ACCSCIENCE PUBLISHING

Tumor Discovery

REVIEW ARTICLE

Peroxisome proliferator-activated receptor agonists as an adjuvant for cancer therapy: A review

Binita Patel[1] and S. R. Kaid Johar[2]*

[1]Department of Life Sciences, School of Sciences, Gujarat University, Ahmedabad, Gujarat, India

[2]Department of Zoology, Biomedical Technology and Human Genetics, School of Sciences, Gujarat University, Ahmedabad, Gujarat, India

(This article belongs to the *Special Issue: Current Evidences in Cancer Chemoprevention*)

Abstract

Cancer is now one of the leading diseases responsible for the highest mortality rates worldwide. Cancer treatment is extremely intricate and is often associated with less targeted effects and more side effects. In the last few years, two significant revolutions in cancer treatment have altered treatment paradigms: immuno-oncology and the pursuit of actionable changes in oncogene-driven cancers. Significant obstacles continue to exist in both areas of cancer treatment. Next-generation sequencing technologies for molecular prescreening in clinical research are advancing, but their widespread clinical use is hindered by challenges related to the clinical interpretation of large genomic data. Moreover, cancer mono-chemotherapy is associated with issues such as inadequate efficacy, drug resistance, and systemic toxicity. It is not possible to administer cytotoxic drugs limitlessly. Combination therapy was developed in response to this circumstance, with the expectation of achieving high therapeutic efficacy at lower dosages of medication. Peroxisome proliferator-activated receptors (PPARs) are a group of essential lipid sensors and metabolic pathway regulators. In addition, they possess the ability to modulate immunity, inflammation, and endothelial nitric oxide synthase activation. Alongside their well-established functions, new insights into the roles of PPAR agonists in cancer research are emerging. After reviewing current research, it is evident that PPAR modulators have significant potential for managing cancer. This review aims to consolidate the functions of PPAR ligands alongside other cancer therapies. We provide a comprehensive perspective on the applicability of PPAR ligands in cancer treatment as an adjuvant.

Keywords: PPAR agonists; Adjuvant; Cancer; Synergism; Cancer therapy; Drug repurposing

***Corresponding author:**
S. R. Kaid Johar
(kaidjohar@gujaratuniversity.ac.in)

Citation: Patel B, Johar SRK. Peroxisome proliferator-activated receptor agonists as an adjuvant for cancer therapy: A review. *Tumor Discov*. 2024;3(4):4003. doi: 10.36922/td.4003

Received: June 21, 2024

Accepted: September 25, 2024

Published Online: November 5, 2024

Copyright: © 2024 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

According to the World Health Organization, 97 million people died from cancer in 2022, with an estimated 20 million new cases. The estimated number of people who were alive 5 years after a cancer diagnosis was 53.5 million. In their lifetime, one in five

people will develop cancer; one in nine men and one in 12 women will die from the disease. The process of treating cancer has always been intricate. Conventional therapeutic modalities, including radiotherapy, chemotherapy, and surgery, have been employed to treat cancer.[1]

The main treatments for cancer are surgery and chemotherapy; however, patients frequently develop chemotherapeutic resistance within a few years after starting treatment.[2] Furthermore, side effects from chemotherapeutic drugs such as paclitaxel, carboplatin, and doxorubicin can significantly worsen quality of life. These side effects include weakness, itching, loss of appetite, hair loss, and facial flushing, among others. Consequently, novel therapeutic approaches and improved predictive markers for chemotherapy, targeted therapies, immunotherapy, and hormonal therapy are required.[3]

Advances in our understanding of the molecular mechanisms underlying cancer progression have made it possible to develop novel targeted therapies that are proving to be innovative and promising approaches for treating the disease.[4] As these therapies specifically target cancer cells while avoiding harm to non-target cells, they are becoming increasingly significant. The strategies used in targeted therapy include prodrugs, nanoparticulate antibody conjugates, small molecule inhibitors, and monoclonal antibodies. However, recent studies have revealed that the presence of molecularly diverse tumors can lead to treatment failures in several cases.[5-8] Furthermore, although it was anticipated that targeted therapy would cause fewer side effects than conventional chemotherapy, significant toxicities are still observed. Trastuzumab, for example, has been linked to congestive heart failure as a known adverse effect.[9] Common side effects of vascular endothelial growth factor (VEGF) inhibitors and VEGF receptor inhibitors include hypertension, thromboembolic events, slowed wound healing, and an elevated risk of bleeding, including tumor-related hemorrhage.[10]

By enhancing the immune response, immunotherapy enables the patient's immune system to destroy cancer cells. As a next-generation treatment for cancer, it has the potential to replace chemotherapy due to its effectiveness against multiple tumors and its innovative therapeutic properties.[11] There are two types of immunotherapy: active and passive. Active immunotherapy includes chimeric antigen receptor T cells, immunostimulatory vaccines, and genetically modified organisms that can recognize specific cancer antigens. Passive immunotherapy, on the other hand, involves using cytokines or checkpoint inhibitors to indirectly enhance the patient's immune response.[12] Although these treatments are novel, clinical trial results indicate that they are only effective against a limited number of cancers and can lead to unfavorable side effects, including cytokine release syndrome and a weakened immune response.[13] Although immunotherapy has been developed as an effective cancer treatment, immunotherapy-based drugs often have poor outcomes in solid tumors due to low infiltration of immune cells and decreased tumor immunogenicity, resulting in an immunosuppressive tumor environment.[14] Furthermore, the lack of appropriate preclinical models for validating distinct biomarkers, as well as inadequate methods for tumor tissue collection, makes it more difficult to assess predictive biomarkers.[15]

Usually, hormonal treatments prevent steroid ligands from attaching to the nuclear hormone receptor family, which includes estrogen receptor and androgen receptor (AR) in breast cancer and prostate cancer, respectively.[16] Various hormone receptors are expressed in cancer and mediate both growth stimulation and inhibition effects. Hormones such as gonadotropin-releasing hormones, gonadotropins, androgens, estrogens, and progestins have been evaluated in several clinical trials to understand the mechanisms of tumorigenesis.[17-20] However, resistance is a common cause of failure in single-agent hormonal therapy, and it is not the only factor at play. Therapies such as leuprorelin and enzalutamide can lead to resistance through various mechanisms, including mutations in the AR ligand-binding domain and the creation of variant AR proteins that can recognize antiandrogens (antagonists) as agonists.[21-23] In this comprehensive review, we have compiled the available research on the utilization of various peroxisome proliferator-activated receptor (PPAR) agonists as a combination therapy with known cancer modalities for different cancers.

2. Combination therapy for cancer

Considering the current situation, a synergistic approach that combines a chemotherapeutic agent with another agent can be employed to target similar or different genes for cancer treatment. Although the combination of cytotoxic drugs has garnered significant interest, concerns remain regarding the potential risks of drug toxicity, cross-resistance, and compromised quality of life.[24] Therefore, incorporating a biological agent alongside an established chemotherapeutic drug presents a promising alternative to optimize therapeutic outcomes while minimizing toxicity. By targeting various molecular pathways implicated in cancer development through diverse mechanisms of action, combination therapy aims to enhance treatment efficacy.[25,26] However, discovering novel therapeutic agents is a complex and resource-intensive process that entails multiple steps, substantial time, and costs, including clinical trials.[27] Thus, drug repurposing offers several advantages

in overcoming the challenges associated with finding new agents.[28] The process of using an already-approved medication or drug candidate for a new medical condition or treatment for which it was not previously recommended is known as "drug repurposing."[29,30] To expedite the drug discovery process and address the pressing needs in healthcare, drug repurposing has become essential. In drug repurposing, a drug is identified, preclinical models are used to assess its efficacy, and Phase II clinical trials are then conducted.[31] Among the various drugs that can be repurposed for synergistic cancer treatment, PPAR agonists show promising results.

3. PPARs

PPARs are a group of nuclear receptor superfamily members that play a major role in gene expression and metabolism regulation. PPARs bind to ligands and translocate to the cell nucleus. Together with their ligands, PPARs act as transcription factors that bind to specific DNA sequences known as peroxisome proliferator-responsive elements and heterodimerize with retinoid X receptors.[32] The PPAR superfamily comprises three subtypes: PPAR-α, PPAR-γ, and PPAR-β/δ. These PPAR subtypes share a relatively high similarity in molecular structure; however, there are significant differences in their biological functions, tissue distribution, and ligand affinities.[33] Figure 1 illustrates the differences between the PPAR subtypes and their interactions with DNA. PPAR-α expression is primarily found in the liver, brown adipose tissue, heart, kidney, and muscle tissue, where it regulates fatty acid β-oxidation and energy homeostasis.[34] PPAR-β/δ is ubiquitously expressed, often at high levels in skeletal muscle, adipose tissue, heart, and the gastrointestinal tract, and it regulates fatty acid metabolism and blood glucose levels.[35,36] PPAR-γ is highly expressed in the heart, muscle, gastrointestinal tract, kidney, adipose tissue, immune cells, and endothelial cells.[37] PPARs are also important lipid sensors and regulators of various metabolic pathways. They can promote endothelial nitric oxide synthase activation and modulate immune and inflammatory responses. In addition to their well-established roles, discoveries are being made regarding the functions of PPARs in cancer.[38,39] Previous studies have shown that the expression of PPAR-β/δ correlates with tumor proliferation, whereas the activation of PPAR-α and PPAR-γ is associated with tumor suppression. Such generalizations may be overly simplistic due to the complex regulatory signals of PPARs, and their intricate mechanisms require further investigation. Consequently, the role of PPARs in cancer has gradually become a focal point of research.[40] More specifically, initially recognized as key players in adipocyte differentiation and glucose regulation, PPAR-γ and PPAR-α have now been identified as therapeutic targets with a wide range of potential applications in cell differentiation, apoptosis, angiogenesis, epithelial–mesenchymal transition, and other biological processes that are deregulated in cancer.[41,42]

4. PPAR modulators

PPAR modulators are molecules that modulate the activity of PPAR receptors. PPAR agonists are compounds that activate the PPAR pathway. These ligands are developed to treat various diseases and disorders related to lipid metabolism, diabetes, and metabolic syndromes. PPAR-α agonists are primarily used to treat dyslipidemia, whereas PPAR-γ agonists are prescribed for the treatment of Type 2 diabetes. PPAR-α agonists include a class of chemicals called fibrates, which encompasses fenofibrate, gemfibrozil, bezafibrate, ciprofibrate, and clofibrate. Several other compounds, such as pemafibrate, Wy-14643 (pirinixic acid), and GW7674, are also known to act as PPAR-α agonists.[43] In addition to these, omega-3 fatty acids, curcumin, and sesquiterpenes are recognized for their PPAR-α agonist activity.[44] PPAR-γ agonists are the most widely used. Several other compounds, including natural compounds and synthetic derivatives, have been identified as PPAR-γ agonists. This group includes a class of drugs called thiazolidinediones (TZDs), whose antidiabetic properties were discovered in the early 1980s.[45] Various natural products derived from traditionally used medicinal plants and foods activate the PPAR-γ receptor.[46] Different fatty acids and fatty acid derivatives, such as eicosanoids (e.g., 8-S-hydroxyeicosatetraenoic acid [HETE] and leukotriene B4), can also activate PPAR-γ. In addition, several prostanoids, such as 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) and 15-HETE, can activate PPAR-γ as well.[47] Many *in vivo* studies have shown that some natural activators of PPAR-γ (e.g., honokiol, amorphofurtin 1, amorphofurtin B, and amorphastilbol) improve metabolic parameters in diabetic animal models.[48-50] TZDs include pioglitazone, rosiglitazone, troglitazone (TGZ), rivoglitazone, and netoglitazone. Dual or pan-PPAR agonists have also been developed, including muraglitazar, tesaglitazar, and saroglitazar.[51-54] We have compiled a comprehensive review that summarizes the available literature supporting the beneficial effects of treatment with PPAR ligands in combination with existing therapies in cancer. Numerous examples exist where combination therapy has produced synergistic or additive effects on apoptosis, differentiation, and the ability to reduce cell proliferation and tumor burden.[55] Some studies indicate that pretreatment with PPAR ligands can overcome resistance and reduce toxicity.[56] Several mechanisms have been investigated to explain these protective effects.[57] This article focuses on studies that provide strong arguments

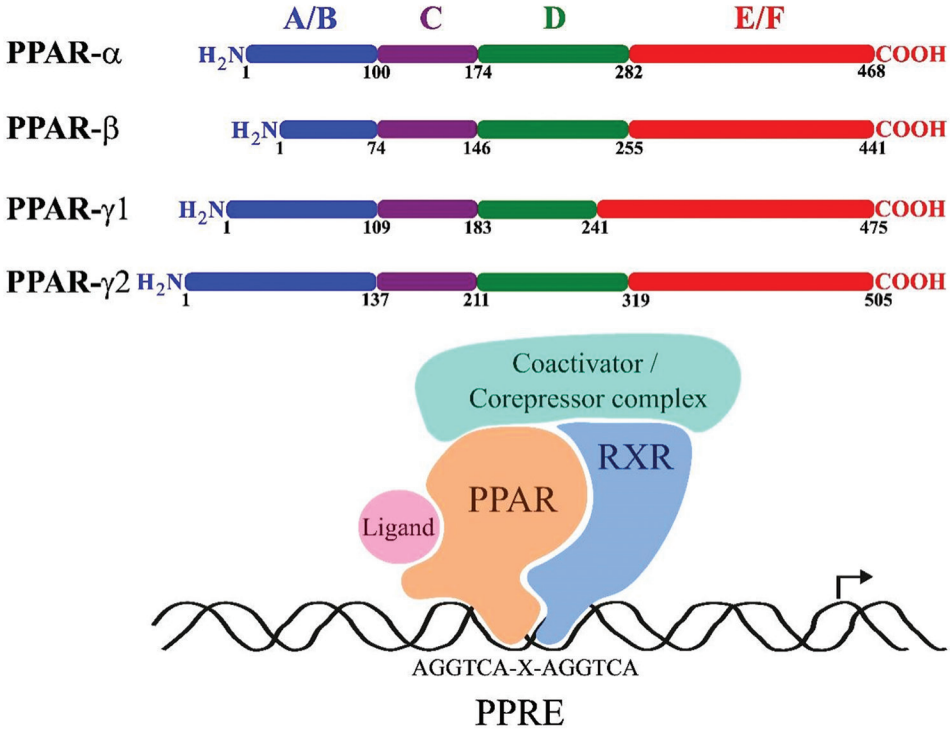


Figure 1. Peroxisome proliferator-activated receptor (PPARs) subtypes and their interaction with DNA. PPAR-α, PPAR-β, and PPAR-γ (γ1, and γ2) are the known PPAR subtypes. All subtypes of PPAR contain the A/B domain or AF-1 domain, C or DNA binding domain, D or hinge region, and E/F or ligand-binding domain (LBD). LBD has the ligand and retinoic acid receptor (RXR) interaction sites. It contains the AF-2 region, which is important for ligand-dependent trans-activation. The difference between the subtypes of PPAR at the A/B, D, and E/F domains determines its subtypes and the efficiency of its interaction with its ligands. The PPAR – RXR complex binds DNA at the peroxisome proliferator response elements.

for the use of PPAR ligands in conjunction with other treatment modalities as anticancer therapy for multiple types of cancer.

4.1. PPAR agonists for antiangiogenic effects

Angiogenesis, a crucial process in the tumor microenvironment involved in metastasis, is the natural progression through which new blood vessels form from existing ones. Growth factors that stimulate angiogenesis and inhibitors that regulate neovascularization act as controllers of this process.[58] The mutation of K-Ras and epidermal growth factor receptors is associated with resistance to conventional chemotherapeutic agents and other targeted therapies.[59] The treatment of PPAR-γ ligand (rosiglitazone) alongside carboplatin induces a dramatic depletion of mutant K-Ras and epidermal growth factor receptors in murine lung adenocarcinomas. In numerous genetically engineered mouse models of lung carcinoma, the combination treatment of rosiglitazone and carboplatin inhibits tumor aggressiveness, indicating its promise as a predominantly effective anticancer strategy.[60] Arachidonic acid (AA), a polyunsaturated fatty acid released from membrane phospholipids, is converted into different bioactive lipid mediators, such as epoxyeicosatrienoic acids (EETs), prostaglandins (PGs), and HETEs, through the action of cytochrome P450 (CYP) epoxygenases, cyclooxygenase (COX), or lipoxygenase pathways.[61] Among these, EETs are particularly potent proangiogenic eicosanoids and are positively linked with cancer progression.[62] PPAR-α ligand AVE8134, in conjunction with COX inhibitor therapy, synergistically halts lung cancer development and angiogenesis by downregulating CYP2c44 expression, reducing the synthesis of EETs (AA-derived EETs), increasing levels of 11-HETE, and altering the catalytic activity of COX enzymes.[63] N-(9-fluorenylmethyloxycarbonyl)-L-leucine (F-L-Leu), a novel PPAR-γ agonist, along with COX-2 inhibitors, induces an anti-tumorigenesis pathway in breast cancer cells. This integrated effect can be utilized at subclinical doses to reduce chemotherapy in women at high risk of developing breast cancer.[64] Malakouti *et al.* studied *CXCR4* and *CXCR7* gene expression to investigate the effects of co-administration of pioglitazone and doxorubicin on the breast cancer cell line MDA-MB-231. They observed that pioglitazone decreased the movement of MDA-MB-231 cells, possibly by upregulating the expression of *CXCR4* and *CXCR7* and

affecting other pathways related to cell migration, without increasing the expression of the surface proteins of these two receptors.[65]

4.2. PPAR agonists for antiproliferative and apoptotic effects

Apoptosis, the body's natural cell death process, is a key area of focus in anticancer treatment. In cancer, the suppression of the apoptotic pathway often occurs through the overexpression of antiapoptotic proteins and the underexpression of proapoptotic proteins. These changes can lead to resistance to chemotherapy, a commonly used cancer treatment method.[66] Several PPAR agonists have demonstrated antiproliferative and apoptosis-inducing effects when used in combination with chemotherapeutic agents, and the underlying pathways are illustrated in Figure 2. Treatment with PPAR-γ through the synthetic ligand TGZ and all-trans-retinoic acid significantly inhibited the growth of MCF7 tumors, which was correlated with the downregulation of Bcl-2 and resulted in significant apoptosis and fibrosis in these tumors.[67]

In certain cancer cell lines, ranpirnase and rosiglitazone work synergistically to reduce cell viability and accelerate cell death. For malignancies with elevated PI3K-dependent Fra-1 expression or survivin, the innovative combination of ranpirnase and rosiglitazone appears promising, as illustrated in Figure 2.[68] The combination of rosiglitazone and all-trans-retinoic acid lowers the expression of COX-2, matrix metallopeptidase 7 (MMP-7), and tissue inhibitor of metalloproteinase 1, induces cell cycle arrest at the G1 phase and consequently inhibits cell proliferation in the human colorectal cancer cell line HCT-15.[69] In hepatocellular carcinoma (HCC) cells treated with 5-fluorouracil, rosiglitazone activates the PPAR-γ signaling pathway, upregulating PTEN expression and downregulating COX-2 expression to promote cancer cell growth.[70] Fenofibrate, an agonist of PPAR-α, hinders cell proliferation and induces apoptosis in Ishikawa endometrial carcinoma cells. These effects are magnified by retinoic acid, an agonist of the retinoid X receptor. DNA content analysis indicates that progression through the G1/S phase of the cell cycle is inhibited. Independent component analysis of gene microarray experiments shows a reduction in the expression of cyclin D1 (*CCND1*) and related changes in cell cycle gene expression.[71]

A PPAR-γ agonist, TGZ, in combination with cisplatin, inhibited EHMES-10 cell growth through cell cycle arrest due to the overexpression of $p21^{waf1/cip1}$ and apoptosis. This synergism may provide therapeutic benefits for patients with malignant pleural mesothelioma.[72] The combination

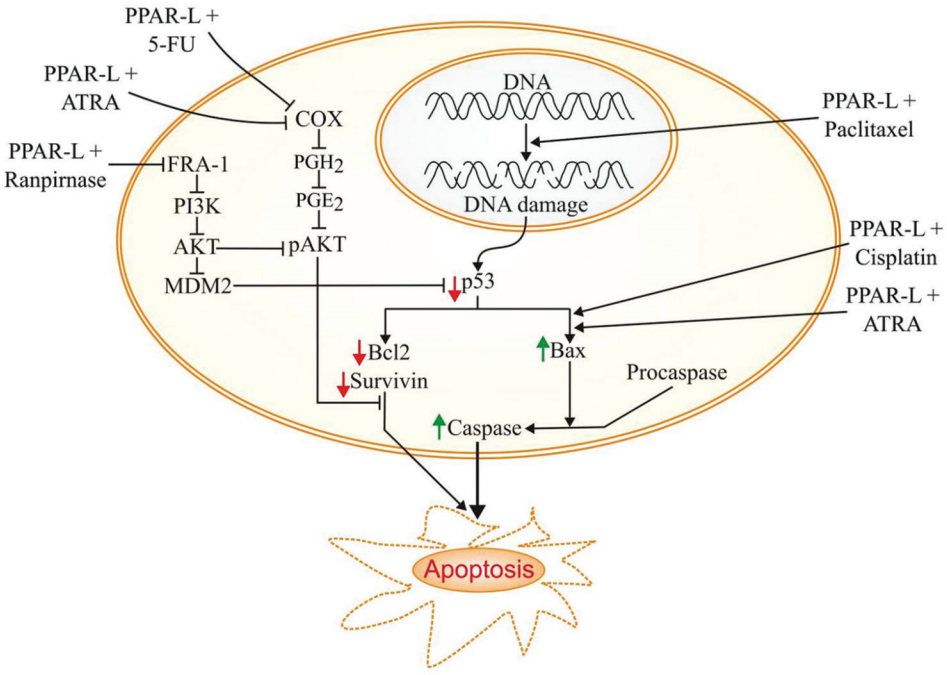


Figure 2. Effect of peroxisome proliferator-activated receptor (PPAR) agonists as an adjuvant on the proliferation and apoptosis of cancer cells. PPAR ligand along with paclitaxel, cisplatin, ranpirnase, all-trans-retinoic acid, and 5-fluorouracil exert more effects than cancer therapy alone. The effects of PPAR agonists were due to the decreased expression of Bcl2, survivin, PI3K, AKT, MDM2, and p53 and the increased expression of Bax. This finally leads to the activation of apoptotic pathways in cancer cells.

of the high-affinity PPAR-γ agonist RS5444 and paclitaxel exhibited a reduction in the proliferation rate of cells and minimized tumor growth of undifferentiated thyroid neoplasm carcinoma *in vivo*. Although RS5444 alone did not induce apoptosis, its combination with paclitaxel increased the apoptotic index twofold compared to paclitaxel alone.[73] Moreover, activation of PPAR-γ by its ligand pioglitazone intensifies the effects of cisplatin, inhibiting MDA-MB-231 cell survival compared to chemotherapy alone. This effect may be attributed to enhanced apoptosis resulting from the downregulation of the antiapoptotic protein Bcl-2 and increased levels of caspase-9 and cleaved PARP, as explained in Figure 2.[74] Pouya *et al.* illustrated that the co-delivery of capecitabine–pioglitazone-loaded triblock nanoparticles effectively destroyed colorectal cancer cells *in vitro*. This approach could achieve the co-delivery of capecitabine and pioglitazone, utilizing the potential of both drugs and increasing the longevity of patients with colorectal cancer.[75]

4.3. PPAR agonists for prevention of cell migration and invasion

The first stage of the metastatic cascade is invasion, which occurs when tumor cells migrate, infiltrate the surrounding tissue, and enter lymphatic and blood vessels to spread. A growing body of research suggests that mutations may drive and accelerate the invasion and migration of various cancer cell types.[76] The antimigration and anti-invasion effects of radiation were enhanced by rosiglitazone, a PPAR-γ agonist that decreased cell viability. Rosiglitazone increased the radiosensitivity of PANC1 xenografts and pancreatic cancer cells. According to microarray studies, the combination of rosiglitazone and radiation altered the expression of several genes and impacted various pathways.[77] In addition, a novel PPAR-γ ligand, CB13, inhibits cell growth by increasing lactate dehydrogenase release, decreasing cell viability, and enhancing caspase-3 and caspase-9 activities in non-small cell lung cancer (NSCLC) and radioresistant NSCLC cell lines (A549R and H460R). Furthermore, CB13 generates reactive oxygen species (ROS) and induces endoplasmic reticulum (ER) stress, leading to cell death. When CB13 is combined with radiation, ER stress, and cell death are significantly increased compared to using CB13 alone.[56]

Lyon *et al.* were the first to demonstrate that long-term *in vivo* treatment with a chemopreventive mixture, which includes selenium (an antioxidant), rosiglitazone, sodium phenylbutyrate or valproic acid (histone deacetylase inhibitors), and hydralazine (a cytosine-demethylating agent), could effectively block the development of premalignant lung cancer in the A/J mouse model treated with NNK (4-methylnitrosamino)-1-(3-pyridyl)-1-butanone.[78]

As shown in Figure 3, the PPAR agonist pioglitazone and the histone deacetylase inhibitor valproic acid synergistically regulate E-cadherin expression and inhibit the growth and invasion of prostate cancer compared to individual therapies.[79] The PPAR-γ agonist rosiglitazone, in combination with radiotherapy, enhances the effectiveness of radiotherapy to improve local tumor control, decrease the risk of distant metastasis, and delay tumor recurrence.[80] Survivin is the smallest member of the apoptosis inhibitor protein family, and its aberrant expression is correlated with tumor cell proliferation, progression, angiogenesis, resistance to therapy, and poor prognosis. Survivin is predominantly expressed in most human malignancies, including lung, pancreatic, and breast cancers, compared to normal tissues.[81] A natural PPAR-γ agonist, 15d-PGJ2 (15-Deoxy-Δ12,14-PGJ2), has been investigated for over a decade. Studies have shown that it possesses pro-apoptotic, anti-inflammatory, antiangiogenic, and anti-metastatic properties, along with significant anticancer effects.[82] Co-treatment with 15d-PGJ2 and survivin RNAi synergistically inhibits the stem cell phenotype and cell proliferation of bladder cancer *in vitro* by upregulating ROS production and generating oxidative stress mediated by NADPH oxidase 2. This study suggests that the combined treatment of survivin inhibitors and PPAR-γ agonists may have therapeutic significance in the clinical treatment of various cancers.[83]

4.4. PPAR agonists for induction of oxidative stress

ROS plays a major role in regulating normal cellular functions, but when they are uncontrolled, they can contribute to diseases such as cancer. Increased ROS generation has been observed in several studies, activating protumorigenic signaling, enhancing cell survival and proliferation, and promoting DNA damage and genetic instability.[84] However, it has also been discovered that higher concentrations of ROS can encourage antitumorigenic signaling by triggering oxidative stress-induced tumor cell death. Tumor cells adapt by producing higher levels of antioxidant proteins to detoxify excess ROS while maintaining protumorigenic signaling and resistance to apoptosis.[85] The effects of various PPAR agonists on elevating ROS levels in cancer cells are summarized in Figure 4.

The combination therapy of PPAR-γ ligands and COX-2 inhibitors has shown anti-inflammatory and antineoplastic effects *in vitro* and has been evaluated for its therapeutic potential in several preclinical and clinical studies.[86] As illustrated in Figure 4, PPAR-γ ligands can enhance γ-H2AX expression, thereby magnifying the DNA damage response induced by γ-radiation. Furthermore, the combined treatment significantly increased ROS generation, whereas

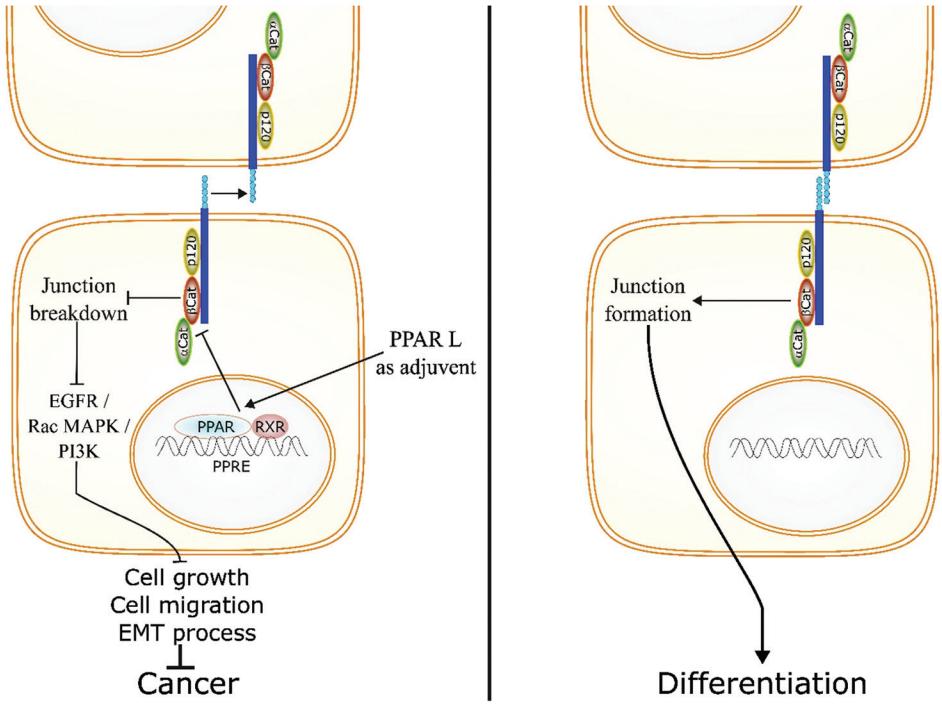


Figure 3. Effect of peroxisome proliferator-activated receptor (PPAR) agonists as an adjuvant on cell migration and invasion of cancer cells. PPAR ligand as an adjuvant regulates the expression of E-cadherin and effects the EGFR/MAPK/PI3K-AKT pathway. This leads to decreased cell growth, cell migration, and epithelial–mesenchymal transition in cancer cells

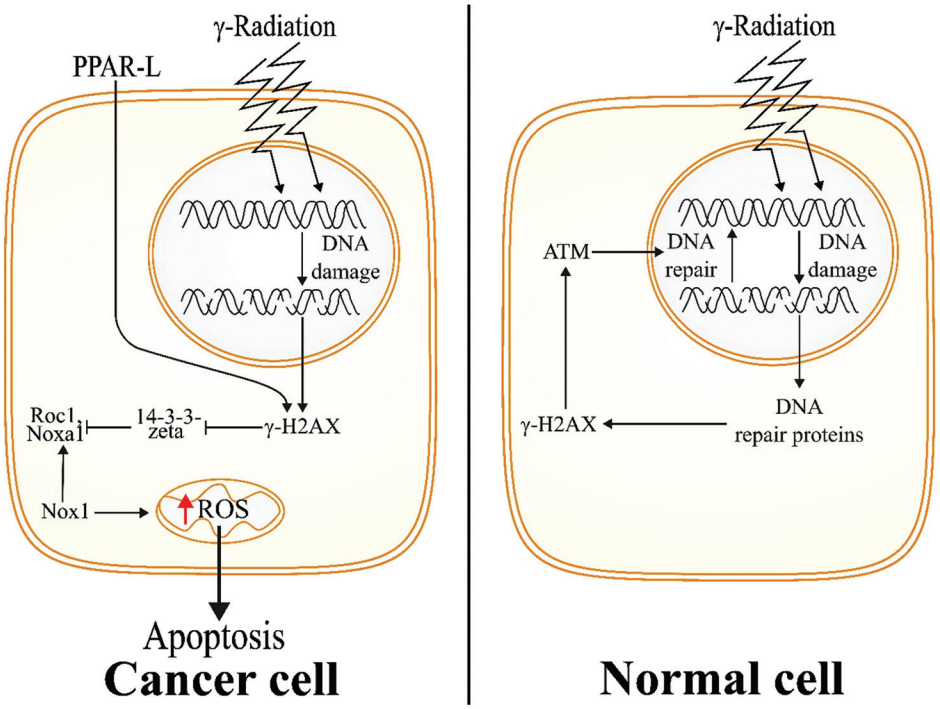


Figure 4. Effect of peroxisome proliferator-activated receptor (PPAR) agonists as adjuvants in inducing oxidative stress in cancer cells. PPAR ligand along with γ-radiation activates the γ-H2AX pathway to generate reactive oxygen species, which mediates the execution of apoptosis in cancer cells

the ROS scavenger N-acetylcysteine inhibited ROS production and the apoptotic cell death induced by this combination treatment.[87] The synergistic treatment of TGZ and heregulin increased the generation of superoxide in mitochondria, which disrupted mitochondrial potential and induced substantial cell death in breast cancer cells.[88]

4.5. PPAR agonists for suppression of multidrug resistance (MDR)

MDR is an acquired resistance that poses a major barrier to the successful treatment of cancer. One of the most common causes of MDR is the overexpression of P-glycoprotein (P-gp), which is encoded by the *MDR1* gene. This gene is a direct target of the Wnt/β-catenin signaling pathway, which plays a key role in cancer progression. The effects of various PPAR agonists on MDR are summarized in Figure 5. Pioglitazone, a PPAR-γ agonist, can modulate P-gp and overcome doxorubicin resistance in a patient-derived orthotopic xenograft model of osteosarcoma.[89] In addition, the PPAR-γ agonist rosiglitazone reverses ABCG2-mediated MDR expression by inhibiting ABCG2 transport activity and facilitating the translocation of ABCG2 from the cell surface to intracellular compartments through the PTEN/PI3K/AKT pathway.[90] It also downregulates the expression of FZD1 and MDR1/P-gp in a dose-dependent manner while significantly decreasing nuclear β-catenin levels and its transcriptional activity in ovarian cancer cells.[91]

Combination therapy using tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) with PPAR ligands may offer a promising experimental approach, as PPAR ligands – particularly d15-PGJ2 – sensitize drug-resistant ovarian cancer cells to TRAIL-induced apoptosis.[92] In general, Wnt/β-catenin signaling is upregulated during inflammatory processes and oxidative stress in many cancers, whereas PPAR-γ is typically downregulated in these contexts. Therefore, PPAR-γ ligands have been shown to prevent cancer development by modulating the Wnt/β-catenin signaling pathway.[93]

4.6. PPAR agonists in clinical trials for cancer therapy

Clinical trials have been organized to evaluate the effects of PPAR agonists in combination with other therapies for the treatment of cancer. Efatutazone, also known as RS5444 and CS-7017, belongs to the TZD class of synthetic PPAR ligands and is an orally bioavailable, selective, and highly potent agonist of PPAR-γ, more so than second-generation TZDs such as pioglitazone and rosiglitazone.[94] When efatutazone is administered with other cytotoxic medications, its selective activation of the PPAR-γ subtype may be enhanced. Efatutazone

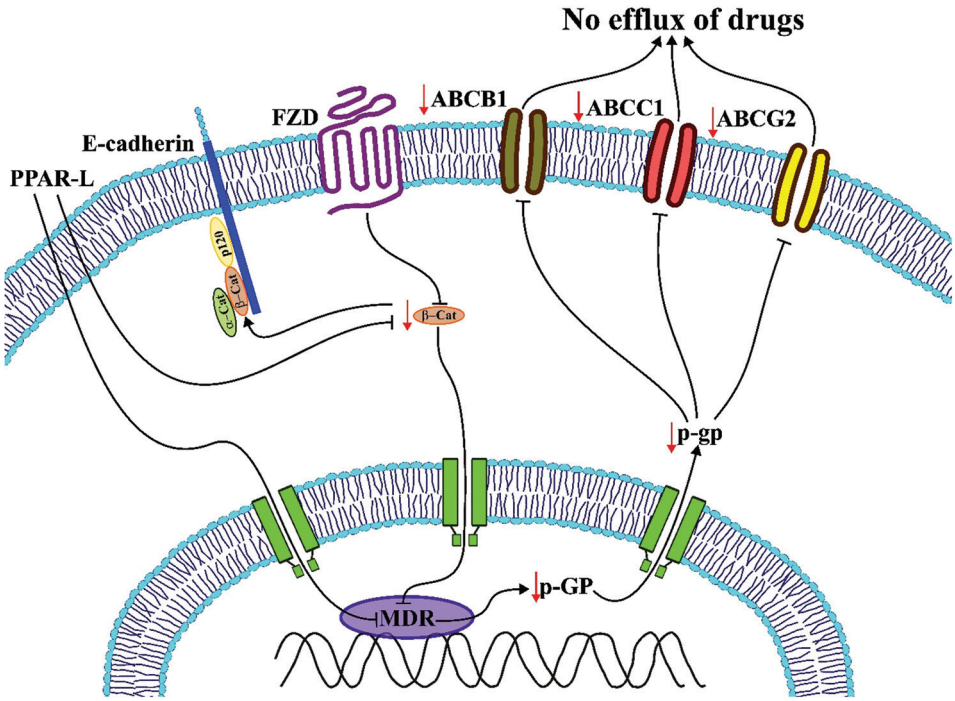


Figure 5. Effect of peroxisome proliferator-activated receptor (PPAR) agonists as an adjuvant in suppressing multidrug resistance in cancer cells. PPAR ligand sensitizes drug-resistant cancer cells by decreasing the expression of P-glycoprotein (P-gp). The reduced P-gp further reduces the expression of ABCB1, ABCC1, and ABCG2 and hence reduces the efflux of drugs from the cancer cells.

is being evaluated alongside paclitaxel in a Phase I trial for the treatment of anaplastic thyroid cancer, based on preclinical research showing that the drug inhibits cell proliferation by upregulating RhoB and p21 while promoting apoptosis.[73,95,96] In patients with advanced solid tumors, efatutazone has demonstrated acceptable safety, tolerability, and disease control when administered orally.[97] In Japanese patients with metastatic colorectal cancer, efatutazone combined with FOLFIRI (5-fluorouracil, levoleucovorin, and irinotecan) showed an acceptable safety profile and evidence of disease stabilization.[98] For patients with high-grade gliomas (glioblastoma or anaplastic glioma), a Phase II trial was initiated to examine the efficacy of continuously administered pioglitazone and rofecoxib in combination with low-dose chemotherapy (capecitabine or temozolomide). The study indicated that this novel regimen is well-tolerated and moderately effective.[99] Patients with advanced vascular malignancies participated in a pilot study assessing the effectiveness of metronomically scheduled, low-dose trofosfamide in combination with pioglitazone and rofecoxib, a selective COX-2 inhibitor, which may offer a new alternative for palliative care.[100] A Phase II trial was initiated to analyze the effectiveness of pioglitazone and rofecoxib combined with sequentially added angiostatic chemotherapy for patients with previously treated metastatic melanoma or soft-tissue sarcoma. This study demonstrated a novel and entirely orally administered chemotherapeutic regimen that is well tolerated in patients with chemotherapeutic malignancies.[101]

4.7. PPAR agonists as a supportive regimen for cancer immunotherapy

Immunotherapy has transformed cancer treatment in recent decades by modifying immune responses against tumor cells to enhance the effectiveness of conventional therapies such as chemotherapy and radiation. Programmed cell death protein 1 (PD-1) is a receptor present on immune cells that plays a crucial role in regulating the immune response. PD-1 restricts the entry and survival of T cells within the tumor microenvironment. However, targeting PD-1 with inhibitors allows T cells to infiltrate the tumor, thereby enhancing the effects of other cancer therapies.[102-104] PPAR agonists are a promising adjunct to immunotherapy, as they can boost the antitumor activity of T cells, even in an immunosuppressive tumor microenvironment. Research has shown that fenofibrate, an agonist of PPAR-α, can work synergistically with PD-1 blockers in cancer immunotherapy by altering the metabolism of effector T cells.[105] PD-1 blockade has also been found to work in conjunction with bezafibrate, an agonist of the PGC-1α/PPAR complex. In this context, fenofibrate increases fatty acid oxidation and mitochondrial respiratory capacity in CD8+ T lymphocytes, which enhances antitumor immunity when combined with PD-1 blockade.[106] TZDs have also been shown to inhibit TGF-β transcription, resulting in a significant reduction of the malignant phenotype in gliomas.[107,108] In addition, inhibiting TGF-β signaling improves survival and restores immune surveillance.[109]

4.8. PPAR agonists for altering tumor microenvironment

The PPAR subtypes may function differently depending on the type of cancer and the stage of the tumor. In addition, the effects of PPAR agonists can vary based on the tumor microenvironment. For instance, the expression of PPAR-γ in breast cancer cells inhibits the NF-κB signaling pathway, reducing the levels of proinflammatory, proangiogenic, and protransfer signaling molecules in the tumor microenvironment, including IL-6, IL-8, CXCR4, MMP-2, and MMP-9. This reduction inhibits tumor cell activity in breast cancer.[110,111] Tumor-associated macrophages (TAMs) are the most prevalent immune cells that promote neovascularization, immunosuppression, and chemoresistance within the tumor microenvironment.[112] The activation of PPAR-γ leads to lipid retention and PGE2 secretion, which causes macrophage polarization toward anti-inflammatory TAMs, converting the M1 phenotype into the M2 phenotype and diminishing the Stat3-mediated proinflammatory response.[113-116] In contrast, PPAR-α in the tumor microenvironment often negatively affects immune cells, leading to immunosuppression or cancer immune escape. Tumor-derived exosomes substantially activate PPAR-α in tumor-infiltrating dendritic cells, increasing intracellular lipid content and mitochondrial respiration, which triggers cytotoxic T-cell activation and immune dysfunction.[117] Cancer stem cells (CSCs) are frequently associated with the development of malignant tumors.[118] Stearoyl-CoA desaturase 1 is an ER enzyme that converts saturated fatty acids into monounsaturated fatty acids.[119] PPAR-α activates the stearoyl-CoA desaturase 1 pathway, which is significantly upregulated to maintain CSC stemness in human liver cancer.[120] Cells in the tumor microenvironment exhibit increased glucose uptake and glycolysis, enhanced glutamine depletion, and the dissolution of carbon and amino nitrogen. This becomes a direct source of energy for the cancer cells.[120-122] PPARs are known regulators of cellular metabolism, particularly carbohydrate and mitochondrial-linked metabolism. Thus, altering PPAR activity through their antagonists can modify the metabolism of cancer cells, which is related to the Warburg effect.[123-125]

4.9. PPAR and its associated genes as biomarkers for evaluating cancer therapy

The expression of PPAR and its associated genes is utilized as a biomarker to evaluate the effects of various cancer therapies. In HCC, molecular subtypes associated with the PPAR signaling pathway were identified through consensus clustering analyses. Based on this study, the authors developed a prognostic prediction model that relies on four gene signatures (*G6PD*, *SLC10A1*, *ABCC1*, and *PKIB*). These gene signatures are closely related to patient survival in HCC.[126] Zhang *et al*. validated a PPAR signaling pathway-based prognostic prediction model for uterine cervical cancer (UCC). They utilized the gene set enrichment analysis algorithm to calculate the PPAR scores of patients with cervical cancer. The study demonstrated that PPAR scores correlate with different sensitivities to immune checkpoint therapy. AC099568.2 was identified as a marker indicating the involvement of the PPAR pathway in patients with UCC.[127] The PPAR signaling pathway is also a potential biomarker for the detection of breast cancer. The study employed various bioinformatics and networking tools to identify 21 differentially expressed genes associated with the PPAR signaling pathway. The results indicated that four key genes – *RXRA*, *LPL*, *FABP4*, and *PPARG* – exhibited a high degree of interaction, suggesting that they may co-function in tumorigenesis by participating in the regulation of the PPAR signaling pathway.[128] Although the studies cited above have identified the use of PPAR-related proteins as biomarkers for cancer treatment, there are currently no studies that have identified biomarkers capable of detecting or explaining the effects of PPAR agonists on cancer progression and the efficacy of anticancer therapies utilizing PPAR agonists. In addition, further research is required to confirm the exact association between PPAR-related genes and cancer progression.

5. Conclusion

Due to its high morbidity and mortality rates, cancer has long been considered one of the most harmful illnesses. At present, combination therapy is widely recommended and practiced as a therapeutic intervention for cancer. One of the drugs suggested for use in combination therapy is PPAR agonists. PPAR agonists have shown significant promise in preventing tumor growth and metastasis in various cancers. Recent studies have elucidated the roles of PPAR ligands as adjuvants, helping to clarify their antitumor effects. PPAR ligands inhibit inflammation and immune responses, suppress cell proliferation, promote cell differentiation and apoptosis, and regulate fat and glucose metabolism. Therefore, it can be concluded that PPAR modulators do not play a primary role in the treatment of tumors but rather an auxiliary one. Despite their encouraging but paradoxical efficacy in reducing cancer metastasis and proliferation, PPAR ligands can increase tumor cell susceptibility to treatments such as radiation and chemotherapy. Among the several known PPAR agonists, only a few have been evaluated for their anticancer activity as adjuvants, whereas the anticancer activity of many other PPAR agonists remains unexplored. In addition, different types of cancer have distinct properties and may respond differently to PPAR agonists. However, such information is still lacking and represents a valuable area for further research.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interest.

Author contributions

Conceptualization: S. R. Kaid Johar
Visualization: S. R. Kaid Johar
Writing–original draft: Binita Patel
Writing–review & editing: S. R. Kaid Johar

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Debela DT, Muzazu SG, Heraro KD, *et al*. New approaches and procedures for cancer treatment: Current perspectives. *SAGE Open Med*. 2021;9:20503121211034366.

   doi: 10.1177/20503121211034366

2. Yang C, Xia BR, Zhang ZC, Zhang YJ, Lou G, Jin WL. Immunotherapy for ovarian cancer: adjuvant, combination, and neoadjuvant. *Front Immunol*. 2020;11:577869.

   doi: 10.3389/fimmu.2020.577869

3. Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: Evolution of management in the era of precision medicine. *CA Cancer J Clin*. 2019;69(4):280-304.

doi: 10.3322/caac.21559

4. Wang ZB, Liu D, Lei G, Liu ZQ, Wu N, Wang J. Ovarian cancer-targeted medication: PARP inhibitors, anti-angiogenic drugs, immunotherapy, and more. *Front Pharmacol*. 2023;14:1222209.

   doi: 10.3389/fphar.2023.1222209

5. Padma VV. An overview of targeted cancer therapy. *Biomedicine* (*Taipei*). 2015;5(4):19.

   doi: 10.7603/s40681-015-0019-4

6. Lim ZF, Ma PC. Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy. *J Hematol Oncol*. 2019;12(1):134.

   doi: 10.1186/s13045-019-0818-2

7. Emran TB, Shahriar A, Mahmud AR, *et al*. Multidrug resistance in cancer: Understanding molecular mechanisms, immunoprevention and therapeutic approaches. *Front Oncol*. 2022;12:891652.

   doi: 10.3389/fonc.2022.891652

8. Safri F, Nguyen R, Zerehpooshnesfchi S, George J, Qiao L. Heterogeneity of hepatocellular carcinoma: From mechanisms to clinical implications. *Cancer Gene Ther*. 2024;31:1105-1112.

   doi: 10.1038/s41417-024-00764-w

9. Jackson C, Finikarides L, Freeman ALJ. The adverse effects of trastuzumab-containing regimes as a therapy in breast cancer: A piggy-back systematic review and meta-analysis. *PLoS One*. 2022;17(12):e0275321.

   doi: 10.1371/journal.pone.0275321

10. Shuel SL. Targeted cancer therapies: Clinical pearls for primary care. *Can Fam Physician*. 2022;68(7):515-518.

    doi: 10.46747/cfp.6807515

11. Levinson K, Dorigo O, Rubin K, Moore K. Immunotherapy in gynecologic cancers: What we know now and where we are headed. *Am Soc Clin Oncol Educ Book*. 2019;39:126-140.

    doi: 10.1200/EDBK_237967

12. Lobenwein D, Kocher F, Dobner S, Gollmann-Tepeköylü C, Holfeld J. Cardiotoxic mechanisms of cancer immunotherapy - A systematic review. *Int J Cardiol*. 2021;323:179-187.

    doi: 10.1016/j.ijcard.2020.08.033

13. Palaia I, Tomao F, Sassu CM, Musacchio L, Benedetti Panici P. immunotherapy for ovarian cancer: Recent advances and combination therapeutic approaches. *Onco Targets Ther*. 2020;13:6109-6129.

    doi: 10.2147/OTT.S205950

14. Muthukutty P, Woo HY, Ragothaman M, Yoo SY. Recent advances in cancer immunotherapy delivery modalities. *Pharmaceutics*. 2023;15(2):504.

    doi: 10.3390/pharmaceutics15020504

15. Li B, Jiang HY, Wang ZH, Ma YC, Bao YN, Jin Y. Effect of fenofibrate on proliferation of SMMC-7721 cells via regulating cell cycle. *Hum Exp Toxicol*. 2021;40(7):1208-1221.

    doi: 10.1177/0960327121991901

16. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics 2009. *CA Cancer J Clin*. 2009;59(4):225-249.

    doi: 10.3322/caac.20006

17. Gunthert AR, Grundker C, Hollmann K, Emons G. Luteinizing hormone-releasing hormone induces JunD-DNA binding and extends cell cycle in human ovarian cancer cells. *Biochem Biophys Res Commun*. 2002;294:11-15.

    doi: 10.1016/S0006-291X(02)00427-8

18. Gründker C, Emons G. The role of gonadotropin-releasing hormone in cancer cell proliferation and metastasis. *Front Endocrinol* (*Lausanne*). 2017;8:187.

    doi: 10.3389/fendo.2017.00187

19. Kara M, Ozcagli E, Fragkiadaki P, *et al*. Determination of DNA damage and telomerase activity in stanozolol-treated rats. *Exp Ther Med*. 2017;13(2):614-618.

    doi: 10.3892/etm.2016.3974

20. George A, McLachlan J, Tunariu N, *et al*. The role of hormonal therapy in patients with relapsed high-grade ovarian carcinoma: A retrospective series of tamoxifen and letrozole. *BMC Cancer*. 2017;17(1):456.

    doi: 10.1186/s12885-017-3440-0

21. Joseph JD, Lu N, Qian J, *et al*. A clinically relevant androgen receptor mutation confers resistance to second-generation antiandrogens enzalutamide and ARN-509. *Cancer Discov*. 2013;3(9):1020-1029.

    doi: 10.1158/2159-8290.CD-13-0226

22. Korpal M, Korn JM, Gao X, *et al*. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). *Cancer Discov*. 2013;3(9):1030-1043.

    doi: 10.1158/2159-8290.CD-13-0142

23. Balbas MD, Evans MJ, Hosfield DJ, *et al*. Overcoming mutation-based resistance to antiandrogens with rational drug design. *Elife*. 2013;2:e00499.

    doi: 10.7554/eLife.00499

24. Feng LX, Li M, Liu YJ, Yang SM, Zhang N. Synergistic enhancement of cancer therapy using a combination of ceramide and docetaxel. *Int J Mol Sci*. 2014;15(3):4201-4220.

    doi: 10.3390/ijms15034201

25. Duarte D, Vale N. Evaluation of synergism in drug combinations and reference models for future orientations in oncology. *Curr Res Pharmacol Drug Discov*. 2022;3:100110.

doi: 10.1016/j.crphar.2022.100110

26. Rathaur P, Soni MN, Gelat B, Rawal R, Pandya HA, Johar K. Network pharmacology-based evaluation of natural compounds with paclitaxel for the treatment of metastatic breast cancer. *Toxicol Appl Pharmacol.* 2021;423:115576.

doi: 10.1016/j.taap.2021.115576

27. Rodrigues R, Duarte D, Vale N. Drug repurposing in cancer therapy: Influence of patient's genetic background in breast cancer treatment. *Int J Mol Sci*. 2022;23(8):4280.

doi: 10.3390/ijms23084280

28. Jourdan JP, Bureau R, Rochais C, Dallemagne P. Drug repositioning: A brief overview. *J Pharm Pharmacol.* 2020;72(9):1145-1151.

doi: 10.1111/jphp.13273

29. Oprea TI, Mestres J. Drug repurposing: Far beyond new targets for old drugs. *AAPS J*. 2012;14(4):759-763.

doi: 10.1208/s12248-012-9390-1

30. Patel B, Gelat B, Soni M, Rathaur P, Kaid Johar SR. Bioinformatics perspective of drug repurposing. *Curr Bioinform.* 2024;19(4):295-315.

doi: 10.2174/0115748936264692230921071504

31. Kulkarni VS, Alagarsamy V, Solomon VR, Jose PA, Murugesan S. Drug repurposing: An effective tool in modern drug discovery. *Russ J Bioorg Chem*. 2023;49(2):157-166.

doi: 10.1134/S1068162023020139

32. Botta M, Audano M, Sahebkar A, Sirtori CR, Mitro N, Ruscica M. PPAR agonists and metabolic syndrome: An established role? *Int J Mol Sci.* 2018;19(4):1197.

doi: 10.3390/ijms19041197

33. Mirza AZ, Althagafi II, Shamshad H. Role of PPAR receptor in different diseases and their ligands: Physiological importance and clinical implications. *Eur J Med* Chem. 2019;166:502-513.

doi: 10.1016/j.ejmech.2019.01.067

34. van Raalte DH, Li M, Pritchard PH, Wasan KM. Peroxisome proliferator-activated receptor (PPAR)-α: A pharmacological target with a promising future. *Pharm Res*. 2004;21:1531-1538.

doi: 10.1023/b: pham.0000041444.06122.8d

35. Corrales P, Vidal-Puig A, Medina-Gómez G. PPARs and metabolic disorders associated with challenged adipose tissue plasticity. *Int J Mol Sci.* 2018;19(7):2124.

doi: 10.3390/ijms19072124

36. Gross B, Pawlak M, Lefebvre P, Staels B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. *Nat Rev Endocrinol*. 2017;13(1):36-49.

doi: 10.1038/nrendo.2016.135.

37. Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. *J Adv Pharm Technol Res.* 2011;2(4):236-240.

doi: 10.4103/2231-4040.90879

38. Tan Y, Wang M, Yang K, Chi T, Liao Z, Wei P. PPAR-α modulators as current and potential cancer treatments. *Front Oncol*. 2021;11:599995.

doi: 10.3389/fonc.2021.599995

39. Chi T, Wang M, Wang X, *et al*. PPAR-γ modulators as current and potential cancer treatments. *Front Oncol.* 2021;11:737776.

doi: 10.3389/fonc.2021.737776

40. Cheng HS, Tan WR, Low ZS, Marvalim C, Lee JYH, Tan NS. Exploration and development of PPAR modulators in health and disease: An update of clinical evidence. *Int J Mol Sci*. 2019;20(20):5055.

doi: 10.3390/ijms20205055

41. Kim SY, Kim MS, Lee MK, *et al*. PPAR-γ induces growth inhibition and apoptosis through upregulation of insulin-like growth factor-binding protein-3 in gastric cancer cells. *Braz J Med Biol Res.* 2015;48(3):226-233.

doi: 10.1590/1414-431X20144212

42. Skelhorne-Gross G, Nicol CJB. The key to unlocking the chemotherapeutic potential of PPAR-γ ligands: Having the right combination. *PPAR Res*. 2012;2012:946943.

doi: 10.1155/2012/946943

43. Panigrahy D, Kaipainen A, Huang S, *et al*. PPARα agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition. *Proc Natl Acad Sci*. 2008;105(3):985-990.

doi: 10.1073/pnas.0711281105

44. Rigano D, Sirignano C, Taglialatela-Scafati O. The potential of natural products for targeting PPARα. *Acta Pharm Sinica B*. 2017;7(4):427-438.

doi: 10.1016/j.apsb.2017.05.005

45. Chiarelli F, Marzio DD. Peroxisome proliferator-activated receptor-γ agonists and diabetes: Current evidence and future perspectives. *Vasc Health Risk Manag.* 2008;4(2):297-304.

doi: 10.2147/vhrm.s993

46. Ngoc LP, Man HY, Besselink H, Cam HD, Brouwer A, van der Burg B. Identification of PPAR-activating compounds in herbal and edible plants and fungi from Vietnam. *Ind Crops Prod*. 2019;129:195-200.

doi: 10.1016/j.indcrop.2018.12.003

47. Korbecki J, Bobiński R, Dutka M. Self-regulation of the inflammatory response by peroxisome proliferator-activated receptors. *Inflamm Res*. 2019;68:443-458.

doi: 10.1007/s00011-019-01231-1

48. Wu L, Guo C, Wu J. Therapeutic potential of PPARγ natural agonists in liver diseases. *J Cell Mol Med*. 2020;24(5):2736-2748.

doi: 10.1111/jcmm.15028

49. Park KS, Choi SH, Chung SS. Re-highlighting the action of PPARγ in treating metabolic diseases [version 1; referees: 2 approved]. *F1000Res*. 2018;7:1127.

doi: 10.12688/f1000research.14136.1

50. Wang L, Waltenberger B, Pferschy-Wenzig EM, *et al*. Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARγ): A review. *Biochem Pharmacol*. 2014;92(1):73-89.

doi: 10.1016/j.bcp.2014.07.018

51. Lebovitz HE. Thiazolidinediones: The forgotten diabetes medications. *Curr Diab Rep*. 2019;19(12):151.

doi: 10.1007/s11892-019-1270-y

52. Krishnappa M, Patil K, Sharma S, *et al. Effectiveness of The PPAR Agonist Saroglitazar in Nonalcoholic Steatohepatitis: Positive Data from Preclinical and Clinical Studies*. Preprint (Version 1), Research Square; 2020.

doi: 10.21203/rs.3.rs-123364/v1

53. Harrity T, Farrelly D, Tieman A, *et al*. Muraglitazar, a novel dual (α/γ) peroxisome proliferator–activated receptor activator, improves diabetes and other metabolic abnormalities and preserves β-cell function in db/db mice. *Diabetes*. 2006;55(1):240-248.

doi: 10.1111/jcmm.15028

54. Fagerberg B, Edwards S, Halmos T, *et al*. Tesaglitazar, a novel dual peroxisome proliferator-activated receptor α/γ agonist, dose-dependently improves the metabolic abnormalities associated with insulin resistance in a non-diabetic population. *Diabetologia*. 2005;48:1716-1725.

doi: 10.1007/s00125-005-1846-8

55. Augimeri G, Giordano C, Gelsomino L, *et al*. The role of PPAR-γ ligands in breast cancer: From basic research to clinical studies. *Cancers* (*Basel*). 2020;12(9):2623.

doi: 10.3390/cancers12092623

56. Kim TW, Hong DW, Hong SH. CB13, a novel PPARγ ligand, overcomes radio-resistance via ROS generation and ER stress in human non-small cell lung cancer. *Cell Death Dis*. 2020;11(10):848.

doi: 10.1038/s41419-020-03065-w

57. Youssef J, Badr M. Peroxisome proliferator-activated receptors and cancer: Challenges and opportunities. *Br J Pharmacol*. 2011;164(1):68-82.

doi: 10.1111/j.1476-5381.2011.01383.x

58. Nguyen M, Shing Y, Folkman J. Quantitation of angiogenesis and antiangiogenesis in the chick embryo chorioallantoic membrane. *Microvasc Res*. 1994;47(1):31-40.

doi: 10.1006/mvre.1994.1003

59. Aviel-Ronen S, Blackhall FH, Shepherd FA, Tsao MS. K-ras mutations in non-small-cell lung carcinoma: A review. *Clin Lung Cancer*. 2006;8(1):30-38.

doi: 10.3816/CLC.2006.n.030

60. Girnun GD, Chen L, Silvaggi J, *et al*. Regression of drug-resistant lung cancer by the combination of rosiglitazone and carboplatin. *Clin Cancer Res*. 2008;14(20):6478-6486.

doi: 10.1158/1078-0432.CCR-08-1128

61. Xu YJ, Zheng Z, Cao C, Li J, Liu Y. Bioanalytical insights into the association between eicosanoids and pathogenesis of hepatocellular carcinoma. *Cancer Metastasis Rev*. 2018;37:269-277.

doi: 10.1007/s10555-018-9747-8

62. Panigrahy D, Kaipainen A, Greene ER, Huang S. Cytochrome P450-derived eicosanoids: the neglected pathway in cancer. *Cancer Metastasis Rev*. 2010;29:723-735.

doi: 10.1007/s10555-010-9264-x

63. Wu L, Wang W, Dai M, Li H, Chen C, Wang D. PPAR-α ligand, AVE8134, and cyclooxygenase inhibitor therapy synergistically suppress lung cancer growth and metastasis. *BMC Cancer*. 2019;19(1):1166.

doi: 10.1186/s12885-019-6379-5

64. Mustafa A, Kruger WD. Suppression of tumor formation by a cyclooxygenase-2 inhibitor and a peroxisome proliferator-activated receptor gamma agonist in an in vivo mouse model of spontaneous breast cancer. *Clin Cancer Res*. 2008;14(15):4935-4942.

doi: 10.1158/1078-0432.CCR-08-0958

65. Malakouti P, Mohammadi M, Boshagh MA, Amini A, Rezaee MA, Rahmani MR. Combined effects of pioglitazone and doxorubicin on migration and invasion of MDA-MB-231 breast cancer cells. *J Egypt Natl Canc Inst*. 2022;34(1):13.

doi: 10.1186/s43046-022-00110-x

66. Pfeffer CM, Singh ATK. Apoptosis: A target for anticancer therapy. *Int J Mol Sci*. 2018;19(2):448.

doi: 10.3390/ijms19020448

67. Elstner E, Müller C, Koshizuka K, *et al*. Ligands for peroxisome proliferator-activated receptorgamma and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells *in vitro* and in BNX mice. *Proc Natl Acad Sci U S A*. 1998;95(15):8806-8811.

doi: 10.1073/pnas.95.15.8806

68. Ramos-Nino ME, Littenberg B. A novel combination: ranpirnase and rosiglitazone induce a synergistic apoptotic effect by down-regulating Fra-1 and Survivin in cancer cells.

Mol Cancer Ther. 2008;7(7):1871-1879.

doi: 10.1158/1535-7163.MCT-08-0308

69. Miao R, Xu T, Liu L, *et al*. Rosiglitazone and retinoic acid inhibit proliferation and induce apoptosis in the HCT-15 human colorectal cancer cell line. *Exp Ther Med*. 2011;2(3):413-417.

doi: 10.3892/etm.2011.227

70. Cao LQ, Wang XL, Wang Q, *et al*. Rosiglitazone sensitizes hepatocellular carcinoma cell lines to 5-fluorouracil antitumor activity through activation of the PPARgamma signaling pathway. *Acta Pharmacol Sin*. 2009;30(9):1316-1322.

doi: 10.1038/aps.2009.119

71. Saidi SA, Holland CM, Charnock-Jones DS, Smith SK. *In vitro* and *in vivo* effects of the PPAR-alpha agonists fenofibrate and retinoic acid in endometrial cancer. *Mol Cancer*. 2006;5:13.

doi: 10.1186/1476-4598-5-13

72. Hamaguchi N, Hamada H, Miyoshi S, *et al*. *In vitro* and *in vivo* therapeutic efficacy of the PPAR-γ agonist troglitazone in combination with cisplatin against malignant pleural mesothelioma cell growth. *Cancer Sci*. 2010;101(9):1955-1964.

doi: 10.1111/j.1349-7006.2010.01632.x

73. Copland JA, Marlow LA, Kurakata S, *et al*. Novel high-affinity PPARgamma agonist alone and in combination with paclitaxel inhibits human anaplastic thyroid carcinoma tumor growth via p21WAF1/CIP1. *Oncogene*. 2006;25(16):2304-2317.

doi: 10.1038/sj.onc.1209267

74. Alqahtani QH, Alkharashi LA, Alajami H, Alkharashi I, Alkharashi L, Alhinti SN. Pioglitazone enhances cisplatin's impact on triple-negative breast cancer: Role of PPAR-γ in cell apoptosis. *Saudi Pharm J*. 2024;32(5):102059.

doi: 10.1016/j.jsps.2024.102059

75. Pouya FD, Salehi R, Rasmi Y, Kheradmand F, Fathi-Azarbayjani A. Combination chemotherapy against colorectal cancer cells: Co-delivery of capecitabine and pioglitazone hydrochloride by polycaprolactone-polyethylene glycol carriers. *Life Sci*. 2023;332:122083.

doi: 10.1016/j.lfs.2023.122083

76. Novikov NM, Zolotaryova SY, Gautreau AM, Denisov EV. Mutational drivers of cancer cell migration and invasion. *Br J Cancer*. 2021;124(1):102-114.

doi: 10.1038/s41416-020-01149-0

77. Wang Q, Peng H, Qi X, Wu M, Zhao X. Targeted therapies in gynecological cancers: A comprehensive review of clinical evidence. *Signal Transduct Target Ther*. 2020;5(1):137.

doi: 10.1038/s41392-020-0199-6

78. Lyon CM, Klinge DM, Do KC, *et al*. Rosiglitazone prevents the progression of preinvasive lung cancer in a murine model. *Carcinogenesis*. 2009;30(12):2095-2099.

doi: 10.1093/carcin/bgp260

79. Annicotte JS, Iankova I, Miard S, *et al*. Peroxisome proliferator-activated receptor gamma regulates E-cadherin expression and inhibits growth and invasion of prostate cancer. *Mol Cell Biol*. 2006;26(20):7561-7574.

doi: 10.1128/MCB.00605-06

80. Huang G, Yin L, Lan J, *et al*. Synergy between peroxisome proliferator-activated receptor γ agonist and radiotherapy in cancer. *Cancer Sci*. 2018;109(7):2243-2255.

doi: 10.1111/cas.13650

81. Chen X, Duan N, Zhang C, Zhang W. Survivin and tumorigenesis: Molecular mechanisms and therapeutic strategies. *J Cancer*. 2016;7(3):314.

doi: 10.7150/jca.13332

82. Bie Q, Dong H, Jin C, Zhang H, Zhang B. 15d-PGJ2 is a new hope for controlling tumor growth. *Am J Transl Res*. 2018;10(3):648-658.

83. Wang Y, Tan H, Xu D, *et al*. The combinatory effects of PPAR-γ agonist and survivin inhibition on the cancer stem-like phenotype and cell proliferation in bladder cancer cells. *Int J Mol Med*. 2014;34(1):262-268.

doi: 10.3892/ijmm.2014.1774

84. Nogueira V, Hay N. Molecular pathways: Reactive oxygen species homeostasis in cancer cells and implications for cancer therapy. *Clin Cancer Res*. 2013;19(16):4309-4314.

doi: 10.1158/1078-0432.CCR-12-1424

85. Arfin S, Jha NK, Jha SK, *et al*. Oxidative stress in cancer cell metabolism. *Antioxidants* (*Basel*). 2021;10(5):642.

doi: 10.3390/antiox10050642

86. Knopfová L, Smarda J. The use of Cox-2 and PPAR-γ signaling in anti-cancer therapies. *Exp Ther Med*. 2010;1(2):257-264.

doi: 10.3892/etm_00000040

87. Han EJ, Im CN, Park SH, Moon EY, Hong SH. Combined treatment with peroxisome proliferator-activated receptor (PPAR) gamma ligands and gamma radiation induces apoptosis by PPAR-γ-independent up-regulation of reactive oxygen species-induced deoxyribonucleic acid damage signals in non-small cell lung cancer cells. *Int J Radiat Oncol Biol Phys*. 2013;85(5):e239-e248.

doi: 10.1016/j.ijrobp.2012.11.040

88. Park BH, Lee SB, Stolz DB, Lee YJ, Lee BC. Synergistic interactions between heregulin and peroxisome proliferator-activated receptor-gamma (PPARgamma) agonist in breast cancer cells. *J Biol Chem*. 2011;286(22):20087-20099.

doi: 10.1074/jbc.M110.191718

89. Higuchi T, Sugisawa N, Miyake K, *et al*. Pioglitazone, an

agonist of PPAR-γ, reverses doxorubicin-resistance in an osteosarcoma patient-derived orthotopic xenograft model by downregulating P-glycoprotein expression. *Biomed Pharmacother*. 2019;118:109356.

doi: 10.1016/j.biopha.2019.109356

90. To KKW, Tomlinson B. Targeting the ABCG2-overexpressing multidrug resistant (MDR) cancer cells by PPAR-γ agonists. *Br J Pharmacol*. 2013;170(5):1137-1151.

doi: 10.1111/bph.12367

91. Zhang H, Jing X, Wu X, *et al*. Suppression of multidrug resistance by rosiglitazone treatment in human ovarian cancer cells through downregulation of FZD1 and MDR1 genes. *Anticancer Drugs*. 2015;26(7):706-715.

doi: 10.1097/CAD.0000000000000236

92. Bräutigam K, Biernath-Wüpping J, Bauerschlag DO, *et al*. Combined treatment with TRAIL and PPAR-γ ligands overcomes chemoresistance of ovarian cancer cell lines. *J Cancer Res Clin Oncol*. 2011;137(5):875-886.

doi: 10.1007/s00432-010-0952-2

93. Vallée A, Lecarpentier Y, Vallée JN. Targeting the canonical WNT/β-catenin pathway in cancer treatment using non-steroidal anti-inflammatory drugs. *Cells*. 2019;8(7):726.

doi: 10.3390/cells8070726

94. Chen L, Bush CR, Necela BM, *et al*. RS5444, a novel PPARγ agonist, regulates aspects of the differentiated phenotype in nontransformed intestinal epithelial cells. *Mol Cell Endocrinol*. 2006;251:17-32.

doi: 10.1016/j.mce.2006.02.006

95. Smallridge RC, Copland JA, Brose MS, *et al*. Efatutazone, an oral PPAR-γ agonist, in combination with paclitaxel in anaplastic thyroid cancer: Results of a multicenter phase 1 trial. *J Clin Endocrinol Metab*. 2013;98(6):2392-2400.

doi: 10.1210/jc.2013-1106

96. Marlow LA, Reynolds LA, Cleland AS, *et al*. Reactivation of suppressed RhoB is a critical step for the inhibition of anaplastic thyroid cancer growth. *Cancer Res*. 2009;69(4):1536-1544.

doi: 10.1158/0008-5472.CAN-08-3718

97. Pishvaian MJ, Marshall JL, Wagner AJ, *et al*. A phase 1 study of efatutazone, an oral peroxisome proliferator-activated receptor gamma agonist, administered to patients with advanced malignancies. *Cancer*. 2012;118(21):5403-5413.

doi: 10.1002/cncr.27526

98. Komatsu Y, Yoshino T, Yamazaki K, *et al*. Phase 1 study of efatutazone, a novel oral peroxisome proliferator-activated receptor gamma agonist, in combination with FOLFIRI as second-line therapy in patients with metastatic colorectal cancer. *Invest New Drugs*. 2014;32:473-480.

doi: 10.1007/s10637-013-0056-3

99. Hau P, Kunz-Schughart L, Bogdahn U, *et al*. Low-dose chemotherapy in combination with COX-2 inhibitors and PPAR-gamma agonists in recurrent high-grade gliomas-a phase II study. *Oncology*. 2008;73(1-2):21-25.

doi: 10.1159/000120028

100. Vogt T, Hafner C, Bross K, *et al*. Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors. *Cancer*. 2003;98(10):2251-2256.

doi: 10.1002/cncr.11775

101. Reichle A, Bross K, Vogt T, *et al*. Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. *Cancer*. 2004;101(10):2247-2256.

doi: 10.1002/cncr.20574

102. Bahrambeigi S, Molaparast M, Sohrabi F, *et al*. Targeting PPAR ligands as possible approaches for metabolic reprogramming of T cells in cancer immunotherapy. *Immunol Lett*. 2020;220:32-37.

doi: 10.1016/j.imlet.2020.01.006

103. Odorizzi PM, Pauken KE, Paley MA, Sharpe A, Wherry EJ. Genetic absence of PD-1 promotes accumulation of terminally differentiated exhausted CD8+ T cells. *J Exp Med*. 2015;212(7):1125.

doi: 10.1084/jem.20142237

104. Tumeh PC, Harview CL, Yearley JH, *et al*. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515(7528):568-571.

doi: 10.1016/j.ejca.2023.03.040

105. Zhang Y, Kurupati R, Liu L, *et al*. Enhancing CD8+ T cell fatty acid catabolism within a metabolically challenging tumor microenvironment increases the efficacy of melanoma immunotherapy. *Cancer Cell*. 2017;32(3):377-391.

doi: 10.1016/j.ccell.2017.08.004

106. Chowdhury PS, Chamoto K, Kumar A, Honjo T. PPAR-induced fatty acid oxidation in T cells increases the number of tumor-reactive CD8+ T cells and facilitates anti–PD-1 therapy. *Cancer Immunol Res*. 2018;6(11):1375-1387.

doi: 10.1158/2326-6066.CIR-18-0095

107. Han J, Alvarez-Breckenridge CA, Wang QE, Yu J. TGF-β signaling and its targeting for glioma treatment. *Am J Cancer Res*. 2015;5(3):945.

108. Coras R, Holsken A, Seufert S, *et al*. The peroxisome proliferator-activated receptor-γ agonist troglitazone inhibits transforming growth factor-β–mediated glioma cell migration and brain invasion. *Mol Cancer Ther*. 2007;6(6):1745-1754.

doi: 10.1158/1535-7163.MCT-06-0763

109. Tran TT, Uhl M, Ma JY, *et al*. Inhibiting TGF-β signaling restores immune surveillance in the SMA-560 glioma model. *Neuro Oncol*. 2007;9(3):259-270.

doi: 10.1215/15228517-2007-010

110. Papi A, De Carolis S, Bertoni S, *et al*. PPARγ and RXR ligands disrupt the inflammatory cross-talk in the hypoxic breast cancer stem cells niche. *J Cell Physiol*. 2014;229(11):1595-1606.

doi: 10.1002/jcp.24601

111. Rovito D, Gionfriddo G, Barone I, *et al*. Ligand-activated PPARγ downregulates CXCR4 gene expression through a novel identified PPAR response element and inhibits breast cancer progression. *Oncotarget*. 2016;7(40):65109.

doi: 10.18632/oncotarget.11371

112. Wang N, Wang S, Wang X, *et al*. Research trends in pharmacological modulation of tumor-associated macrophages. *Clin Transl Med*. 2021;11(1):e288.

doi: 10.1002/ctm2.288

113. Penas F, Mirkin GA, Vera M, *et al*. Treatment *in vitro* with PPARα and PPARγ ligands drives M1-to-M2 polarization of macrophages from T. cruzi-infected mice. *Biochim Biophys Acta*. 2015;1852(5):893-904.

doi: 10.1016/j.bbadis.2014.12.019

114. Souza-Moreira L, Soares VC, Dias SD, Bozza PT. Adipose-derived mesenchymal stromal cells modulate lipid metabolism and lipid droplet biogenesis via AKT/mTOR–PPARγ signalling in macrophages. *Sci Rep.* 2019;9(1):20304.

doi: 10.1038/s41598-019-56835-8

115. Gionfriddo G, Plastina P, Augimeri G, *et al*. Modulating tumor-associated macrophage polarization by synthetic and natural PPARγ ligands as a potential target in breast cancer. *Cells*. 2020;9(1):174.

doi: 10.3390/cells9010174

116. Christofides A, Konstantinidou E, Jani C, Boussiotis VA. The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. *Metabolism*. 2021;114:154338.

doi: 10.1016/j.metabol.2020.154338

117. Sun J, Yu L, Qu X, Huang T. The role of peroxisome proliferator-activated receptors in the tumor microenvironment, tumor cell metabolism, and anticancer therapy. *Front Pharmacol*. 2023;14:1184794.

doi: 10.3389/fphar.2023.1184794

118. Nayak A, Warrier NM, Kumar P. Cancer stem cells and the tumor microenvironment: Targeting the critical crosstalk through nanocarrier systems. *Stem Cell Rev Rep.* 2022;18(7):2209-2233.

doi: 10.1007/s12015-022-10426-9

119. Min JY, Kim DH. Stearoyl-CoA desaturase 1 as a therapeutic biomarker: Focusing on cancer stem cells. *Int J Mol Sci*. 2023;24(10):8951.

doi: 10.3390/ijms24108951

120. Ma XL, Sun YF, Wang BL, *et al*. Sphere-forming culture enriches liver cancer stem cells and reveals Stearoyl-CoA desaturase 1 as a potential therapeutic target. *BMC Cancer*. 2019;19:1-2.

doi: 10.1186/s12885-019-5963-z

121. Altman BJ, Stine ZE, Dang CV. From Krebs to clinic: Glutamine metabolism to cancer therapy. *Nat Rev Cancer*. 2016;16(10):619-634.

doi: 10.1038/nrc.2016.114

122. Hay N. Reprogramming glucose metabolism in cancer: Can it be exploited for cancer therapy? *Nat Rev Cancer*. 2016;16(10):635-649.

doi: 10.1038/nrc.2016.77

123. Luo X, Cheng C, Tan Z, *et al*. Emerging roles of lipid metabolism in cancer metastasis. *Mol Cancer*. 2017;16(1):76.

doi: 10.1186/s12943-017-0646-3

124. Vamecq J, Colet JM, Vanden Eynde JJ, Briand G, Porchet N, Rocchi S. PPARs: interference with Warburg' effect and clinical anticancer trials. *PPAR Res*. 2012;2012(1):304760.

doi: 10.1155/2012/304760

125. Antonosante A, d'Angelo M, Castelli V, *et al*. The involvement of PPARs in the peculiar energetic metabolism of tumor cells. *Int J Mol Sci*. 2018;19(7):1907.

doi: 10.3390/ijms19071907

126. Shi Q, Zeng Y, Xue C, Chu Q, Yuan X, Li L. Development of a promising PPAR signaling pathway-related prognostic prediction model for hepatocellular carcinoma. *Sci Rep.* 2024 Feb 28;14(1):4926.

doi: 10.1038/s41598-024-55086-6

127. Zhang Y, Li X, Zhang J, *et al*. Development and validation of the promising PPAR signaling pathway-based prognostic prediction model in uterine cervical cancer. *PPAR Res*. 2023;2023(1):4962460.

doi: 10.1155/2023/4962460

128. Wang H, Yang Y, Luo Q, *et al*. The PPAR signaling pathway as a potential biomarker for the diagnosis of breast cancer. *Int J Clin Exp Med*. 2019;12(6):7327-7336.