. (1999). Endothelial cell apoptosis induced by the peroxisome proliferator-activated receptor (PPAR) ligand 15-deoxy-Delta12, 14-prostaglandin J2. *J. Biol. Chem.* 274 (24), 17042–17048. doi:10.1074/jbc.274.24.17042
- Boroughs, L. K., and DeBerardinis, R. J. (2015). Metabolic pathways promoting cancer cell survival and growth. *Nat. Cell Biol.* 17 (4), 351–359. doi:10.1038/ncb3124
- Boutoual, R., Meseguer, S., Villarroja, M., Martín-Hernández, E., Errami, M., Martín, M. A., et al. (2018). Defects in the mitochondrial-tRNA modification enzymes MTO1 and GTPBP3 promote different metabolic reprogramming through a HIF-PPAR γ -UCP2-AMPK axis. *Sci. Rep.* 8 (1), 1163. doi:10.1038/s41598-018-19587-5
- Bräutigam, K., Biernath-Wüpping, J., Bauersschlag, D. O., von Kaisenberg, C. S., Jonat, W., Maass, N., et al. (2011). Combined treatment with TRAIL and PPAR γ ligands overcomes chemoresistance of ovarian cancer cell lines. *J. Cancer Res. Clin. Oncol.* 137 (5), 875–886. doi:10.1007/s00432-010-0952-2
- Brunelli, L., Cieslik, K. A., Alcorn, J. L., Vatta, M., and Baldini, A. (2007). Peroxisome proliferator-activated receptor-delta upregulates 14-3-3 epsilon in human endothelial cells via CCAAT/enhancer binding protein-beta. *Circ. Res.* 100 (5), e59–e71. doi:10.1161/01.RES.0000260805.99076.22
- Cai, Z., Liang, Y., Xing, C., Wang, H., Hu, P., Li, J., et al. (2019). Cancer-associated adipocytes exhibit distinct phenotypes and facilitate tumor progression in pancreatic cancer. *Oncol. Rep.* 42 (6), 2537–2549. doi:10.3892/or.2019.7365
- Cao, L. Q., Wang, X., Wang, Q., Xue, P., Jiao, X. Y., Peng, H. P., et al. (2009). Rosiglitazone sensitizes hepatocellular carcinoma cell lines to 5-fluorouracil antitumor activity through activation of the PPAR γ signaling pathway. *Acta Pharmacol. Sin.* 30 (9), 1316–1322. doi:10.1038/aps.2009.119
- Carracedo, A., Weiss, D., Leliaert, A. K., Bhasin, M., de Boer, V. C. J., Laurent, G., et al. (2012). A metabolic prosurvival role for PML in breast cancer. *J. Clin. Invest.* 122 (9), 3088–3100. doi:10.1172/JCI62129
- Castelli, V., Catanesi, M., Alfonsetti, M., Laezza, C., Lombardi, F., Cinque, B., et al. (2021). Ppara-selective antagonist GW6471 inhibits cell growth in breast cancer stem cells inducing energy imbalance and metabolic stress. *Biomedicines* 9 (2), 127. doi:10.3390/biomedicines9020127
- Chakravarthi, M. V., Pan, Z., Zhu, Y., Tordjman, K., Schneider, J. G., Coleman, T., et al. (2005). New^h hepatic fat activates PPAR α to maintain glucose, lipid, and cholesterol homeostasis. *Cell Metab.* 1 (5), 309–322. doi:10.1016/j.cmet.2005.04.002
- Chakravarthi, M. V., Zhu, Y., López, M., Yin, L., Wozniak, D. F., Coleman, T., et al. (2007). Brain fatty acid synthase activates PPAR α to maintain energy homeostasis. *J. Clin. Invest.* 117 (9), 2539–2552. doi:10.1172/JCI31183
- Chan, J. S. K., Sng, M. K., Teo, Z. Q., Chong, H. C., Twang, J. S., and Tan, N. S. (2018). Targeting nuclear receptors in cancer-associated fibroblasts as concurrent therapy to inhibit development of chemoresistant tumors. *Oncogene* 37 (2), 160–173. doi:10.1038/onc.2017.319
- Chandran, K., Goswami, S., and Sharma-Walia, N. (2016). Implications of a peroxisome proliferator-activated receptor alpha (PPAR α) ligand clofibrate in breast cancer. *Oncotarget* 7 (13), 15577–15599. doi:10.18632/oncotarget.6402
- Chang, N. W., and Huang, Y. P. (2019). The RNA degradation pathway is involved in PPAR α -modulated anti-oral tumorigenesis. *Biomed. (Taipei)* 9 (4), 27. doi:10.1051/bmdcn/2019090427
- Chen, F., Kim, E., Wang, C. C., and Harrison, L. E. (2005). Ciglitazone-induced p27 gene transcriptional activity is mediated through Sp1 and is negatively regulated by the MAPK signaling pathway. *Cell Signal* 17 (12), 1572–1577. doi:10.1016/j.cellsig.2005.03.012
- Chen, L., Peng, J., Wang, Y., Jiang, H., Wang, W., Dai, J., et al. (2020). Fenofibrate-induced mitochondrial dysfunction and metabolic reprogramming reversal: The anti-tumor effects in gastric carcinoma cells mediated by the PPAR pathway. *Am. J. Transl. Res.* 12 (2), 428–446.
- Chen, Y., Wang, Y., Huang, Y., Zeng, H., Hu, B., Guan, L., et al. (2017a). PPAR α regulates tumor cell proliferation and senescence via a novel target gene carnitine palmitoyltransferase 1C. *Carcinogenesis* 38 (4), 474–483. doi:10.1093/carcin/bgx023
- Chen, S. W., Chou, C. T., Chang, C. C., Li, Y. J., Lin, I. C., Kok, S. H., et al. (2017b). HMGCS2 enhances invasion and metastasis via direct interaction with PPAR α to activate Src signaling in colorectal cancer and oral cancer. *Oncotarget* 8 (14), 22460–22476. doi:10.18632/oncotarget.13006

- Chen, S. Z., Ling, Y., Yu, L. X., Song, Y. T., Chen, X. F., Cao, Q. Q., et al. (2021a). 4-pentenylbutyric acid promotes hepatocellular carcinoma via initiating cancer stem cells through activation of PPAR- α . *Clin. Transl. Med.* 11 (4), e379. doi:10.1002/ctm2.379
- Chen, J., Wang, Y., Zhang, W., Zhao, D., Zhang, L., Zhang, J., et al. (2021b). NOX5 mediates the crosstalk between tumor cells and cancer-associated fibroblasts via regulating cytokine network. *Clin. Transl. Med.* 11 (8), e472. doi:10.1002/ctm2.472
- Cheng, H. S., Tan, W. R., Low, Z. S., Marvalim, C., Lee, J. Y. H., and Tan, N. S. (2019). Exploration and development of PPAR modulators in health and disease: An update of clinical evidence. *Int. J. Mol. Sci.* 20 (20), 5055. doi:10.3390/ijms20205055
- Chi, T., Wang, M., Wang, X., Yang, K., Xie, F., Liao, Z., et al. (2021). PPAR- Γ modulators as current and potential cancer treatments. *Front. Oncol.* 11, 737776. doi:10.3389/fonc.2021.737776
- Choi, Y., Oh, S. T., Won, M. A., Choi, K. M., Ko, M. J., Seo, D., et al. (2016). Targeting ODC1 inhibits tumor growth through reduction of lipid metabolism in human hepatocellular carcinoma. *Biochem. Biophys. Res. Commun.* 478 (4), 1674–1681. doi:10.1016/j.bbrc.2016.09.002
- Christofides, A., Konstantinidou, E., Jani, C., and Boussiotis, V. A. (2021). The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. *Metabolism* 114, 154338. doi:10.1016/j.metabol.2020.154338
- Coleman, J. D., Thompson, J. T., Smith, R. W., Prokopczyk, B., and Vanden Heuvel, J. P. (2013). Role of peroxisome proliferator-activated receptor β/δ and B-cell lymphoma-6 in regulation of genes involved in metastasis and migration in pancreatic cancer cells. *PPAR Res.* 2013, 121956. doi:10.1155/2013/121956
- Corrales, P., Vidal-Puig, A., and Medina-Gómez, G. (2018). PPARs and metabolic disorders associated with challenged adipose tissue plasticity. *Int. J. Mol. Sci.* 19 (7), 2124. doi:10.3390/ijms19072124
- Daikoku, T., Tranguch, S., Chakrabarty, A., Wang, D., Khabele, D., Orsulic, S., et al. (2007). Extracellular signal-regulated kinase is a target of cyclooxygenase-1-peroxisome proliferator-activated receptor-delta signaling in epithelial ovarian cancer. *Cancer Res.* 67 (11), 5285–5292. doi:10.1158/0008-5472.CAN-07-0828
- Deng, Y., and Scherer, P. E. (2010). Adipokines as novel biomarkers and regulators of the metabolic syndrome. *Ann. N. Y. Acad. Sci.* 1212, e1–e19. doi:10.1111/j.1749-6632.2010.05875.x
- Derosa, G., Sahebkar, A., and Maffioli, P. (2018). The role of various peroxisome proliferator-activated receptors and their ligands in clinical practice. *J. Cell Physiol.* 233 (1), 153–161. doi:10.1002/jcp.25804
- Di-Poi, N., Tan, N. S., Michalik, L., Wahli, W., and Desvergne, B. (2002). Antiapoptotic role of PPARbeta in keratinocytes via transcriptional control of the Akt1 signaling pathway. *Mol. Cell* 10 (4), 721–733. doi:10.1016/s1097-2765(02)00646-9
- Diamond, M. S., Kinder, M., Matsushita, H., Mashayekhi, M., Dunn, G. P., Archambault, J. M., et al. (2011). Type I interferon is selectively required by dendritic cells for immune rejection of tumors. *J. Exp. Med.* 208 (10), 1989–2003. doi:10.1084/jem.20101158
- Ding, J., Gou, Q., Jin, J., Shi, J., Liu, Q., and Hou, Y. (2019). Metformin inhibits PPAR δ agonist-mediated tumor growth by reducing Glut1 and SLC1A5 expressions of cancer cells. *Eur. J. Pharmacol.* 857, 172425. doi:10.1016/j.ejphar.2019.172425
- Dreyer, C., Krey, G., Keller, H., Givel, F., Helftenbein, G., and Wahli, W. (1992). Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors. *Cell* 68 (5), 879–887. doi:10.1016/0092-8674(92)90031-7
- Drori, S., Girnun, G. D., Tou, L., Szwajca, J. D., Mueller, E., Xia, K., et al. (2005). Hic-5 regulates an epithelial program mediated by PPARgamma. *Genes. Dev.* 19 (3), 362–375. doi:10.1101/gad.1240705
- Drukala, J., Urbanska, K., Wilk, A., Grabacka, M., Wybialska, E., Del Valle, L., et al. (2010). ROS accumulation and IGF-IR inhibition contribute to fenofibrate/PPARalpha-mediated inhibition of glioma cell motility *in vitro*. *Mol. Cancer* 9, 159. doi:10.1186/1476-4598-9-159
- Eales, K. L., Hollingshead, K. E., and Tennant, D. A. (2016). Hypoxia and metabolic adaptation of cancer cells. *Oncogenesis* 5 (1), e190. doi:10.1038/oncsis.2015.50
- Elstner, E., Williamson, E. A., Zang, C., Fritz, J., Heber, D., Fenner, M., et al. (2002). Novel therapeutic approach: Ligands for PPARgamma and retinoid receptors induce apoptosis in bcl-2-positive human breast cancer cells. *Breast Cancer Res. Treat.* 74 (2), 155–165. doi:10.1023/a:1016114026769
- Feige, J. N., Gelman, L., Michalik, L., Desvergne, B., and Wahli, W. (2006). From molecular action to physiological outputs: Peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. *Prog. Lipid Res.* 45 (2), 120–159. doi:10.1016/j.plipres.2005.12.002
- Fidoamore, A., Cristiano, L., Antonosante, A., d'Angelo, M., Di Giacomo, E., Astarita, C., et al. (2016). Glioblastoma stem cells microenvironment: The paracrine roles of the niche in drug and radioresistance. *Stem Cells Int.* 2016, 6809105. doi:10.1155/2016/6809105
- Fidoamore, A., Cristiano, L., Laezza, C., Galzio, R., Benedetti, E., Cinque, B., et al. (2017). Energy metabolism in glioblastoma stem cells: PPARa a metabolic adaptor to intratumoral microenvironment. *Oncotarget* 8 (65), 108430–108450. doi:10.18632/oncotarget.19086
- Finck, B. N., Bernal-Mizrachi, C., Han, D. H., Coleman, T., Sambandam, N., LaRiviere, L. L., et al. (2005). A potential link between muscle peroxisome proliferator-activated receptor-alpha signaling and obesity-related diabetes. *Cell Metab.* 1 (2), 133–144. doi:10.1016/j.cmet.2005.01.006
- Florio, R., De Lellis, L., Di Giacomo, V., Di Marcantonio, M. C., Cristiano, L., Basile, M., et al. (2017). Effects of PPARa inhibition in head and neck paraganglioma cells. *PLoS One* 12 (6), e0178995. doi:10.1371/journal.pone.0178995
- Fröhlich, E., and Wahl, R. (2015). Chemotherapy and chemoprevention by thiazolidinediones. *Biomed. Res. Int.* 2015, 845340. doi:10.1155/2015/845340
- Fukumoto, K., Yano, Y., Virgona, N., Hagiwara, H., Sato, H., Senba, H., et al. (2005). Peroxisome proliferator-activated receptor delta as a molecular target to regulate lung cancer cell growth. *FEBS Lett.* 579 (17), 3829–3836. doi:10.1016/j.febslet.2005.06.004
- Galbraith, L. C. A., Mui, E., Nixon, C., Hedley, A., Strachan, D., MacKay, G., et al. (2021). PPAR-gamma induced AKT3 expression increases levels of mitochondrial biogenesis driving prostate cancer. *Oncogene* 40 (13), 2355–2366. doi:10.1038/s41388-021-01707-7
- Garrido-Urbani, S., Jemelin, S., Deffert, C., Carnesecchi, S., Basset, O., Szyndralewicz, C., et al. (2011). Targeting vascular NADPH oxidase 1 blocks tumor angiogenesis through a PPARa mediated mechanism. *PLoS One* 6 (2), e14665. doi:10.1371/journal.pone.0014665
- Genini, D., Garcia-Escudero, R., Carbone, G. M., and Catapano, C. V. (2012). Transcriptional and non-transcriptional functions of ppar β/δ in non-small cell lung cancer. *PLoS One* 7 (9), e46009. doi:10.1371/journal.pone.0046009
- Gionfriddo, G., Plastina, P., Augimeri, G., Catalano, S., Giordano, C., Barone, I., et al. (2020). Modulating tumor-associated macrophage polarization by synthetic and natural PPAR γ ligands as a potential target in breast cancer. *Cells* 9 (1), 174. doi:10.3390/cells9010174
- Girroir, E. E., Hollingshead, H. E., Billin, A. N., Willson, T. M., Robertson, G. P., Sharma, A. K., et al. (2008). Peroxisome proliferator-activated receptor-beta/delta (PPARbeta/delta) ligands inhibit growth of UACC903 and MCF7 human cancer cell lines. *Toxicology* 243 (1–2), 236–243. doi:10.1016/j.tox.2007.10.023
- Göttlicher, M., Widmark, E., Li, Q., and Gustafsson, J. A. (1992). Fatty acids activate a chimera of the clofibrate acid-activated receptor and the glucocorticoid receptor. *Proc. Natl. Acad. Sci. U. S. A.* 89 (10), 4653–4657. doi:10.1073/pnas.89.10.4653
- Gou, Q., Dong, C., Jin, J., Liu, Q., Lu, W., Shi, J., et al. (2019). PPARa agonist alleviates tumor growth and chemo-resistance associated with the inhibition of glucose metabolic pathway. *Eur. J. Pharmacol.* 863, 172664. doi:10.1016/j.ejphar.2019.172664
- Grabacka, M., Pierzchalska, M., and Reiss, K. (2013). Peroxisome proliferator activated receptor a ligands as anticancer drugs targeting mitochondrial metabolism. *Curr. Pharm. Biotechnol.* 14 (3), 342–356. doi:10.2174/1389201011314030009
- Grabacka, M., Plonka, P. M., and Reiss, K. (2020). Melanoma-time to fast or time to feast? An interplay between PPARs, metabolism and immunity. *Exp. Dermatol* 29 (4), 436–445. doi:10.1111/exd.14072
- Grabacka, M., Plonka, P. M., Urbanska, K., and Reiss, K. (2006). Peroxisome proliferator-activated receptor alpha activation decreases metastatic potential of melanoma cells *in vitro* via down-regulation of Akt. *Clin. Cancer Res.* 12 (10), 3028–3036. doi:10.1158/1078-0432.CCR-05-2556
- Grau, R., Punzón, C., Fresno, M., and Iñiguez, M. A. (2006). Peroxisome-proliferator-activated receptor alpha agonists inhibit cyclo-oxygenase 2 and vascular endothelial growth factor transcriptional activation in human colorectal carcinoma cells via inhibition of activator protein-1. *Biochem. J.* 395 (1), 81–88. doi:10.1042/BJ20050964
- Gross, B., Pawlak, M., Lefebvre, P., and Staels, B. (2017). PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. *Nat. Rev. Endocrinol.* 13 (1), 36–49. doi:10.1038/nrendo.2016.135
- Guan, Y., Zhang, Y., Davis, L., and Breyer, M. D. (1997). Expression of peroxisome proliferator-activated receptors in urinary tract of rabbits and humans. *Am. J. Physiol.* 273 (6), F1013–F1022. doi:10.1152/ajprenal.1997.273.6.F1013
- Gupta, R. A., Wang, D., Katkuri, S., Wang, H., Dey, S. K., and DuBois, R. N. (2004). Activation of nuclear hormone receptor peroxisome proliferator-activated receptor-delta accelerates intestinal adenoma growth. *Nat. Med.* 10 (3), 245–247. doi:10.1038/nm993
- Ham, S. A., Yoo, T., Hwang, J. S., Kang, E. S., Lee, W. J., Paek, K. S., et al. (2014). Ligand-activated PPAR δ modulates the migration and invasion of melanoma cells by regulating Snail expression. *Am. J. Cancer Res.* 4 (6), 674–682.
- Ham, S. A., Yoo, T., Lee, W. J., Hwang, J. S., Hur, J., Paek, K. S., et al. (2017). ADAMTS1-mediated targeting of TSP-1 by PPAR δ suppresses migration and invasion of breast cancer cells. *Oncotarget* 8 (55), 94091–94103. doi:10.18632/oncotarget.21584
- Han, D., Wei, W., Chen, X., Zhang, Y., Wang, Y., Zhang, J., et al. (2015). NF- κ B/RelA-PKM2 mediates inhibition of glycolysis by fenofibrate in glioblastoma cells. *Oncotarget* 6 (28), 26119–26128. doi:10.18632/oncotarget.4444
- Han, L., Shen, W. J., Bittner, S., Kraemer, F. B., and Azhar, S. (2017a). PPARs: Regulators of metabolism and as therapeutic targets in cardiovascular disease. Part I: PPAR- α . *Future Cardiol.* 13 (3), 259–278. doi:10.2217/fca-2016-0059

- Han, L., Shen, W. J., Bittner, S., Kraemer, F. B., and Azhar, S. (2017b). PPARs: Regulators of metabolism and as therapeutic targets in cardiovascular disease. Part II: PPAR- β/δ and PPAR- γ . *Future Cardiol.* 13 (3), 279–296. doi:10.2217/fca-2017-0019
- Hardy, S., Langelier, Y., and Prentki, M. (2000). Oleate activates phosphatidylinositol 3-kinase and promotes proliferation and reduces apoptosis of MDA-MB-231 breast cancer cells, whereas palmitate has opposite effects. *Cancer Res.* 60 (22), 6353–6358.
- Hargadon, K. M. (2020). Tumor microenvironmental influences on dendritic cell and T cell function: A focus on clinically relevant immunologic and metabolic checkpoints. *Clin. Transl. Med.* 10 (1), 374–411. doi:10.1002/ctm2.37
- Hatae, T., Wada, M., Yokoyama, C., Shimonishi, M., and Tanabe, T. (2001). Prostacyclin-dependent apoptosis mediated by PPAR delta. *J. Biol. Chem.* 276 (49), 46260–46267. doi:10.1074/jbc.M107180200
- Hay, N. (2016). Reprogramming glucose metabolism in cancer: Can it be exploited for cancer therapy? *Nat. Rev. Cancer* 16 (10), 635–649. doi:10.1038/nrc.2016.77
- He, T. C., Chan, T. A., Vogelstein, B., and Kinzler, K. W. (1999). PPARdelta is an APC-regulated target of nonsteroidal anti-inflammatory drugs. *Cell* 99 (3), 335–345. doi:10.1016/s0092-8674(00)81664-5
- Heidari, Z., Chrisman, I. M., Nemetchek, M. D., Novick, S. J., Blayo, A. L., Patton, T., et al. (2019). Definition of functionally and structurally distinct repressive states in the nuclear receptor PPAR γ . *Nat. Commun.* 10 (1), 5825. doi:10.1038/s41467-019-13768-0
- Her, N. G., Jeong, S. I., Cho, K., Ha, T. K., Han, J., Ko, K. P., et al. (2013). PPAR δ promotes oncogenic redirection of TGF- β 1 signaling through the activation of the ABCA1-Cav1 pathway. *Cell Cycle* 12 (10), 1521–1535. doi:10.4161/cc.24636
- Heudobler, D., Rechenmacher, M., Lüke, F., Vogelhuber, M., Pukrop, T., Herr, W., et al. (2018). Peroxisome proliferator-activated receptors (PPAR) γ agonists as master modulators of tumor tissue. *Int. J. Mol. Sci.* 19 (11), 3540. doi:10.3390/ijms19113540
- Hodge, A. M., Williamson, E. J., Bassett, J. K., MacInnis, R. J., Giles, G. G., and English, D. R. (2015). Dietary and biomarker estimates of fatty acids and risk of colorectal cancer. *Int. J. Cancer* 137 (5), 1224–1234. doi:10.1002/ijc.29479
- Hong, F., Pan, S., Guo, Y., Xu, P., and Zhai, Y. (2019). PPARs as nuclear receptors for nutrient and energy metabolism. *Molecules* 24 (14), 2545. doi:10.3390/molecules24142545
- Hong, F., Xu, P., and Zhai, Y. (2018). The opportunities and challenges of peroxisome proliferator-activated receptors ligands in clinical drug discovery and development. *Int. J. Mol. Sci.* 19 (8), 2189. doi:10.3390/ijms19082189
- Hopkins, B. D., Goncalves, M. D., and Cantley, L. C. (2016). Obesity and cancer mechanisms: Cancer metabolism. *J. Clin. Oncol.* 34 (35), 4277–4283. doi:10.1200/JCO.2016.67.9712
- Horiguchi, A., Asano, T., Asano, T., Ito, K., Sumitomo, M., and Hayakawa, M. (2008). Fatty acid synthase over expression is an indicator of tumor aggressiveness and poor prognosis in renal cell carcinoma. *J. Urol.* 180 (3), 1137–1140. doi:10.1016/j.juro.2008.04.135
- Huang, J., Das, S. K., Jha, P., Al Zoughbi, W., Schauer, S., Claudel, T., et al. (2013). The PPAR α agonist fenofibrate suppresses B-cell lymphoma in mice by modulating lipid metabolism. *Biochim. Biophys. Acta* 1831 (10), 1555–1565. doi:10.1016/j.bbali.2013.04.012
- Huang, J. W., Shiau, C. W., Yang, Y. T., Kulp, S. K., Chen, K. F., Brueggemeier, R. W., et al. (2005). Peroxisome proliferator-activated receptor gamma-independent ablation of cyclin D1 by thiazolidinediones and their derivatives in breast cancer cells. *Mol. Pharmacol.* 67 (4), 1342–1348. doi:10.1124/mol.104.007732
- Hwang, Y. P., Won, S. S., Jin, S. W., Lee, G. H., Pham, T. H., Choi, J. H., et al. (2019). WY-14643 regulates CYP11B1 expression through peroxisome proliferator-activated receptor α -mediated signaling in human breast cancer cells. *Int. J. Mol. Sci.* 20 (23), 5928. doi:10.3390/ijms20235928
- Isseman, I., and Green, S. (1990). Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature* 347 (6294), 645–650. doi:10.1038/347645a0
- Ito, K., Carracedo, A., Weiss, D., Arai, F., Ala, U., Avigan, D. E., et al. (2012). A PML-PPAR- δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance. *Nat. Med.* 18 (9), 1350–1358. doi:10.1038/nm.2882
- Jan, C. I., Tsai, M. H., Chiu, C. F., Huang, Y. P., Liu, C. J., and Chang, N. W. (2016). Fenofibrate suppresses oral tumorigenesis via reprogramming metabolic processes: Potential drug repurposing for oral cancer. *Int. J. Biol. Sci.* 12 (7), 786–798. doi:10.7150/ijbs.13851
- Jellinger, P. S., Handelsman, Y., Rosenblit, P. D., Bloomgarden, Z. T., Fonseca, V. A., Garber, A. J., et al. (2017). American association of clinical endocrinologists and American College of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr. Pract.* 23 (2), 1–87. doi:10.4158/EP171764.APPGL
- Jeong, E., Koo, J. E., Yeon, S. H., Kwak, M. K., Hwang, D. H., and Lee, J. Y. (2014). PPAR δ deficiency disrupts hypoxia-mediated tumorigenic potential of colon cancer cells. *Mol. Carcinog.* 53 (11), 926–937. doi:10.1002/mc.22144
- Johnson, J. A., Carstensen, B., Witte, D., Bowker, S. L., Lipscombe, L., Renehan, A. G., et al. (2012). Diabetes and cancer (1): Evaluating the temporal relationship between type 2 diabetes and cancer incidence. *Diabetologia* 55 (6), 1607–1618. doi:10.1007/s00125-012-2525-1
- Jones, D. C., Ding, X., and Daynes, R. A. (2002). Nuclear receptor peroxisome proliferator-activated receptor alpha (PPARalpha) is expressed in resting murine lymphocytes. The PPARalpha in T and B lymphocytes is both transactivation and transrepression competent. *J. Biol. Chem.* 277 (9), 6838–6845. doi:10.1074/jbc.M106908200
- Kadosh, E., Snir-Alkalay, I., Venkatchalam, A., May, S., Lasry, A., Elyada, E., et al. (2020). The gut microbiome switches mutant p53 from tumour-suppressive to oncogenic. *Nature* 586 (7827), 133–138. doi:10.1038/s41586-020-2541-0
- Kim, Y., Suh, N., Sporn, M., and Reed, J. C. (2002). An inducible pathway for degradation of FLIP protein sensitizes tumor cells to TRAIL-induced apoptosis. *J. Biol. Chem.* 277 (25), 22320–22329. doi:10.1074/jbc.M202458200
- Kota, B. P., Huang, T. H., and Roufogalis, B. D. (2005). An overview on biological mechanisms of PPARs. *Pharmacol. Res.* 51 (2), 85–94. doi:10.1016/j.phrs.2004.07.012
- Kourtidis, A., Srinivasaiah, R., Carkner, R. D., Brosnan, M. J., and Conklin, D. S. (2009). Peroxisome proliferator-activated receptor-gamma protects ERBB2-positive breast cancer cells from palmitate toxicity. *Breast Cancer Res.* 11 (2), R16. doi:10.1186/bcr2240
- Kumar, A. P., Quake, A. L., Chang, M. K. X., Zhou, T., Lim, K. S. Y., Singh, R., et al. (2009). Repression of NHE1 expression by PPARgamma activation is a potential new approach for specific inhibition of the growth of tumor cells *in vitro* and *in vivo*. *Cancer Res.* 69 (22), 8636–8644. doi:10.1158/0008-5472.CAN-09-0219
- Kuramoto, K., Yamamoto, M., Suzuki, S., Togashi, K., Sanomachi, T., Kitanaka, C., et al. (2021). Inhibition of the lipid droplet-peroxisome proliferator-activated receptor α Axis suppresses cancer stem cell properties. *Genes (Basel)* 12 (1), 99. doi:10.3390/genes12010099
- Kurokawa, T., Shimomura, Y., Bajotto, G., Kotake, K., Arikawa, T., Ito, N., et al. (2011). Peroxisome proliferator-activated receptor α (PPAR α) mRNA expression in human hepatocellular carcinoma tissue and non-cancerous liver tissue. *World J. Surg. Oncol.* 9, 167. doi:10.1186/1477-7819-9-167
- Lecarpentier, Y., Claes, V., Duthoit, G., and Hébert, J. L. (2014). Circadian rhythms, Wnt/beta-catenin pathway and PPAR alpha/gamma profiles in diseases with primary or secondary cardiac dysfunction. *Front. Physiol.* 5, 429. doi:10.3389/fphys.2014.00429
- Lecarpentier, Y., Claes, V., Vallée, A., and Hébert, J. L. (2017). Thermodynamics in cancers: Opposing interactions between PPAR gamma and the canonical WNT/beta-catenin pathway. *Clin. Transl. Med.* 6 (1), 14. doi:10.1186/s40169-017-0144-7
- Lee, C. H., Olson, P., Hevener, A., Mehl, I., Chong, L. W., Olefsky, J. M., et al. (2006). PPARdelta regulates glucose metabolism and insulin sensitivity. *Proc. Natl. Acad. Sci. U. S. A.* 103 (9), 3444–3449. doi:10.1073/pnas.0511253103
- Levi, L., Wang, Z., Doud, M. K., Hazen, S. L., and Noy, N. (2015). Saturated fatty acids regulate retinoic acid signalling and suppress tumorigenesis by targeting fatty acid-binding protein 5. *Nat. Commun.* 6, 8794. doi:10.1038/ncomms9794
- Li, C., Zhao, X., Toline, E. C., Siegal, G. P., Evans, L. M., Ibrahim-Hashim, A., et al. (2011). Prevention of carcinogenesis and inhibition of breast cancer tumor burden by dietary stearate. *Carcinogenesis* 32 (8), 1251–1258. doi:10.1093/carcin/bgr092
- Li, H., Wang, Q., Dong, L., Liu, C., Sun, Z., Gao, L., et al. (2015). Morusin suppresses breast cancer cell growth *in vitro* and *in vivo* through C/EBP β and PPAR γ -mediated lipopoptosis. *J. Exp. Clin. Cancer Res.* 34, 137. doi:10.1186/s13046-015-0252-4
- Li, Y. J., Sun, L., Shi, Y., Wang, G., Wang, X., Dunn, S. E., et al. (2017). PPAR-delta promotes survival of chronic lymphocytic leukemia cells in energetically unfavorable conditions. *Leukemia* 31 (9), 1905–1914. doi:10.1038/leu.2016.395
- Liang, H., Kowalczyk, P., Junco, J. J., Klug-De Santiago, H. L., Malik, G., Wei, S. J., et al. (2014). Differential effects on lung cancer cell proliferation by agonists of glucocorticoid and PPAR α receptors. *Mol. Carcinog.* 53 (9), 753–763. doi:10.1002/mc.22029
- Liou, J. Y., Lee, S., Ghelani, D., Matijevic-Aleksic, N., and Wu, K. K. (2006). Protection of endothelial survival by peroxisome proliferator-activated receptor-delta mediated 14-3-3 upregulation. *Arterioscler. Thromb. Vasc. Biol.* 26 (7), 1481–1487. doi:10.1161/01.ATV.0000223875.14120.93
- Liu, Y., Deguchi, Y., Tian, R., Wei, D., Wu, L., Chen, W., et al. (2019a). Pleiotropic effects of PPARd accelerate colorectal tumorigenesis, progression, and invasion. *Cancer Res.* 79 (5), 954–969. doi:10.1158/0008-5472.CAN-18-1790
- Liu, C., Lim, S. T., Teo, M. H. Y., Tan, M. S. Y., Kulkarni, M. D., Qiu, B., et al. (2019b). Collaborative regulation of LRG1 by TGF- β 1 and PPAR- β/δ modulates chronic pressure overload-induced cardiac fibrosis. *Circ. Heart Fail* 12 (12), e005962. doi:10.1161/CIRCHEARTFAILURE.119.005962
- Liu, L., Si, N., Ma, Y., Ge, D., Yu, X., Fan, A., et al. (2018). Hydroxysafflor-yellow A induces human gastric carcinoma BGC-823 cell apoptosis by activating peroxisome proliferator-activated receptor gamma (PPAR γ). *Med. Sci. Monit.* 24, 803–811. doi:10.12659/msm.905587
- Liu, L., Yang, Z., Xu, Y., Li, J., Xu, D., Zhang, L., et al. (2013a). Inhibition of oxidative stress-elicited AKT activation facilitates PPAR γ agonist-mediated inhibition of stem cell character and tumor growth of liver cancer cells. *PLoS One* 8 (8), e73038. doi:10.1371/journal.pone.0073038
- Liu, Y., Zhu, Z., Zhang, S. N., Mou, J., Liu, L., Cui, T., et al. (2013b). Combinational effect of PPAR γ agonist and RXR agonist on the growth of SGC7901 gastric carcinoma cells *in vitro*. *Tumour Biol.* 34 (4), 2409–2418. doi:10.1007/s13277-013-0791-2

- Liu, Y., Meng, Y., Li, H., Li, J., Fu, J., Chen, X. G., et al. (2006). Growth inhibition and differentiation induced by peroxisome proliferator activated receptor gamma ligand rosiglitazone in human melanoma cell line A375. *Med. Oncol.* 23 (3), 393–402. doi:10.1385/mo:23:3:393
- Luo, X., Cheng, C., Tan, Z., Tang, M., Yang, L., Li, N., et al. (2017). Emerging roles of lipid metabolism in cancer metastasis. *Mol. Cancer* 16 (1), 76. doi:10.1186/s12943-017-0646-3
- Luo, Y., Xie, C., Brocker, C. N., Fan, J., Wu, X., Feng, L., et al. (2019). Intestinal PPARα protects against colon carcinogenesis via regulation of methyltransferases DNMT1 and PRMT6. *Gastroenterology* 157 (3), 744–759. doi:10.1053/j.gastro.2019.05.057
- Luty, M., Piwowarczyk, K., Łabędź-Masłowska, A., Wróbel, T., Szczygieł, M., Catapano, J., et al. (2019). Fenofibrate augments the sensitivity of drug-resistant prostate cancer cells to docetaxel. *Cancers (Basel)* 11 (1), 77. doi:10.3390/cancers11010077
- Ma, X. L., Sun, Y. F., Wang, B. L., Shen, M. N., Zhou, Y., Chen, J. W., et al. (2019). Sphere-forming culture enriches liver cancer stem cells and reveals Stearoyl-CoA desaturase 1 as a potential therapeutic target. *BMC Cancer* 19 (1), 760. doi:10.1186/s12885-019-5963-z
- Maggiora, M., Oraldi, M., Muzio, G., and Canuto, R. A. (2010). Involvement of PPARα and PPARγ in apoptosis and proliferation of human hepatocarcinoma HepG2 cells. *Cell Biochem. Funct.* 28 (7), 571–577. doi:10.1002/cbf.1691
- Mao, F., Xu, M., Zuo, X., Yu, J., Xu, W., Moussalli, M. J., et al. (2015). 15-Lipoxygenase-1 suppression of colitis-associated colon cancer through inhibition of the IL-6/STAT3 signaling pathway. *Faseb J.* 29 (6), 2359–2370. doi:10.1096/fj.14-264515
- Margalit, O., Wang, D., and Dubois, R. N. (2012). PPARγ agonists target aromatase via both PGE2 and BRCA1. *Cancer Prev. Res. (Phila)* 5 (10), 1169–1172. doi:10.1158/1940-6207.CAPR-12-0365
- Marin, H. E., Peraza, M. A., Billin, A. N., Willson, T. M., Ward, J. M., Kennett, M. J., et al. (2006). Ligand activation of peroxisome proliferator-activated receptor beta inhibits colon carcinogenesis. *Cancer Res.* 66 (8), 4394–4401. doi:10.1158/0008-5472.CAN-05-4277
- Meissner, M., Hrgovic, I., Doll, M., Naidenow, J., Reichenbach, G., Hailemariam-Jahn, T., et al. (2010). Peroxisome proliferator-activated receptor {delta} activators induce IL-8 expression in nonstimulated endothelial cells in a transcriptional and posttranscriptional manner. *J. Biol. Chem.* 285 (44), 33797–33804. doi:10.1074/jbc.M110.137943
- Meng, X. M., Nikolic-Paterson, D. J., and Lan, H. Y. (2016). TGF-β: The master regulator of fibrosis. *Nat. Rev. Nephrol.* 12 (6), 325–338. doi:10.1038/nrneph.2016.48
- Meylan, P., Pich, C., Winkler, C., Ginster, S., Mury, L., Sgandurra, M., et al. (2021). Low expression of the PPARγ-regulated gene thioredoxin-interacting protein accompanies human melanoma progression and promotes experimental lung metastases. *Sci. Rep.* 11 (1), 7847. doi:10.1038/s41598-021-86329-5
- Miao, R., Xu, T., Liu, L., Wang, M., Jiang, Y., Li, J., et al. (2011). Rosiglitazone and retinoic acid inhibit proliferation and induce apoptosis in the HCT-15 human colorectal cancer cell line. *Exp. Ther. Med.* 2 (3), 413–417. doi:10.3892/etm.2011.227
- Michiels, J. F., Perrin, C., Leccia, N., Massi, D., Grimaldi, P., and Wagner, N. (2010). PPARβ activation inhibits melanoma cell proliferation involving repression of the Wilms' tumour suppressor WT1. *Pflugers Arch.* 459 (5), 689–703. doi:10.1007/s00424-009-0776-6
- Montagner, A., Delgado, M. B., Tallichet-Blanc, C., Chan, J. S. K., Sng, M. K., Mottaz, H., et al. (2014). Src is activated by the nuclear receptor peroxisome proliferator-activated receptor β/δ in ultraviolet radiation-induced skin cancer. *EMBO Mol. Med.* 6 (1), 80–98. doi:10.1002/emmm.201302666
- Moon, H. S., Guo, D. D., Lee, H. G., Choi, Y. J., Kang, J. S., Jo, K., et al. (2010). Alpha-eleostearic acid suppresses proliferation of MCF-7 breast cancer cells via activation of PPARγ and inhibition of ERK 1/2. *Cancer Sci.* 101 (2), 396–402. doi:10.1111/j.1349-7006.2009.01389.x
- Motomura, W., Okumura, T., Takahashi, N., Obara, T., and Kohgo, Y. (2000). Activation of peroxisome proliferator-activated receptor gamma by troglitazone inhibits cell growth through the increase of p27Kip1 in human. Pancreatic carcinoma cells. *Cancer Res.* 60 (19), 5558–5564.
- Müller-Brüsselbach, S., Kömhoff, M., Rieck, M., Meissner, W., Kaddatz, K., Adamkiewicz, J., et al. (2007). Deregulation of tumor angiogenesis and blockade of tumor growth in PPARβ-deficient mice. *Embo J.* 26 (15), 3686–3698. doi:10.1038/sj.emboj.7601803
- Mustafa, H. A., Albkrye, A. M. S., AbdAlla, B. M., Khair, M. A. M., Abdelwahid, N., and Elnasri, H. A. (2020). Computational determination of human PPARG gene: SNPs and prediction of their effect on protein functions of diabetic patients. *Clin. Transl. Med.* 9 (1), 7. doi:10.1186/s40169-020-0258-1
- Ni, J., Zhou, L. L., Ding, L., Zhang, X. Q., Zhao, X., Li, H., et al. (2018). Efatutazone and T901317 exert synergistically therapeutic effects in acquired gefitinib-resistant lung adenocarcinoma cells. *Cancer Med.* 7 (5), 1955–1966. doi:10.1002/cam4.1440
- Ni, J., Zhou, L. L., Ding, L., Zhao, X., Cao, H., Fan, F., et al. (2017). PPARγ agonist efatutazone and gefitinib synergistically inhibit the proliferation of EGFR-TKI-resistant lung adenocarcinoma cells via the PPARγ/PTEN/Akt pathway. *Exp. Cell Res.* 361 (2), 246–256. doi:10.1016/j.yexcr.2017.10.024
- O'Connor, M. N., Kallenberg, D. M., Camilli, C., Pilotti, C., Dritsoula, A., Jackstadt, R., et al. (2021). IRLG1 destabilizes tumor vessels and restricts immunotherapeutic potency. *Med. (N Y)* 2 (11), 1231–1252.e10. doi:10.1016/j.medj.2021.10.002
- Ouyang, N., Williams, J. L., and Rigas, B. (2006). NO-donating aspirin isomers downregulate peroxisome proliferator-activated receptor (PPAR)δ expression in APC(min/+) mice proportionally to their tumor inhibitory effect: Implications for the role of PPARδ in carcinogenesis. *Carcinogenesis* 27 (2), 232–239. doi:10.1093/carcin/bgi221
- Palakurthi, S. S., Aktas, H., Grubisich, L. M., Mortensen, R. M., and Halperin, J. A. (2001). Anticancer effects of thiazolidinediones are independent of peroxisome proliferator-activated receptor gamma and mediated by inhibition of translation initiation. *Cancer Res.* 61 (16), 6213–6218.
- Pang, X., Wei, Y., Zhang, Y., Zhang, M., Lu, Y., and Shen, P. (2013). Peroxisome proliferator-activated receptor-γ activation inhibits hepatocellular carcinoma cell invasion by upregulating plasminogen activator inhibitor-1. *Cancer Sci.* 104 (6), 672–680. doi:10.1111/cas.12143
- Panigrahy, D., Kaipainen, A., Huang, S., Butterfield, C. E., Barnés, C. M., Fannon, M., et al. (2008). PPARα agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition. *Proc. Natl. Acad. Sci. U. S. A.* 105 (3), 985–990. doi:10.1073/pnas.0711281105
- Papi, A., De Carolis, S., Bertoni, S., Storci, G., Sceberas, V., Santini, D., et al. (2014). PPARγ and RXR ligands disrupt the inflammatory cross-talk in the hypoxic breast cancer stem cells niche. *J. Cell Physiol.* 229 (11), 1595–1606. doi:10.1002/jcp.24601
- Pearce, L. R., Komander, D., and Alessi, D. R. (2010). The nuts and bolts of AGC protein kinases. *Nat. Rev. Mol. Cell Biol.* 11 (1), 9–22. doi:10.1038/nrm2822
- Penas, F., Mirkin, G. A., Vera, M., Cevey, A., González, C. D., Gómez, M. I., et al. (2015). Treatment *in vitro* with PPARα and PPARγ ligands drives M1-to-M2 polarization of macrophages from T. cruzi-infected mice. *Biochim. Biophys. Acta* 1852 (5), 893–904. doi:10.1016/j.bbdis.2014.12.019
- Perroud, B., Ishimaru, T., Borowsky, A. D., and Weiss, R. H. (2009). Grade-dependent proteomics characterization of kidney cancer. *Mol. Cell Proteomics* 8 (5), 971–985. doi:10.1074/mcp.M800252-MCP200
- Pestereva, E., Kanakasabai, S., and Bright, J. J. (2012). PPARγ agonists regulate the expression of stemness and differentiation genes in brain tumour stem cells. *Br. J. Cancer* 106 (10), 1702–1712. doi:10.1038/bjc.2012.161
- Phua, W. W. T., Wong, M. X. Y., Liao, Z., and Tan, N. S. (2018). An aPPARent functional consequence in skeletal muscle physiology via peroxisome proliferator-activated receptors. *Int. J. Mol. Sci.* 19 (5), 1425. doi:10.3390/ijms19051425
- Piqueras, L., Reynolds, A. R., Hodivala-Dilke, K. M., Alfranca, A., Redondo, J. M., Hatae, T., et al. (2007). Activation of PPARβ/delta induces endothelial cell proliferation and angiogenesis. *Arterioscler. Thromb. Vasc. Biol.* 27 (1), 63–69. doi:10.1161/01.ATV.0000250972.83623.61
- Plissonnier, M. L., Fauconnet, S., Bittard, H., Mougou, C., Rommelaere, J., and Lascombe, I. (2017). Cell death and restoration of TRAIL-sensitivity by ciglitazone in resistant cervical cancer cells. *Oncotarget* 8 (64), 107744–107762. doi:10.18632/oncotarget.22632
- Pollock, C. B., Yin, Y., Yuan, H., Zeng, X., King, S., Li, X., et al. (2011). PPARδ activation acts cooperatively with 3-phosphoinositide-dependent protein kinase-1 to enhance mammary tumorigenesis. *PLoS One* 6 (1), e16215. doi:10.1371/journal.pone.0016215
- Pozzi, A., Ibanez, M. R., Gatica, A. E., Yang, S., Wei, S., Mei, S., et al. (2007). Peroxisomal proliferator-activated receptor-α-dependent inhibition of endothelial cell proliferation and tumorigenesis. *J. Biol. Chem.* 282 (24), 17685–17695. doi:10.1074/jbc.M701429200
- Pozzi, A., Popescu, V., Yang, S., Mei, S., Shi, M., Puolitaival, S. M., et al. (2010). The anti-tumorigenic properties of peroxisomal proliferator-activated receptor alpha are arachidonic acid epoxigenase-mediated. *J. Biol. Chem.* 285 (17), 12840–12850. doi:10.1074/jbc.M109.081554
- Qin, L., Gong, C., Chen, A. M., Guo, F. J., Xu, F., Ren, Y., et al. (2014). Peroxisome proliferator-activated receptor γ agonist rosiglitazone inhibits migration and invasion of prostate cancer cells through inhibition of the CXCR4/CXCL12 axis. *Mol. Med. Rep.* 10 (2), 695–700. doi:10.3892/mmr.2014.2232
- Rakhshandehroo, M., Knoch, B., Müller, M., and Kersten, S. (2010). Peroxisome proliferator-activated receptor alpha target genes. *PPAR Res.* 2010, 612089. doi:10.1155/2010/612089
- Reka, A. K., Kurapati, H., Narala, V. R., Bommer, G., Chen, J., Standiford, T. J., et al. (2010). Peroxisome proliferator-activated receptor-gamma activation inhibits tumor metastasis by antagonizing Smad3-mediated epithelial-mesenchymal transition. *Mol. Cancer Ther.* 9 (12), 3221–3232. doi:10.1158/1535-7163.MCT-10-0570
- Rovito, D., Gionfriddo, G., Barone, I., Giordano, C., Grande, F., De Amicis, F., et al. (2016). Ligand-activated PPARγ downregulates CXCR4 gene expression through a novel identified PPAR response element and inhibits breast cancer progression. *Oncotarget* 7 (40), 65109–65124. doi:10.18632/oncotarget.11371
- Saez, E., Tontonoz, P., Nelson, M. C., Alvarez, J. G., Ming, U. T., Baird, S. M., et al. (1998). Activators of the nuclear receptor PPARγ enhance colon polyp formation. *Nat. Med.* 4 (9), 1058–1061. doi:10.1038/2042

- Saidi, S. A., Holland, C. M., Charnock-Jones, D. S., and Smith, S. K. (2006). *In vitro* and *in vivo* effects of the PPAR-alpha agonists fenofibrate and retinoic acid in endometrial cancer. *Mol. Cancer* 5, 13. doi:10.1186/1476-4598-5-13
- Saraon, P., Cretu, D., Mustrap, N., Karagiannis, G. S., Batruch, I., Drabovich, A. P., et al. (2013). Quantitative proteomics reveals that enzymes of the ketogenic pathway are associated with prostate cancer progression. *Mol. Cell Proteomics* 12 (6), 1589–1601. doi:10.1074/mcp.M112.023887
- Sarraf, P., Mueller, E., Jones, D., King, F. J., DeAngelo, D. J., Partridge, J. B., et al. (1998). Differentiation and reversal of malignant changes in colon cancer through PPARgamma. *Nat. Med.* 4 (9), 1046–1052. doi:10.1038/2030
- Schmidt, A., Endo, N., Rutledge, S. J., Vogel, R., Shinar, D., and Rodan, G. A. (1992). Identification of a new member of the steroid hormone receptor superfamily that is activated by a peroxisome proliferator and fatty acids. *Mol. Endocrinol.* 6 (10), 1634–1641. doi:10.1210/mend.6.10.1333051
- Schoonjans, K., Peinado-Onsurbe, J., Lefebvre, A. M., Heyman, R. A., Briggs, M., Deeb, S., et al. (1996). PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *Embo J.* 15 (19), 5336–5348. doi:10.1002/j.1460-2075.1996.tb00918.x
- Schupp, M., and Lazar, M. A. (2010). Endogenous ligands for nuclear receptors: Digging deeper. *J. Biol. Chem.* 285 (52), 40409–40415. doi:10.1074/jbc.R110.182451
- Shah, Y. M., Morimura, K., Yang, Q., Tanabe, T., Takagi, M., and Gonzalez, F. J. (2007). Peroxisome proliferator-activated receptor alpha regulates a microRNA-mediated signaling cascade responsible for hepatocellular proliferation. *Mol. Cell Biol.* 27 (12), 4238–4247. doi:10.1128/MCB.00317-07
- Shen, B., Chu, E. S. H., Zhao, G., Man, K., Wu, C. W., Cheng, J. T. Y., et al. (2012). PPARgamma inhibits hepatocellular carcinoma metastases *in vitro* and in mice. *Br. J. Cancer* 106 (9), 1486–1494. doi:10.1038/bjc.2012.130
- Sher, T., Yi, H. F., McBride, O. W., and Gonzalez, F. J. (1993). cDNA cloning, chromosomal mapping, and functional characterization of the human peroxisome proliferator activated receptor. *Biochemistry* 32 (21), 5598–5604. doi:10.1021/bi00072a015
- Shiau, C. W., Yang, C. C., Kulp, S. K., Chen, K. F., Chen, C. S., Huang, J. W., et al. (2005). Thiazolidinediones mediate apoptosis in prostate cancer cells in part through inhibition of Bcl-xL/Bcl-2 functions independently of PPARgamma. *Cancer Res.* 65 (4), 1561–1569. doi:10.1158/0008-5472.CAN-04-1677
- Shinohara, H., Taniguchi, K., Kumazaki, M., Yamada, N., Ito, Y., Otsuki, Y., et al. (2015). Anti-cancer fatty-acid derivative induces autophagic cell death through modulation of PKM isoform expression profile mediated by bcr-abl in chronic myeloid leukemia. *Cancer Lett.* 360 (1), 28–38. doi:10.1016/j.canlet.2015.01.039
- Skelhorne-Gross, G., Reid, A. L., Apostoli, A. J., Di Lena, M. A., Rubino, R. E., Peterson, N. T., et al. (2012). Stromal adipocyte PPARy protects against breast tumorigenesis. *Carcinogenesis* 33 (7), 1412–1420. doi:10.1093/carcin/bgs173
- Skrypnik, N., Chen, X., Hu, W., Su, Y., Mont, S., Yang, S., et al. (2014). PPARa activation can help prevent and treat non-small cell lung cancer. *Cancer Res.* 74 (2), 621–631. doi:10.1158/0008-5472.CAN-13-1928
- Smallridge, R. C., Copland, J. A., Brose, M. S., Wadsworth, J. T., Houvras, Y., Menefee, M. E., et al. (2013). Efatutazone, an oral PPAR-gamma agonist, in combination with paclitaxel in anaplastic thyroid cancer: Results of a multicenter phase 1 trial. *J. Clin. Endocrinol. Metab.* 98 (6), 2392–2400. doi:10.1210/jc.2013-1106
- Sng, M. K., Chan, J. S. K., Teo, Z., Phua, T., Tan, E. H. P., Wee, J. W. K., et al. (2018). Selective deletion of PPARβ/δ in fibroblasts causes dermal fibrosis by attenuated LRG1 expression. *Cell Discov.* 4, 15. doi:10.1038/s41421-018-0014-5
- Souza-Moreira, L., Soares, V. C., Dias, S. D. S. G., and Bozza, P. T. (2019). Adipose-derived mesenchymal stromal cells modulate lipid metabolism and lipid droplet biogenesis via AKT/mTOR -PPARy signalling in macrophages. *Sci. Rep.* 9 (1), 20304. doi:10.1038/s41598-019-56835-8
- Srivastava, N., Kollipara, R. K., Singh, D. K., Sudderth, J., Hu, Z., Nguyen, H., et al. (2014). Inhibition of cancer cell proliferation by PPARy is mediated by a metabolic switch that increases reactive oxygen species levels. *Cell Metab.* 20 (4), 650–661. doi:10.1016/j.cmet.2014.08.003
- Strack, E., Rolfe, P. A., Fink, A. F., Bankov, K., Schmid, T., Solbach, C., et al. (2020). Identification of tumor-associated macrophage subsets that are associated with breast cancer prognosis. *Clin. Transl. Med.* 10 (8), e239. doi:10.1002/ctm2.239
- Suchanek, K. M., May, F. J., Robinson, J. A., Lee, W. J., Holman, N. A., Monteith, G. R., et al. (2002). Peroxisome proliferator-activated receptor alpha in the human breast cancer cell lines MCF-7 and MDA-MB-231. *Mol. Carcinog.* 34 (4), 165–171. doi:10.1002/mc.10061
- Sun, L., Shi, Y., Wang, G., Wang, X., Zeng, S., Dunn, S. E., et al. (2018). PPAR-delta modulates membrane cholesterol and cytokine signaling in malignant B cells. *Leukemia* 32 (1), 184–193. doi:10.1038/leu.2017.162
- Sun, W. H., Chen, G. S., Ou, X. L., Yang, Y., Luo, C., Zhang, Y., et al. (2009). Inhibition of COX-2 and activation of peroxisome proliferator-activated receptor gamma synergistically inhibits proliferation and induces apoptosis of human pancreatic carcinoma cells. *Cancer Lett.* 275 (2), 247–255. doi:10.1016/j.canlet.2008.10.023
- Tan, E. H. P., Sng, M. K., How, I. S. B., Chan, J. S. K., Chen, J., Tan, C. K., et al. (2018). ROS release by PPARβ/δ-null fibroblasts reduces tumor load through epithelial antioxidant response. *Oncogene* 37 (15), 2067–2078. doi:10.1038/s41388-017-0109-8
- Tan, M. W. Y., Sng, M. K., Cheng, H. S., Low, Z. S., Leong, B. J. J., Chua, D., et al. (2020). Deficiency in fibroblast PPARβ/δ reduces nonmelanoma skin cancers in mice. *Cell Death Differ.* 27 (9), 2668–2680. doi:10.1038/s41418-020-0535-y
- Tan, Y., Wang, M., Yang, K., Chi, T., Liao, Z., and Wei, P. (2021). PPAR-A modulators as current and potential cancer treatments. *Front. Oncol.* 11, 599995. doi:10.3389/fonc.2021.599995
- Tsai, S. C., Tsai, M. H., Chiu, C. F., Lu, C. C., Kuo, S. C., Chang, N. W., et al. (2016). AMPK-dependent signaling modulates the suppression of invasion and migration by fenofibrate in CAL 27 oral cancer cells through NF-κB pathway. *Environ. Toxicol.* 31 (7), 866–876. doi:10.1002/tox.22097
- Urbanska, K., Pannizzo, P., Grabacka, M., Croul, S., Del Valle, L., Khalili, K., et al. (2008). Activation of PPARalpha inhibits IGF-I-mediated growth and survival responses in medulloblastoma cell lines. *Int. J. Cancer* 123 (5), 1015–1024. doi:10.1002/ijc.23588
- Vallée, A., and Lecarpentier, Y. (2018). Crosstalk between peroxisome proliferator-activated receptor gamma and the canonical WNT/β-Catenin pathway in chronic inflammation and oxidative stress during carcinogenesis. *Front. Immunol.* 9, 745. doi:10.3389/fimmu.2018.00745
- Vandoros, G. P., Konstantinopoulos, P. A., Sotiropoulou-Bonikou, G., Kominea, A., Papachristou, G. I., Karamouzis, M. V., et al. (2006). PPAR-gamma is expressed and NF-κB pathway is activated and correlates positively with COX-2 expression in stromal myofibroblasts surrounding colon adenocarcinomas. *J. Cancer Res. Clin. Oncol.* 132 (2), 76–84. doi:10.1007/s00432-005-0042-z
- Vu-Dac, N., Gervois, P., Jakel, H., Nowak, M., Bauge, E., Dehondt, H., et al. (2003). Apolipoprotein A5, a crucial determinant of plasma triglyceride levels, is highly responsive to peroxisome proliferator-activated receptor alpha activators. *J. Biol. Chem.* 278 (20), 17982–17985. doi:10.1074/jbc.M212191200
- Wagner, K. D., Du, S., Martin, L., Leccia, N., Michiels, J. F., and Wagner, N. (2019). Vascular pparβ/δ promotes tumor angiogenesis and progression. *Cells* 8 (12), 1623. doi:10.3390/cells8121623
- Wagner, N., and Wagner, K. D. (2020). PPAR beta/delta and the hallmarks of cancer. *Cells* 9 (5), 1133. doi:10.3390/cells9051133
- Wang, C., Lisanti, M. P., and Liao, D. J. (2011). Reviewing once more the c-myc and ras collaboration: Converging at the cyclin D1-CDK4 complex and challenging basic concepts of cancer biology. *Cell Cycle* 10 (1), 57–67. doi:10.4161/cc.10.1.14449
- Wang, D., Wang, H., Guo, Y., Ning, W., Katkuri, S., Wahli, W., et al. (2006). Crosstalk between peroxisome proliferator-activated receptor delta and VEGF stimulates cancer progression. *Proc. Natl. Acad. Sci. U. S. A.* 103 (50), 19069–19074. doi:10.1073/pnas.0607948103
- Wang, N., Wang, S., Wang, X., Zheng, Y., Yang, B., Zhang, J., et al. (2021). Research trends in pharmacological modulation of tumor-associated macrophages. *Clin. Transl. Med.* 11 (1), e288. doi:10.1002/ctm2.288
- Wang, S., Kandadi, M. R., and Ren, J. (2019). Double knockout of Akt2 and AMPK predisposes cardiac aging without affecting lifespan: Role of autophagy and mitophagy. *Biochim. Biophys. Acta Mol. Basis Dis.* 1865 (7), 1865–1875. doi:10.1016/j.bbadis.2018.08.011
- Wang, X., Sun, Y., Wong, J., and Conklin, D. S. (2013). PPARy maintains ERBB2-positive breast cancer stem cells. *Oncogene* 32 (49), 5512–5521. doi:10.1038/onc.2013.217
- Wang, X., Wang, G., Shi, Y., Sun, L., Gorczynski, R., Li, Y. J., et al. (2016). PPAR-delta promotes survival of breast cancer cells in harsh metabolic conditions. *Oncogenesis* 5 (6), e232. doi:10.1038/oncsis.2016.41
- Wei, S., Yang, J., Lee, S. L., Kulp, S. K., and Chen, C. S. (2009). PPARgamma-independent antitumor effects of thiazolidinediones. *Cancer Lett.* 276 (2), 119–124. doi:10.1016/j.canlet.2008.08.008
- Wejszka, K., Lee-Chang, C., Bodogai, M., Bonzo, J., Gonzalez, F. J., Lehmann, E., et al. (2013). Cancer-produced metabolites of 5-lipoxygenase induce tumor-evoked regulatory B cells via peroxisome proliferator-activated receptor α. *J. Immunol.* 190 (6), 2575–2584. doi:10.4049/jimmunol.1201920
- Werman, A., Hollenberg, A., Solanes, G., Bjorbaek, C., Vidal-Puig, A. J., and Flier, J. S. (1997). Ligand-independent activation domain in the N terminus of peroxisome proliferator-activated receptor gamma (PPARgamma). Differential activity of PPARgamma1 and -2 isoforms and influence of insulin. *J. Biol. Chem.* 272 (32), 20230–20235. doi:10.1074/jbc.272.32.20230
- Wolins, N. E., Quaynor, B. K., Skinner, J. R., Tzekov, A., Park, C., Choi, K., et al. (2006). OP9 mouse stromal cells rapidly differentiate into adipocytes: Characterization of a useful new model of adipogenesis. *J. Lipid Res.* 47 (2), 450–460. doi:10.1194/jlr.D500037-JLR200
- Woller, A., Duez, H., Staels, B., and Lefranc, M. (2016). A mathematical model of the liver circadian clock linking feeding and fasting cycles to clock function. *Cell Rep.* 17 (4), 1087–1097. doi:10.1016/j.celrep.2016.09.060

- Xie, Z. B., Zhang, Y. F., Jin, C., Mao, Y. S., and Fu, D. L. (2019). LRG-1 promotes pancreatic cancer growth and metastasis via modulation of the EGFR/p38 signaling. *J. Exp. Clin. Cancer Res.* 38 (1), 75. doi:10.1186/s13046-019-1088-0
- Xin, X., Yang, S., Kowalski, J., and Gerritsen, M. E. (1999). Peroxisome proliferator-activated receptor gamma ligands are potent inhibitors of angiogenesis *in vitro* and *in vivo*. *J. Biol. Chem.* 274 (13), 9116–9121. doi:10.1074/jbc.274.13.9116
- Xu, Y. Y., Liu, H., Su, L., Xu, N., Xu, D. H., Liu, H. Y., et al. (2019). PPAR γ inhibits breast cancer progression by upregulating PTPRF expression. *Eur. Rev. Med. Pharmacol. Sci.* 23 (22), 9965–9977. doi:10.26355/eurrev_201911_19563
- Xue, J., Zhu, W., Song, J., Jiao, Y., Luo, J., Yu, C., et al. (2018). Activation of PPAR α by clofibrate sensitizes pancreatic cancer cells to radiation through the Wnt/ β -catenin pathway. *Oncogene* 37 (7), 953–962. doi:10.1038/onc.2017.401
- Yaghoubzadeh, M., Pishkar, L., and Basati, G. (2020). Aberrant expression of peroxisome proliferator-activated receptors in colorectal cancer and their association with cancer progression and prognosis. *Gastrointest. Tumors* 7 (1-2), 11–20. doi:10.1159/000503995
- Yan, K. H., Yao, C. J., Chang, H. Y., Lai, G. M., Cheng, A. L., and Chuang, S. E. (2010). The synergistic anticancer effect of troglitazone combined with aspirin causes cell cycle arrest and apoptosis in human lung cancer cells. *Mol. Carcinog.* 49 (3), 235–246. doi:10.1002/mc.20593
- Yang, D., Guo, P., and Powell, C. A. (2021). Role of endothelial cells in tumor microenvironment. *Clin. Transl. Med.* 11 (6), e450. doi:10.1002/ctm2.450
- Yang, Y., Zhao, L. H., Huang, B., Wang, R. Y., Yuan, S. X., Tao, Q. F., et al. (2015). Pioglitazone, a PPAR γ agonist, inhibits growth and invasion of human hepatocellular carcinoma via blockade of the rage signaling. *Mol. Carcinog.* 54 (12), 1584–1595. doi:10.1002/mc.22231
- Yao, C. J., Lai, G. M., Chan, C. F., Cheng, A. L., Yang, Y. Y., and Chuang, S. E. (2006). Dramatic synergistic anticancer effect of clinically achievable doses of lovastatin and troglitazone. *Int. J. Cancer* 118 (3), 773–779. doi:10.1002/ijc.21361
- Yao, P. L., Morales, J. L., Zhu, B., Kang, B. H., Gonzalez, F. J., and Peters, J. M. (2014). Activation of peroxisome proliferator-activated receptor- β/δ (PPAR- β/δ) inhibits human breast cancer cell line tumorigenicity. *Mol. Cancer Ther.* 13 (4), 1008–1017. doi:10.1158/1535-7163.MCT-13-0836
- Yin, X., Zeng, W., Wu, B., Wang, L., Wang, Z., Tian, H., et al. (2020). PPAR α inhibition overcomes tumor-derived exosomal lipid-induced dendritic cell dysfunction. *Cell Rep.* 33 (3), 108278. doi:10.1016/j.celrep.2020.108278
- Yin, Y., Russell, R. G., Dettin, L. E., Bai, R., Wei, Z. L., Kozikowski, A. P., et al. (2005). Peroxisome proliferator-activated receptor delta and gamma agonists differentially alter tumor differentiation and progression during mammary carcinogenesis. *Cancer Res.* 65 (9), 3950–3957. doi:10.1158/0008-5472.CAN-04-3990
- Ying, H., Kimmelman, A. C., Lyssiotis, C. A., Hua, S., Chu, G. C., Fletcher-Sanankone, E., et al. (2012). Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell* 149 (3), 656–670. doi:10.1016/j.cell.2012.01.058
- Yokoyama, Y., Xin, B., Shigeto, T., and Mizunuma, H. (2011). Combination of ciglitazone, a peroxisome proliferator-activated receptor gamma ligand, and cisplatin enhances the inhibition of growth of human ovarian cancers. *J. Cancer Res. Clin. Oncol.* 137 (8), 1219–1228. doi:10.1007/s00432-011-0993-1
- Yoshida, G. J., Azuma, A., Miura, Y., and Orimo, A. (2019). Activated fibroblast program orchestrates tumor initiation and progression; molecular mechanisms and the associated therapeutic strategies. *Int. J. Mol. Sci.* 20 (9), 2256. doi:10.3390/ijms20092256
- Yoshinaga, M., Kitamura, Y., Chaen, T., Yamashita, S., Tsuruta, S., Hisano, T., et al. (2009). The simultaneous expression of peroxisome proliferator-activated receptor delta and cyclooxygenase-2 may enhance angiogenesis and tumor venous invasion in tissues of colorectal cancers. *Dig. Dis. Sci.* 54 (5), 1108–1114. doi:10.1007/s10620-008-0465-x
- You, M., Gao, J., Jin, J., and Hou, Y. (2018). PPAR α enhances cancer cell chemotherapy sensitivity by autophagy induction. *J. Oncol.* 2018, 6458537. doi:10.1155/2018/6458537
- You, M., Jin, J., Liu, Q., Xu, Q., Shi, J., and Hou, Y. (2017). PPAR α promotes cancer cell Glut1 transcription repression. *J. Cell Biochem.* 118 (6), 1556–1562. doi:10.1002/jcb.25817
- Yousefi, B., Azimi, A., Majidinia, M., Shafiei-Irannejad, V., Badalzadeh, R., Baradaran, B., et al. (2017). Balaglitazone reverses P-glycoprotein-mediated multidrug resistance via upregulation of PTEN in a PPAR γ -dependent manner in leukemia cells. *Tumour Biol.* 39 (10), 1010428317716501. doi:10.1177/1010428317716501
- Yu, H. N., Noh, E. M., Lee, Y. R., Roh, S. G., Song, E. K., Han, M. K., et al. (2008). Troglitazone enhances tamoxifen-induced growth inhibitory activity of MCF-7 cells. *Biochem. Biophys. Res. Commun.* 377 (1), 242–247. doi:10.1016/j.bbrc.2008.09.111
- Yuan, H., Lu, J., Xiao, J., Upadhyay, G., Umans, R., Kallakury, B., et al. (2013). PPAR δ induces estrogen receptor-positive mammary neoplasia through an inflammatory and metabolic phenotype linked to mTOR activation. *Cancer Res.* 73 (14), 4349–4361. doi:10.1158/0008-5472.CAN-13-0322
- Zhang, M. A., Rego, D., Moshkova, M., Kebir, H., Chruscinski, A., Nguyen, H., et al. (2012). Peroxisome proliferator-activated receptor (PPAR) α and γ regulate IFN γ and IL-17A production by human T cells in a sex-specific way. *Proc. Natl. Acad. Sci. U. S. A.* 109 (24), 9505–9510. doi:10.1073/pnas.1118458109
- Zhang, N., Chu, E. S. H., Zhang, J., Li, X., Liang, Q., Chen, J., et al. (2014). Peroxisome proliferator activated receptor alpha inhibits hepatocarcinogenesis through mediating NF- κ B signaling pathway. *Oncotarget* 5 (18), 8330–8340. doi:10.18632/oncotarget.2212
- Zhang, W., Xu, Y., Xu, Q., Shi, H., Shi, J., and Hou, Y. (2017). PPAR δ promotes tumor progression via activation of Glut1 and SLC1A5 transcription. *Carcinogenesis* 38 (7), 748–755. doi:10.1093/carcin/bgx035
- Zhang, Z., Xu, Y., Xu, Q., and Hou, Y. (2013). PPAR γ against tumors by different signaling pathways. *Onkologie* 36 (10), 598–601. doi:10.1159/000355328
- Zheng, S., Liang, J. Y., Tang, Y., Xie, J., Zou, Y., Yang, A., et al. (2023). Dissecting the role of cancer-associated fibroblast-derived biglycan as a potential therapeutic target in immunotherapy resistance: A tumor bulk and single-cell transcriptomic study. *Clin. Transl. Med.* 13 (2), e1189. doi:10.1002/ctm2.1189
- Zhong, W. B., Tsai, Y. C., Chin, L. H., Tseng, J. H., Tang, L. W., Horng, S., et al. (2018). A synergistic anti-cancer effect of troglitazone and lovastatin in a human anaplastic thyroid cancer cell line and in a mouse xenograft model. *Int. J. Mol. Sci.* 19 (7), 1834. doi:10.3390/ijms19071834
- Zhou, Y., Zhang, X., Zhang, J., Fang, J., Ge, Z., and Li, X. (2017). LRG1 promotes proliferation and inhibits apoptosis in colorectal cancer cells via RUNX1 activation. *PLoS One* 12 (4), e0175122. doi:10.1371/journal.pone.0175122
- Zhu, B., Bai, R., Kennett, M. J., Kang, B. H., Gonzalez, F. J., and Peters, J. M. (2010). Chemoprevention of chemically induced skin tumorigenesis by ligand activation of peroxisome proliferator-activated receptor-beta/delta and inhibition of cyclooxygenase 2. *Mol. Cancer Ther.* 9 (12), 3267–3277. doi:10.1158/1535-7163.MCT-10-0820
- Zoico, E., Darra, E., Rizzatti, V., Budui, S., Franceschetti, G., Mazzali, G., et al. (2016). Adipocytes WNT5a mediated dedifferentiation: A possible target in pancreatic cancer microenvironment. *Oncotarget* 7 (15), 20223–20235. doi:10.18632/oncotarget.7936
- Zuo, Q., He, J., Zhang, S., Wang, H., Jin, G., Jin, H., et al. (2021). PPAR γ coactivator-1 α suppresses metastasis of hepatocellular carcinoma by inhibiting Warburg effect by ppar γ -dependent WNT/ β -Catenin/Pyruvate dehydrogenase kinase isozyme 1 Axis. *Hepatology* 73 (2), 644–660. doi:10.1002/hep.31280
- Zuo, X., Xu, W., Xu, M., Tian, R., Moussalli, M. J., Mao, F., et al. (2017). Metastasis regulation by PPAR δ expression in cancer cells. *JCI Insight* 2 (1), e91419. doi:10.1172/jci.insight.91419