

Review

PPAR γ Modulators in Lung Cancer: Molecular Mechanisms, Clinical Prospects, and Challenges

Jiyun Zhang ^{1,2,3}, Miru Tang ^{2,*} and Jinsai Shang ^{1,2,*} 

¹ School of Basic Medical Sciences, Guangzhou Laboratory, Guangzhou Medical University, Guangzhou 511436, China; zhang_jiyun@gzlab.ac.cn

² Guangzhou National Laboratory, Guangzhou 510005, China

³ School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

* Correspondence: tang_miru@gzlab.ac.cn (M.T.); shang_jinsai@gzlab.ac.cn (J.S.)

Abstract: Lung cancer is one of the most lethal malignancies worldwide. Peroxisome proliferator-activated receptor gamma (PPAR γ , NR1C3) is a ligand-activated transcriptional factor that governs the expression of genes involved in glucolipid metabolism, energy homeostasis, cell differentiation, and inflammation. Multiple studies have demonstrated that PPAR γ activation exerts anti-tumor effects in lung cancer through regulation of lipid metabolism, induction of apoptosis, and cell cycle arrest, as well as inhibition of invasion and migration. Interestingly, PPAR γ activation may have pro-tumor effects on cells of the tumor microenvironment, especially myeloid cells. Recent clinical data has substantiated the potential of PPAR γ agonists as therapeutic agents for lung cancer. Additionally, PPAR γ agonists also show synergistic effects with traditional chemotherapy and radiotherapy. However, the clinical application of PPAR γ agonists remains limited due to the presence of adverse side effects. Thus, further research and clinical trials are necessary to comprehensively explore the actions of PPAR γ in both tumor and stromal cells and to evaluate the *in vivo* toxicity. This review aims to consolidate the molecular mechanism of PPAR γ modulators and to discuss their clinical prospects and challenges in tackling lung cancer.

Keywords: peroxisome proliferator-activated receptor gamma; lung cancer; agonists; transcriptional activity



Citation: Zhang, J.; Tang, M.; Shang, J. PPAR γ Modulators in Lung Cancer: Molecular Mechanisms, Clinical Prospects, and Challenges.

Biomolecules **2024**, *14*, 190. <https://doi.org/10.3390/biom14020190>

Academic Editors: Roberta Montanari, Davide Capelli and William Cho

Received: 30 December 2023

Revised: 22 January 2024

Accepted: 2 February 2024

Published: 4 February 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related death, with an estimated 2.2 million new incidences and 1.8 million mortalities worldwide in 2020 [1]. It can be broadly categorized into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), comprising ~85% and ~15% of all cases, respectively. The etiological factors of lung cancer are diverse, of which tobacco exposure is the primary risk factor, while environmental exposures such as biomass fuels, industrial carcinogens, and air pollution also strongly contribute to the development of lung cancer [2]. Unfortunately, patients with lung cancer often lack obvious specific symptoms initially and are diagnosed at an advanced stage, which might drastically reduce the 5-year survival rate from 90% (stage IA) to 10% (stage IV) [3]. Currently, the therapeutic options for lung cancer mainly include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Although multiple treatment options are available, therapeutic resistance remains a major obstacle for patients to gain continuous clinical benefits [4]. Therefore, there is an urgent need to explore more therapeutic strategies to improve the clinical outcomes of patients with lung cancer.

Peroxisome proliferator-activated receptor gamma (PPAR γ), namely nuclear receptor superfamily 1 group C member 3 (NR1C3), serves as a ligand-activated transcription factor that controls the expression of genes related to lipid and glucose metabolism, energy homeostasis, cell differentiation, and inflammation [5]. Dysregulation of PPAR γ target gene

profiles is closely linked to tumorigenesis, as underscored by the loss of CD36 resulting from repression of the PPAR γ transcriptional program in breast cancer progression [6–8]. Furthermore, a growing body of evidence indicates that PPAR γ activation prevents cancer in tissues such as the colon, breasts, and lungs [9]. PPAR γ agonists have been demonstrated to exert anti-lung cancer effects by promoting cell differentiation, inhibiting cell proliferation, and inducing cell death [10,11]. Thus, PPAR γ holds great potential as a therapeutic target for tackling lung cancer. In this review, we summarize the molecular mechanism underlying the action of PPAR γ agonists and highlight the role of PPAR γ activation in the complex regulatory network of lung cancer, aiming to provide a reference for developing novel therapeutic strategies for lung cancer.

2. Structure of PPAR γ

The *PPARG* gene gives rise to four transcripts by differential promoter usage and alternative splicing, which results in the production of PPAR γ 1 (encoded by *PPARG1*, *PPARG3*, *PPARG4* mRNAs) and PPAR γ 2 (encoded by *PPARG2* mRNA) isoforms [12–15]. PPAR γ 2 has the same sequence as PPAR γ 1, except for an additional 28 amino acids at its N-terminus [12]. PPAR γ 1 is ubiquitously abundant in many tissues, whereas PPAR γ 2 is preferably expressed in adipocytes.

PPAR γ shares a typical NR domain structure composed of five domains: A/B, C, D, E, and F domain (Figure 1A) [16]. The N-terminal A/B domain is highly variable among the NR family, and harbors a ligand-independent transcriptional activation function region termed AF-1 that regulates PPAR γ activation through interdomain coordination and phosphorylation [17,18]. The C domain, also known as the DNA-binding domain (DBD), is the most conserved part of NRs and consists of two zinc finger motifs with nine cysteines [17]. This domain specifically recognizes and binds to the PPAR response elements (PPRE) on the target gene promoter to initiate transcription after forming a heterodimer with the retinoic X receptor α (RXR α) [19,20]. The poorly conserved D domain serves as a flexible hinge that allows rotation between the DNA-binding and ligand-binding domains, as well as containing a nuclear localization signal [17]. The E domain, also named the ligand binding domain (LBD), is the largest region of PPAR γ and has four main functions, including a second dimerization interface, the ligand binding pocket, a coregulator binding surface, and ligand-dependent activation function referred to as AF-2 [21]. The C-terminal F domain is relatively small, and may contribute to interaction with cofactors [22].

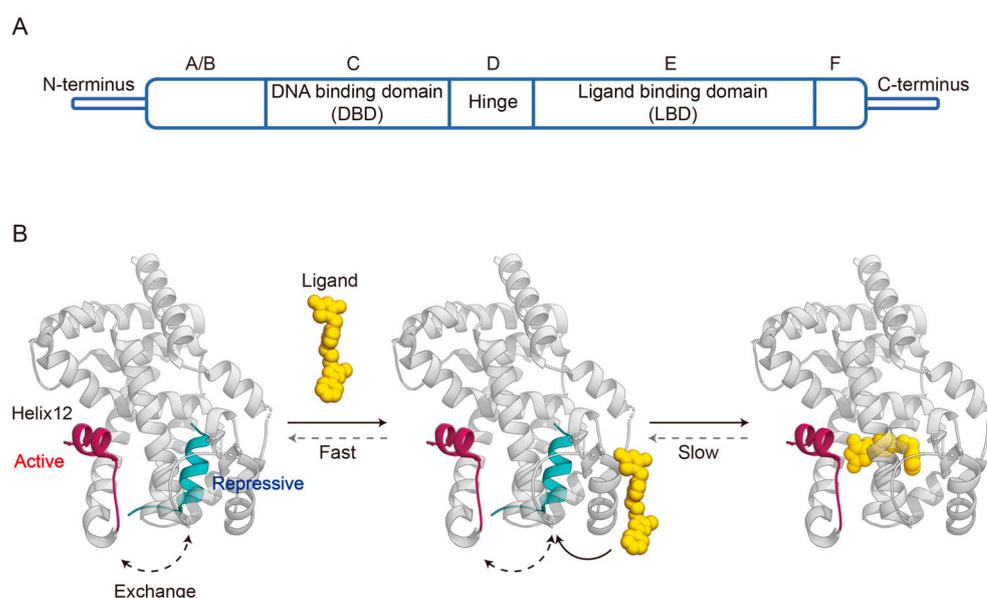


Figure 1. Domain organization of PPAR γ (A) and schematic of agonist binding with PPAR γ LBD (PDB code: 6ONJ and 6DGL) (B).

Among PPAR γ domain structures, the LBD was the first one to be characterized in conformation [23]. The PPAR γ LBD consists of 13 α -helices (termed helix 1–12 and helix 2') arranged in a three-layered sandwich and a small four-stranded β -sheet. The ligand binding pocket is located in the center of the LBD, and has a large Y- or T-shaped cavity with three branches [21]. Branch I is composed of helix3, helix5, helix11, and helix12 in the C-terminal AF-2 region; branch II is positioned around helix2', helix3, helix6, helix7, and the β -sheet region; while branch III is surrounded by the β -sheet, helix2, helix3, and helix5. Adjacent to the ligand-binding pocket, there is an AF-2 coregulator interaction surface formed by the three-dimensional association of helix3, helix4, helix5, and helix12 [23,24].

3. Transcriptional Activities of PPAR γ

PPAR γ regulates gene expression through transactivation and transrepression. In the absence of ligands, PPAR γ -RXR α heterodimer binds to PPREs and subsequently recruits corepressors and associated chromatin-modifying enzymes to silence target gene transcription, a process known as ligand-independent repression [25]. Once the ligand binds to PPAR γ , the PPAR γ -RXR α heterodimer undergoes a conformational change that releases corepressors in exchange for coactivators, resulting in the transcription of target genes. Furthermore, PPAR γ can also negatively regulate gene expression in a ligand-dependent manner by antagonizing other transcription factors, such as nuclear factor- κ B and activator protein-1 [26].

4. Ligands of PPAR γ

The majority of the molecular functions of PPAR γ are regulated by its ligand molecules that can be grouped as natural and synthetic ligands (Table 1). The natural ligands, also termed endogenous agonists, can be further divided into four subgroups, namely the eicosanoid prostaglandin-A1 and the cyclopentenone prostaglandin 15-deoxy-D12,14-prostaglandin J2, the unsaturated fatty acids, the nitroalkanes, and the oxidized phospholipids [27]. Notably, the natural ligands are not always efficient for PPAR γ activation and target gene transcription [28,29]. Synthetic ligands can be classified as full agonists, partial agonists, antagonists, and inverse agonists. A well-known example of a full agonist is thiazolidinediones (TZDs), which are recognized for their potent insulin-sensitizing effects in type II diabetes mellitus [30]. However, TZDs also cause undesired effects such as weight gain, edema, and heart failure, which has driven the development of safer PPAR γ partial agonists to avoid the toxicity induced by full agonists [31]. Partial agonists, referred to as SPPARMs, retain high affinity to the PPAR γ , but show reduced transcription of given genes [21]. In contrast, antagonists such as GW9662 suppress the transcription of PPAR γ -responsive genes, which is achieved by competitively binding the LBD pocket with agonists [32]. T0070907, an inverse agonist with a similar chemical structure to GW9662, but a different effect on PPAR γ transcriptional regulation, inhibits the transactivation potential of PPAR γ below basal cellular levels by recruiting corepressors [33,34]. Generally, synthetic ligands are thought to regulate the transcription activation of PPAR γ by completely displacing natural/endogenous ligands upon binding to the ligand-binding pocket in a competitive or "one-for-one" manner. Our recent research put forward a cooperative cobinding concept of endogenous and synthetic ligands to synergistically activate PPAR γ , extending the understanding of nuclear receptor ligand exchange models [35].

Table 1. Chemical structure and transactivation of common PPAR γ ligands.

Class	Compound	Structure	Transactivation (EC ₅₀)	Refs.
Natural ligand	15-deoxy-D12,14-prostaglandin J2		0.42 μ M	[36]
	Ciglitazone		3 μ M	[37]
	Troglitazone		0.55 μ M	[37]
Full agonist	Pioglitazone		0.58 μ M	[37]
	Rosiglitazone		43 nM	[37]
	Efatutazone		0.038 nM	[38]
Partial agonist	KR-62980		15 nM	[39]
	Telmisartan		4.3 μ M	[40]
Inverse agonist	T0070907		1.0 nM	[41]
Antagonist	GW9662		3.3 nM	[41]

5. Dynamic Mechanisms of Ligand Binding Agonism

In the absence of ligands, helix 12 acts as a highly flexible switching element in equilibrium between many different conformations, ranging from active to repressive (Figure 1B) [34,42]. Agonists stabilize helix 12 in a conformation that exposes the AF-2 surface for the binding of coregulators that control target genes transcription [43]. Full PPAR γ agonists stabilize an active AF-2 surface conformation via forming a critical hydrogen bond with Y473 residues on helix 12, facilitating the recruitment and binding of

coactivators [44]. Partial agonists generally do not form hydrogen bonds with the key residues of the AF-2 regions, including Y473, but mildly stabilize helix 12 through interactions with other regions of the ligand-binding pocket, resulting in differential coactivator recruitment profiles and weak transcriptional activation compared to full agonists [21,45,46]. In contrast, inverse agonists exert transcriptional repression via stabilizing in a conformation that favors the recruitment of corepressors. However, the structural mechanism underlying the ligand-induced repression state is limited. Brust et al. identified R288 as the critical corepressor-selective inverse agonist (T0070907) switch residue, and found that T0070907-bound PPAR γ exchanges between two long-lived conformations, one similar to the coactivator-bound state and the other similar to the corepressor-bound state [33]. Subsequently, our study further verified the structurally diverse mechanism of the inverse agonist-bound state and revealed the mechanism of action of T0070907 [34]. Briefly, T0070907 can stabilize helix 12 within the orthosteric pocket by pointing the pyridyl group toward the AF-2 surface, thereby increasing corepressor binding affinity.

The preceding section has provided a description of the binding modes demonstrated by various agonists. Subsequently, the dynamic changes in agonist binding with PPAR γ LBD will be outlined below. Prior studies remain controversial as to whether ligand binding proceeds through induced fitting or conformational selection mechanisms. Notably, our recent study supported the existence of the induced fit mechanism involving a two-step process of an initial ligand encounter complex followed by a conformational change (Figure 1B) [47]. In the absence of ligand, helix 12 in apo-PPAR γ LBD exchanges between transcriptionally repressive and a solvent-exposed active conformation through entering and exiting the orthosteric ligand-binding pocket. Agonist binds to the ligand entry site via an initial fast step to form an encounter complex, and this process can occur to either of these conformations. Subsequently, the agonist slowly enters the orthosteric ligand-binding pocket and forms the final ligand-binding pose. In this step, agonist binding to the repressive LBD conformation (helix 12 within the orthosteric pocket) would push helix 12 into an active conformation, while agonist binding to the active LBD conformation (helix 12 outside the orthosteric pocket) would facilitate transition into the final ligand-binding pose.

6. Role of PPAR γ Activation in Lung Cancer

6.1. Regulation of Lipid Metabolism

Metabolic reprogramming is a crucial hallmark of malignancy, allowing tumor cells to meet demands for growth, proliferation, and metastasis, as well as be robust against unfavorable environments [48,49]. Thus, targeting abnormal tumor metabolic activities, including lipid metabolism, is a rapidly emerging direction for anti-cancer therapy [50]. PPAR γ is a central regulator of lipid metabolism. Several studies have shown that PPAR γ upregulates fatty acid synthesis and β -oxidation in lung cancer (Figure 2). For example, Phan et al. found that pioglitazone-mediated PPAR γ activation induced de novo fatty acid synthesis and β -oxidation in lung cancer [51]. Importantly, dramatic lipid synthesis could deplete nicotinamide adenine dinucleotide phosphate (NADPH), a major reducing agent important for cellular anti-oxidation systems, leading to disrupted redox balance which, in turn, suppresses lung cancer. Moreover, Andela et al. reported a shift in cellular energy metabolism towards fatty acid oxidation in the lung alveolar carcinoma cell line via treatment with PPAR γ agonist troglitazone [52].

Aldehyde dehydrogenases (ALDHs) act as an 'aldehyde scavenger' during lipid peroxidation and exhibit high activity in lung cancer [53,54]. Inhibition of ALDHs can expose cancer cells to highly reactive and toxic aldehydes, resulting in cell damage and apoptosis [55]. Notably, PPAR γ has been reported to downregulate certain members of the ALDH family to function as a lung cancer inhibitor. For instance, arachidonic acid-induced PPAR γ activation suppressed the growth of A549 cells through increasing lipid peroxidation and decreasing ALDH3A1 expression [56]. Additionally, TZD-mediated PPAR γ activation inhibited ALDH1A3 expression to exert anti-proliferative functions in H1993 cells [57].

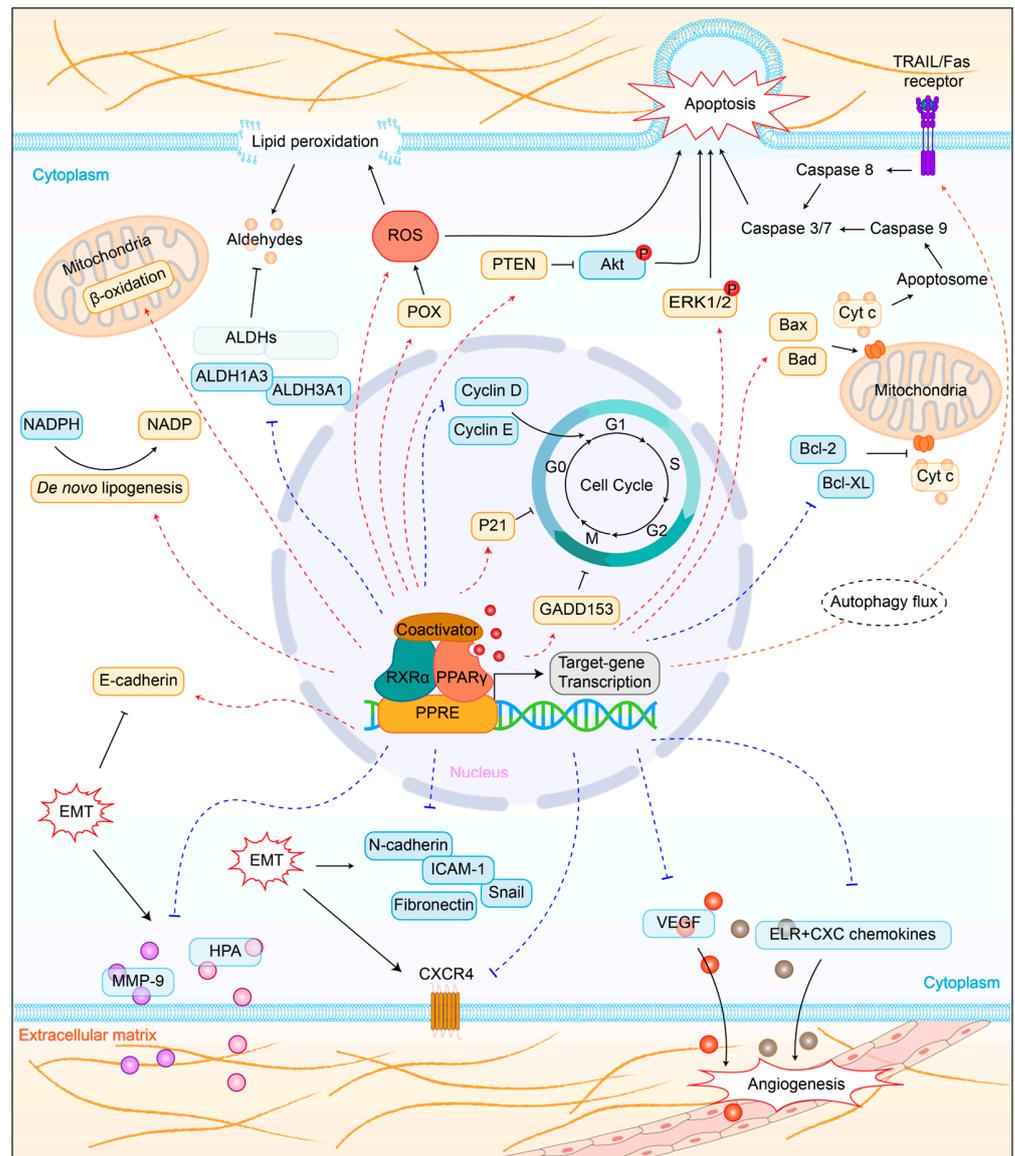


Figure 2. Role of PPAR γ activation in lung cancer cells. PPAR γ , peroxisome proliferator-activated receptor gamma; RXR α , retinoic X receptor α ; PPARE, PPAR response elements; GADD153, DNA-damage inducible gene 153; NADPH, nicotinamide adenine dinucleotide phosphate; ALDH, aldehyde dehydrogenases; ROS, reactive oxygen species; POX, proline oxidase; PTEN, phosphatase and tensin homolog; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; cyt-c, mitochondrial cytochrome c; EMT, epithelial-mesenchymal transition; MMP-9, matrix metalloproteinase 9; HPA, heparanase; ICAM-1, intercellular adhesion molecule-1; VEGF, vascular endothelial growth factor.

6.2. Promotion of Cell Apoptosis

Apoptosis is a homeostatic mechanism to maintain cell populations in normal tissues, whereas tumor cells engage various mechanisms to evade apoptosis for unrestricted proliferation [58,59]. Classical pathways of apoptosis include the intrinsic mitochondrial pathway and the extrinsic pathway that induces via the activation of death receptors on the cell surface, both of which result in the activation of cysteine aspartyl-specific proteases (also known as Caspases) to cleave several proteins leading to cell death [60,61]. PPAR γ promotes apoptosis in lung cancer through dysregulating critical factors in these pathways (Figure 2). Specifically, PPAR γ activation could increase the expression of proapoptotic factors Bax and Bad, decrease the expression of anti-apoptotic factors Bcl-2 and Bcl-XL, enhance caspase3 and caspase9 activity, and trigger mitochondrial cytochrome

c release [62–67]. Furthermore, PPAR γ activation enhanced TRAIL-induced apoptosis in human lung adenocarcinoma cells via autophagy flux [68]. Notably, PPAR γ is also able to regulate the upstream signaling pathways to provoke apoptosis. For instance, KR-62980 or rosiglitazone-mediated PPAR γ activation promoted the generation of reactive oxygen species (ROS) via proline oxidase (POX) induction, leading to apoptotic cell death in NSCLC [69]. Troglitazone-mediated PPAR γ activation induced the phosphorylation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) and subsequently caused apoptosis in NCI-H23 lung cancer cells via a mitochondrial pathway [70]. Another study showed that troglitazone-mediated PPAR γ activation stimulated the expression of DNA-damage inducible gene 153 (GADD153) to trigger growth arrest and endoplasmic reticulum stress-induced apoptosis of NSCLC cells [71]. PPAR γ agonist efatutazone could induce the cell cycle arrest and apoptosis of EGFR-TKI-resistant lung adenocarcinoma cells via PPAR γ /phosphatase and tensin homolog (PTEN)/Akt pathway [72].

6.3. Induction of Cell Cycle Arrest

Cell division is tightly regulated by multiple conserved cell cycle control mechanisms, such as cyclins and cyclin-dependent kinases (CDKs), G1-S transcriptional regulation, DNA damage checkpoint, DNA replication stress checkpoint, and spindle assembly checkpoint [73]. The eukaryotic cell cycle can be divided into G0, G1, S, G2, and M phases. DNA replicates during the S phase and cell separates during the M phase. Several lines of evidence have shown that PPAR γ is involved in cell cycle processes to induce the growth arrest of lung cancer cells (Figure 2). Troglitazone-mediated PPAR γ activation could induce cell cycle arrest in the G0/G1 phase by downregulation of cyclins D and E [74]. The PPAR γ ligands PGJ2, ciglitazone, troglitazone, and GW1929 suppressed human lung carcinoma cell growth by stimulating cyclin-dependent kinase inhibitor p21 expression and reducing cyclin D1 expression [75].

6.4. Inhibition of Tumor Metastasis

Metastasis is the cause of 90% of cancer-related deaths [76]. In the process of metastasis, normal cells transform into carcinogenic cells that proliferate uncontrollably, evade the immune system, resist programmed cell death, stimulate angiogenesis, acquire invasive potential, survive in the bloodstream, and establish cancerous growth in distant organs [77]. Epithelial–mesenchymal transition (EMT), a process through which epithelial cells lose apical–basal polarity, and cell–cell junctions, as well as attain a mesenchymal phenotype with invasive and migratory capabilities, is a critical event in the initiation of metastasis [77,78]. The mechanism of PPAR γ in lung cancer-related EMT is not yet fully understood. Multiple studies have shown that PPAR γ can regulate the expression of EMT-related molecules to exert an inhibitory effect on metastasis (Figure 2). Specifically, PPAR γ activation increased expression of epithelial marker E-cadherin, decreased expression of mesenchymal marker N-cadherin, Snail, and fibronectin, as well as down-regulated expression of matrix metalloproteinase 9 (MMP-9) and heparanase (HPA) [79–83]. Moreover, PPAR γ activation could also suppress the expression of invasion-related proteins, such as intercellular adhesion molecule-1 (ICAM-1) and C-X-C chemokine receptor type 4 (CXCR4), which function as facilitators in EMT [80,81,83].

Angiogenesis is the major route by which cancer cells spread from the primary tumor to other sites [77]. Tumor angiogenesis is regulated by both pro- and anti-angiogenic factors, and an imbalance between the two can lead to malformation of the vasculature with excessive branching, hyperpermeability, and leakage [77,84]. PPAR γ has been reported to be involved in regulating angiogenic factors (Figure 2). For instance, PPAR γ activation could inhibit angiogenesis by blocking the production of ELR + CXC chemokines in NSCLC [85]. Moreover, vascular endothelial growth factor (VEGF) was drastically downregulated through the PPAR γ /NF- κ B signaling pathway in human lung carcinoma 95D cells [64].

6.5. Influence on Tumor Immunity

The role of PPAR γ activation in lung cancer immunity remains a controversial issue, which may correlate with the complexity of the immune microenvironment. Notably, the tumor microenvironment encompasses not only malignant cells, but also stromal cells, vascular endothelial cells, as well as various types of immune cells including tumor-associated macrophages and myeloid-derived suppressor cells (MDSCs) [86]. Interestingly, PPAR γ seems to have opposing effects on cancer progression among different cells, with anti-oncogenic effects on cancer cells but pro-oncogenic effects on cancer-associated immune cells [87,88]. Gou et al. found that PPAR γ inhibits the tumor immune escape by inducing PD-L1 autophagic degradation in NSCLC cells [89]. Interestingly, this process was independent of the transcriptional activity of PPAR γ , but rather formed autophagy receptors through the binding of PPAR γ to microtubule-associated protein 1A/1B-light chain 3 (LC3), leading to degradation of PD-L1 in lysosomes. Nevertheless, Li et al. suggested that PPAR γ activation in myeloid cells promoted lung cancer progression and metastasis [87].

7. Therapeutic Exploration of PPAR γ Agonists

Given the multiple functions of PPAR γ activation in lung cancer, PPAR γ agonists included thiazolidinediones and non-thiazolidinediones have been used as therapeutic agents to tackle lung cancer in preclinical and clinical studies.

7.1. Thiazolidinediones

Thiazolidinediones (TZDs), also known as glitazones, were first reported as insulin sensitizers in the early 1980s and were found to be ligands for PPAR γ until the 1990s [90,91]. Ciglitazone is the prototype of all TZDs, but has never been approved for clinical application due to its weak therapeutic effect on diabetics. Troglitazone was the first TZD introduced in 1997, but was quickly removed from the market in 2000 because of its serious hepatotoxicity [92]. Both rosiglitazone and pioglitazone were second-generation TZDs and were released in 1999. However, rosiglitazone was temporarily withdrawn due to a connection to adverse cardiovascular effects, while pioglitazone was restricted in light of a possible increased risk of bladder cancer [93,94]. Efatutazone is a novel third-generation TZD with highly selective and is currently undergoing clinical evaluation. Although TZDs were developed as an anti-diabetic drug and known to cause side effects, the potent PPAR γ activating effects of TZDs have driven extensive exploration of their potential as anti-cancer therapies for lung cancer. TZDs exert anti-lung cancer functions in PPAR γ -dependent and PPAR γ -independent manners, of which PPAR γ -dependent effects have been summarized in the above section.

Several studies have shown that PPAR γ antagonist or siRNA-mediated silencing of PPAR γ expression failed to abrogate certain anti-tumor effects of TZDs. Han et al. provided evidence that rosiglitazone inhibited NSCLC cell proliferation via down-regulation of the Akt/mTOR/p70S6K signaling pathway [95]. Moreover, Sun et al. found that nicotine-induced NSCLC cell proliferation was partly mediated through α 4 nAChR, which could be blocked by rosiglitazone through activating the ERK/p38 MAPK/p53 signaling pathway in a PPAR γ -independent manner [96]. Zou et al. reported that the PPAR γ ligands troglitazone, ciglitazone, and GW1929 exerted PPAR γ -independent effects to upregulate expression of death receptor 5 and downregulate c-FLIP levels, thereby enhancing TRAIL-induced apoptosis [97]. Similarly, ciglitazone could inhibit NSCLC cell proliferation in a PPAR γ -independent mechanism. Hann et al. found that ciglitazone suppressed the expression of phosphoinositide-dependent protein kinase 1, which was not blocked by GW9662, leading to the inhibition of the growth of NSCLC cells [98].

7.2. Other Agonists

Non-TZD PPAR γ agonists have also been explored the potential of the treatment of lung cancer. 13-S-hydroxyoctadecadienoic acid (13(S)-HODE) and 15(S)-hydroxyicosatetraenoic acid (15(S)-HETE), as endogenous ligands for PPAR γ , were significantly reduced in NNK-

induced lung cancer and could inhibit NSCLC when exogenously supplemented [99,100]. KR-62980, a selective PPAR γ agonist, induced apoptotic cell death in NSCLC mainly through ROS formation via POX induction [39,69]. Telmisartan, a partial agonist with a benzimidazole scaffold, inhibited the expression of ICAM-1 and MMP-9 to exhibit an anti-proliferative effect in A549 cells [80]. Bavachinin, a natural bioactive flavanone from *Psoralea corylifolia*, induced the death of A549 cells through mediating ROS generation [62,101]. All of CB11, CB13, and PPZ023, designed by Kim et al., were suggested to overcome the radioresistance of lung cancer [66,67,102].

7.3. Potential for the Combination of PPAR γ Agonists and Other Therapies

Therapeutic resistance remains a major obstacle to achieving cures in patients with cancer [103]. The discovery of epidermal growth factor receptor (EGFR) gene alterations in lung cancer has fueled the development of targeted therapy using tyrosine kinase inhibitors (TKIs) [104]. EGFR-TKIs act as a first-line treatment for patients with EGFR mutation; however, most patients fail to gain sustainable benefit due to developing resistance [105]. In preclinical studies, PPAR γ has been demonstrated to exert synergistic therapeutic potential with EGFR-TKIs. Lee et al. suggested that rosiglitazone potentiated the antiproliferative effects of gefitinib by increased PTEN expression [106]. Serizawa et al. reported that efatutazone inhibited cell motility by antagonizing the TGF- β /Smad2 pathway and effectively prevented metastasis in NSCLC patients with acquired resistance to EGFR-TKI [107]. Another study completed by Ni et al. found that efatutazone and gefitinib synergistically inhibited the proliferation of EGFR-TKI-resistant lung adenocarcinoma cells via the PPAR γ /PTEN/Akt pathway [72]. To et al. suggested that PPAR γ agonists enhanced the anti-cancer effects of gefitinib through activating the PTEN/PI3K/Akt signaling pathway [108]. Furthermore, PPAR γ can also increase the efficacy of conventional chemotherapy and radiotherapy. Specifically, troglitazone could synergize with cisplatin or paclitaxel to inhibit NSCLC both in vitro and in vivo in a sequence-specific manner, while rosiglitazone combination with carboplatin reduced the growth of KRAS- or EGFR-mutated lung cancers [109,110]. In addition, PPAR γ agonists, including ciglitazone, PPZ023, and CB13, could function as a radiosensitizer in radioresistance-related lung cancer through inducing ROS generation or ER stress [66,67,111].

7.4. Clinical Trials

A retrospective analysis of 87,678 male diabetics demonstrated that TZD users showed a 33% reduction in the risk of lung cancer compared with nonusers [112]. Subsequently, several clinical trials were launched to test the efficacy of PPAR γ agonists in the treatment of lung cancer. Wigle et al. suggested a potential preventive effect for pioglitazone in early stage NSCLC through a clinical trial in patients with stage IA-IIIa NSCLC [113]. Nicotine exposure remains a major risk factor for lung cancer [2]. Keith et al. conducted a phase II trial to investigate pioglitazone as a chemoprevention for lung cancer in high-risk smokers and found that pioglitazone could slightly improve endobronchial dysplasia [114]. Jones et al. verified that pioglitazone could reduce nicotine craving in heavy smokers [115]. This interesting study indicated that pioglitazone might exert its anti-lung cancer effects via multiple mechanisms, rather than only targeting malignant cells. Indeed, pioglitazone-mediated PPAR γ activation has been reported to attenuate the expression of physical and emotional nicotine withdrawal symptoms through mechanisms involving amygdala and hippocampal neurotransmission [116]. Furthermore, a preclinical study identified that glitazone could inhibit nicotine-induced inflammation via downregulation of the Toll-like receptor 4 signaling pathway in alveolar macrophages [117].

8. Conclusions and Prospects

PPAR γ agonists have shown beneficial effects in anti-lung cancer, including disruption of tumor metabolic homeostasis, promotion of cell apoptosis, induction of cell cycle arrest, as well as inhibition of cell invasion and angiogenesis. However, the role of PPAR γ

in tumor immune microenvironment is still controversial. Specifically, PPAR γ induced PD-L1 degradation in malignant cells, which contributes to enhancing the sensitivity to immunotherapy, whereas PPAR γ activation in myeloid cells promotes lung cancer progression and metastasis. Therefore, it is essential to evaluate the systemic effects of PPAR γ agonists in tumor sites. Even so, PPAR γ remains a viable target for the treatment and prevention of lung cancer due to the effectiveness of PPAR γ agonists as monotherapy and in combination with traditional radiotherapy or chemotherapy in preclinical studies. Notably, although TZDs have some side effects, they are the most potent PPAR γ agonists and have been conducted to explore anti-lung cancer effects in clinical settings. While most partial agonists with fewer side effects were initially developed for the treatment of metabolic diseases, their gene expression signatures could also be optimized to provide more anti-tumor benefits in the future. Herein, we summarized the molecular mechanisms of action of agonists and the complex signaling networks resulting from PPAR γ activation, which may contribute to the design of PPAR γ agonists characterized by more efficient, safer, and potent anti-tumor effects in the future.

Author Contributions: J.Z.: Conceptualization, Writing—original draft; M.T.: Conceptualization, Writing—review and editing, Supervision. J.S.: Conceptualization, Writing—review and editing, Supervision, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by grants from the National Natural Science Foundation of China (821704730), the startup and R&D Program of Guangzhou National Laboratory (GZNL2023A02012, YW-YWYM0202, SRPG22-002, SRPG22-003), and the Guangdong Natural Science Foundation (2021QN020451).

Acknowledgments: We thank the joint graduate program between Guangzhou National Laboratory and Sun Yat-Sen University.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ALDH	Aldehyde dehydrogenase
CDK	Cyclin-dependent kinase
CXCR4	C-X-C chemokine receptor type 4
DBD	DNA-binding domain
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
ERK1/2	Extracellular signal-regulated protein kinases 1 and 2
GADD153	DNA-damage inducible gene 153
HPA	Heparanase
ICAM-1	Intercellular adhesion molecule-1
LBD	Ligand binding domain
MDSC	Myeloid-derived suppressor cell
MMP-9	Matrix metalloproteinase 9
NADPH	Nicotinamide adenine dinucleotide phosphate
NR	Nuclear receptor
NR1C3	Nuclear receptor superfamily 1 group C member 3
NSCLC	Non-small cell lung cancer
POX	Proline oxidase
PPAR γ	Peroxisome proliferator-activated receptor gamma
PPRE	PPAR response element
PTEN	Phosphatase and tensin homolog
ROS	Reactive oxygen species
RXR α	Retinoic X receptor α
SCLC	Small cell lung cancer
TKI	Tyrosine kinase inhibitor
TZD	Thiazolidinedione

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA A Cancer J. Clin.* **2021**, *71*, 209–249. [[CrossRef](#)]
2. Leiter, A.; Veluswamy, R.R.; Wisnivesky, J.P. The global burden of lung cancer: Current status and future trends. *Nat. Rev. Clin. Oncol.* **2023**, *20*, 624–639. [[CrossRef](#)] [[PubMed](#)]
3. Ning, J.; Ge, T.; Jiang, M.; Jia, K.; Wang, L.; Li, W.; Chen, B.; Liu, Y.; Wang, H.; Zhao, S.; et al. Early diagnosis of lung cancer: Which is the optimal choice? *Aging* **2021**, *13*, 6214–6227. [[CrossRef](#)]
4. Ashrafi, A.; Akter, Z.; Modareszadeh, P.; Modareszadeh, P.; Berisha, E.; Alemi, P.S.; Chacon Castro, M.D.C.; Deese, A.R.; Zhang, L. Current Landscape of Therapeutic Resistance in Lung Cancer and Promising Strategies to Overcome Resistance. *Cancers* **2022**, *14*, 4562. [[CrossRef](#)] [[PubMed](#)]
5. Ahmadian, M.; Suh, J.M.; Hah, N.; Liddle, C.; Atkins, A.R.; Downes, M.; Evans, R.M. PPAR γ signaling and metabolism: The good, the bad and the future. *Nat. Med.* **2013**, *19*, 557–566. [[CrossRef](#)]
6. Venkatachalam, G.; Kumar, A.P.; Sakharkar, K.R.; Thangavel, S.; Clement, M.V.; Sakharkar, M.K. PPAR γ disease gene network and identification of therapeutic targets for prostate cancer. *J. Drug Target.* **2011**, *19*, 781–796. [[CrossRef](#)]
7. Liu, Q.; Zhang, J.; Guo, C.; Wang, M.; Wang, C.; Yan, Y.; Sun, L.; Wang, D.; Zhang, L.; Yu, H.; et al. Proteogenomic characterization of small cell lung cancer identifies biological insights and subtype-specific therapeutic strategies. *Cell* **2024**, *187*, 184–203.e128. [[CrossRef](#)]
8. Caruso, J.A.; Wang, X.; Murrow, L.M.; Rodriguez, C.I.; Chen-Tanyolac, C.; Vu, L.; Chen, Y.Y.; Gascard, P.; Gartner, Z.J.; Kerlikowske, K.; et al. Loss of PPAR γ activity characterizes early protumorigenic stromal reprogramming and dictates the therapeutic window of opportunity. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2303774120. [[CrossRef](#)] [[PubMed](#)]
9. Peters, J.M.; Shah, Y.M.; Gonzalez, F.J. The role of peroxisome proliferator-activated receptors in carcinogenesis and chemoprevention. *Nat. Rev. Cancer* **2012**, *12*, 181–195. [[CrossRef](#)]
10. Reddy, A.T.; Lakshmi, S.P.; Reddy, R.C. PPAR γ as a Novel Therapeutic Target in Lung Cancer. *PPAR Res.* **2016**, *2016*, 8972570. [[CrossRef](#)]
11. Chi, T.; Wang, M.; Wang, X.; Yang, K.; Xie, F.; Liao, Z.; Wei, P. PPAR- γ Modulators as Current and Potential Cancer Treatments. *Front. Oncol.* **2021**, *11*, 737776. [[CrossRef](#)]
12. Fajas, L.; Auboeuf, D.; Raspé, E.; Schoonjans, K.; Lefebvre, A.M.; Saladin, R.; Najib, J.; Laville, M.; Fruchart, J.C.; Deeb, S.; et al. The organization, promoter analysis, and expression of the human PPAR γ gene. *J. Biol. Chem.* **1997**, *272*, 18779–18789. [[CrossRef](#)]
13. Fajas, L.; Fruchart, J.C.; Auwerx, J. PPAR γ 3 mRNA: A distinct PPAR γ mRNA subtype transcribed from an independent promoter. *FEBS Lett.* **1998**, *438*, 55–60. [[CrossRef](#)]
14. Sundvold, H.; Lien, S. Identification of a novel peroxisome proliferator-activated receptor (PPAR) gamma promoter in man and transactivation by the nuclear receptor ROR α 1. *Biochem. Biophys. Res. Commun.* **2001**, *287*, 383–390. [[CrossRef](#)]
15. Tontonoz, P.; Hu, E.; Graves, R.A.; Budavari, A.I.; Spiegelman, B.M. mPPAR gamma 2: Tissue-specific regulator of an adipocyte enhancer. *Genes Dev.* **1994**, *8*, 1224–1234. [[CrossRef](#)] [[PubMed](#)]
16. Blanquart, C.; Barbier, O.; Fruchart, J.C.; Staels, B.; Glineur, C. Peroxisome proliferator-activated receptors: Regulation of transcriptional activities and roles in inflammation. *J. Steroid Biochem. Mol. Biol.* **2003**, *85*, 267–273. [[CrossRef](#)] [[PubMed](#)]
17. Aranda, A.; Pascual, A. Nuclear hormone receptors and gene expression. *Physiol. Rev.* **2001**, *81*, 1269–1304. [[CrossRef](#)] [[PubMed](#)]
18. Shao, D.; Rangwala, S.M.; Bailey, S.T.; Krakow, S.L.; Reginato, M.J.; Lazar, M.A. Interdomain communication regulating ligand binding by PPAR-gamma. *Nature* **1998**, *396*, 377–380. [[CrossRef](#)] [[PubMed](#)]
19. Guan, Y.; Breyer, M.D. Peroxisome proliferator-activated receptors (PPARs): Novel therapeutic targets in renal disease. *Kidney Int.* **2001**, *60*, 14–30. [[CrossRef](#)] [[PubMed](#)]
20. Chandra, V.; Huang, P.; Hamuro, Y.; Raghuram, S.; Wang, Y.; Burris, T.P.; Rastinejad, F. Structure of the intact PPAR-gamma-RXR-nuclear receptor complex on DNA. *Nature* **2008**, *456*, 350–356. [[CrossRef](#)] [[PubMed](#)]
21. Kroker, A.J.; Bruning, J.B. Review of the Structural and Dynamic Mechanisms of PPAR γ Partial Agonism. *PPAR Res.* **2015**, *2015*, 816856. [[CrossRef](#)]
22. Danielian, P.S.; White, R.; Lees, J.A.; Parker, M.G. Identification of a conserved region required for hormone dependent transcriptional activation by steroid hormone receptors. *EMBO J.* **1992**, *11*, 1025–1033. [[CrossRef](#)]
23. Nolte, R.T.; Wisely, G.B.; Westin, S.; Cobb, J.E.; Lambert, M.H.; Kurokawa, R.; Rosenfeld, M.G.; Willson, T.M.; Glass, C.K.; Milburn, M.V. Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma. *Nature* **1998**, *395*, 137–143. [[CrossRef](#)]
24. Frkic, R.L.; Marshall, A.C.; Blayo, A.L.; Pukala, T.L.; Kamenecka, T.M.; Griffin, P.R.; Bruning, J.B. PPAR γ in Complex with an Antagonist and Inverse Agonist: A Tumble and Trap Mechanism of the Activation Helix. *iScience* **2018**, *5*, 69–79. [[CrossRef](#)] [[PubMed](#)]
25. Hernandez-Quiles, M.; Broekema, M.F.; Kalkhoven, E. PPAR γ in Metabolism, Immunity, and Cancer: Unified and Diverse Mechanisms of Action. *Front. Endocrinol.* **2021**, *12*, 624112. [[CrossRef](#)] [[PubMed](#)]
26. Ricote, M.; Glass, C.K. PPARs and molecular mechanisms of transrepression. *Biochim. Biophys. Acta* **2007**, *1771*, 926–935. [[CrossRef](#)] [[PubMed](#)]

27. Corona, J.C.; Duchen, M.R. PPAR γ as a therapeutic target to rescue mitochondrial function in neurological disease. *Free Radic. Biol. Med.* **2016**, *100*, 153–163. [[CrossRef](#)] [[PubMed](#)]
28. Grygiel-Górniak, B. Peroxisome proliferator-activated receptors and their ligands: Nutritional and clinical implications—A review. *Nutr. J.* **2014**, *13*, 17. [[CrossRef](#)]
29. Bell-Parikh, L.C.; Ide, T.; Lawson, J.A.; McNamara, P.; Reilly, M.; FitzGerald, G.A. Biosynthesis of 15-deoxy-delta12,14-PGJ2 and the ligation of PPARgamma. *J. Clin. Investig.* **2003**, *112*, 945–955. [[CrossRef](#)]
30. Takada, I.; Makishima, M. PPAR γ ligands and their therapeutic applications: A patent review (2008–2014). *Expert Opin. Ther. Pat.* **2015**, *25*, 175–191. [[CrossRef](#)]
31. Ballav, S.; Biswas, B.; Sahu, V.K.; Ranjan, A.; Basu, S. PPAR- γ Partial Agonists in Disease-Fate Decision with Special Reference to Cancer. *Cells* **2022**, *11*, 3215. [[CrossRef](#)]
32. Leesnitzer, L.M.; Parks, D.J.; Bledsoe, R.K.; Cobb, J.E.; Collins, J.L.; Consler, T.G.; Davis, R.G.; Hull-Ryde, E.A.; Lenhard, J.M.; Patel, L.; et al. Functional consequences of cysteine modification in the ligand binding sites of peroxisome proliferator activated receptors by GW9662. *Biochemistry* **2002**, *41*, 6640–6650. [[CrossRef](#)]
33. Brust, R.; Shang, J.; Fuhrmann, J.; Mosure, S.A.; Bass, J.; Cano, A.; Heidari, Z.; Chrisman, I.M.; Nemetcheck, M.D.; Blayo, A.L.; et al. A structural mechanism for directing corepressor-selective inverse agonism of PPAR γ . *Nat. Commun.* **2018**, *9*, 4687. [[CrossRef](#)]
34. Shang, J.; Mosure, S.A.; Zheng, J.; Brust, R.; Bass, J.; Nichols, A.; Solt, L.A.; Griffin, P.R.; Kojetin, D.J. A molecular switch regulating transcriptional repression and activation of PPAR γ . *Nat. Commun.* **2020**, *11*, 956. [[CrossRef](#)]
35. Shang, J.; Brust, R.; Mosure, S.A.; Bass, J.; Munoz-Tello, P.; Lin, H.; Hughes, T.S.; Tang, M.; Ge, Q.; Kamenekca, T.M.; et al. Cooperative cobinding of synthetic and natural ligands to the nuclear receptor PPAR γ . *eLife* **2018**, *7*, e43320. [[CrossRef](#)]
36. Groeger, A.L.; Cipollina, C.; Cole, M.P.; Woodcock, S.R.; Bonacci, G.; Rudolph, T.K.; Rudolph, V.; Freeman, B.A.; Schopfer, F.J. Cyclooxygenase-2 generates anti-inflammatory mediators from omega-3 fatty acids. *Nat. Chem. Biol.* **2010**, *6*, 433–441. [[CrossRef](#)]
37. Menendez-Gutierrez, M.P.; Roszer, T.; Ricote, M. Biology and therapeutic applications of peroxisome proliferator-activated receptors. *Curr. Top. Med. Chem.* **2012**, *12*, 548–584. [[CrossRef](#)]
38. Shinozuka, T.; Tsukada, T.; Fujii, K.; Tokumaru, E.; Shimada, K.; Onishi, Y.; Matsui, Y.; Wakimoto, S.; Kuroha, M.; Ogata, T.; et al. Discovery of DS-6930, a potent selective PPAR γ modulator. Part I: Lead identification. *Bioorg. Med. Chem.* **2018**, *26*, 5079–5098. [[CrossRef](#)]
39. Kim, K.R.; Lee, J.H.; Kim, S.J.; Rhee, S.D.; Jung, W.H.; Yang, S.D.; Kim, S.S.; Ahn, J.H.; Cheon, H.G. KR-62980: A novel peroxisome proliferator-activated receptor gamma agonist with weak adipogenic effects. *Biochem. Pharmacol.* **2006**, *72*, 446–454. [[CrossRef](#)]
40. Schoepf, A.M.; Salcher, S.; Obexer, P.; Gust, R. Identification and development of non-cytotoxic cell death modulators: Impact of sartans and derivatives on PPAR γ activation and on growth of imatinib-resistant chronic myelogenous leukemia cells. *Eur. J. Med. Chem.* **2020**, *195*, 112258. [[CrossRef](#)]
41. Deng, G.; Liu, Z.; Ye, F.; Luo, X.; Zhu, W.; Shen, X.; Liu, H.; Jiang, H. Tryptophan-containing dipeptide derivatives as potent PPARgamma antagonists: Design, synthesis, biological evaluation, and molecular modeling. *Eur. J. Med. Chem.* **2008**, *43*, 2699–2716. [[CrossRef](#)]
42. Kallenberger, B.C.; Love, J.D.; Chatterjee, V.K.; Schwabe, J.W. A dynamic mechanism of nuclear receptor activation and its perturbation in a human disease. *Nat. Struct. Biol.* **2003**, *10*, 136–140. [[CrossRef](#)]
43. Brzozowski, A.M.; Pike, A.C.; Dauter, Z.; Hubbard, R.E.; Bonn, T.; Engström, O.; Ohman, L.; Greene, G.L.; Gustafsson, J.A.; Carlquist, M. Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature* **1997**, *389*, 753–758. [[CrossRef](#)]
44. Johnson, B.A.; Wilson, E.M.; Li, Y.; Moller, D.E.; Smith, R.G.; Zhou, G. Ligand-induced stabilization of PPARgamma monitored by NMR spectroscopy: Implications for nuclear receptor activation. *J. Mol. Biol.* **2000**, *298*, 187–194. [[CrossRef](#)]
45. Bruning, J.B.; Chalmers, M.J.; Prasad, S.; Busby, S.A.; Kamenecka, T.M.; He, Y.; Nettles, K.W.; Griffin, P.R. Partial agonists activate PPARgamma using a helix 12 independent mechanism. *Structure* **2007**, *15*, 1258–1271. [[CrossRef](#)]
46. Hughes, T.S.; Chalmers, M.J.; Novick, S.; Kuruvilla, D.S.; Chang, M.R.; Kamenecka, T.M.; Rance, M.; Johnson, B.A.; Burris, T.P.; Griffin, P.R.; et al. Ligand and receptor dynamics contribute to the mechanism of graded PPAR γ agonism. *Structure* **2012**, *20*, 139–150. [[CrossRef](#)]
47. Shang, J.; Kojetin, D.J. Structural mechanism underlying ligand binding and activation of PPAR γ . *Structure* **2021**, *29*, 940–950.e944. [[CrossRef](#)]
48. Yoshida, G.J. Metabolic reprogramming: The emerging concept and associated therapeutic strategies. *J. Exp. Clin. Cancer Res. CR* **2015**, *34*, 111. [[CrossRef](#)]
49. Faubert, B.; Solmonson, A.; DeBerardinis, R.J. Metabolic reprogramming and cancer progression. *Science* **2020**, *368*, eaaw5473. [[CrossRef](#)]
50. Phan, L.M.; Yeung, S.C.; Lee, M.H. Cancer metabolic reprogramming: Importance, main features, and potentials for precise targeted anti-cancer therapies. *Cancer Biol. Med.* **2014**, *11*, 1–19. [[CrossRef](#)]
51. Phan, A.N.H.; Vo, V.T.A.; Hua, T.N.M.; Kim, M.K.; Jo, S.Y.; Choi, J.W.; Kim, H.W.; Son, J.; Suh, Y.A.; Jeong, Y. PPAR γ sumoylation-mediated lipid accumulation in lung cancer. *Oncotarget* **2017**, *8*, 82491–82505. [[CrossRef](#)] [[PubMed](#)]
52. Andela, V.B.; Altuwajiri, S.; Wood, J.; Rosier, R.N. Inhibition of beta-oxidative respiration is a therapeutic window associated with the cancer chemo-preventive activity of PPARgamma agonists. *FEBS Lett.* **2005**, *579*, 1765–1769. [[CrossRef](#)]
53. Singh, S.; Brocker, C.; Koppaka, V.; Chen, Y.; Jackson, B.C.; Matsumoto, A.; Thompson, D.C.; Vasiliou, V. Aldehyde dehydrogenases in cellular responses to oxidative/electrophilic stress. *Free Radic. Biol. Med.* **2013**, *56*, 89–101. [[CrossRef](#)] [[PubMed](#)]

54. Pors, K.; Moreb, J.S. Aldehyde dehydrogenases in cancer: An opportunity for biomarker and drug development? *Drug Discov. Today* **2014**, *19*, 1953–1963. [[CrossRef](#)] [[PubMed](#)]
55. Dinavahi, S.S.; Bazewicz, C.G.; Gowda, R.; Robertson, G.P. Aldehyde Dehydrogenase Inhibitors for Cancer Therapeutics. *Trends Pharmacol. Sci.* **2019**, *40*, 774–789. [[CrossRef](#)]
56. Muzio, G.; Trombetta, A.; Maggiora, M.; Martinasso, G.; Vasiliou, V.; Lassen, N.; Canuto, R.A. Arachidonic acid suppresses growth of human lung tumor A549 cells through down-regulation of ALDH3A1 expression. *Free. Radic. Biol. Med.* **2006**, *40*, 1929–1938. [[CrossRef](#)] [[PubMed](#)]
57. Hua, T.N.M.; Namkung, J.; Phan, A.N.H.; Vo, V.T.A.; Kim, M.K.; Jeong, Y.; Choi, J.W. PPAR γ -mediated ALDH1A3 suppression exerts anti-proliferative effects in lung cancer by inducing lipid peroxidation. *J. Recept. Signal Transduct. Res.* **2018**, *38*, 191–197. [[CrossRef](#)] [[PubMed](#)]
58. Elmore, S. Apoptosis: A review of programmed cell death. *Toxicol. Pathol.* **2007**, *35*, 495–516. [[CrossRef](#)]
59. Sharma, A.; Boise, L.H.; Shanmugam, M. Cancer Metabolism and the Evasion of Apoptotic Cell Death. *Cancers* **2019**, *11*, 1144. [[CrossRef](#)]
60. Nicholson, D.W.; Thornberry, N.A. Caspases: Killer proteases. *Trends Biochem. Sci.* **1997**, *22*, 299–306. [[CrossRef](#)]
61. Reed, J.C. Apoptosis-targeted therapies for cancer. *Cancer Cell* **2003**, *3*, 17–22. [[CrossRef](#)]
62. Ge, L.N.; Yan, L.; Li, C.; Cheng, K. Bavachinin exhibits antitumor activity against non-small cell lung cancer by targeting PPAR γ . *Mol. Med. Rep.* **2019**, *20*, 2805–2811. [[CrossRef](#)]
63. Li, M.Y.; Hsin, M.K.; Yip, J.; Mok, T.S.; Underwood, M.J.; Chen, G.G. PPAR γ activation extinguishes smoking carcinogen by inhibiting NNK-mediated proliferation. *Am. J. Respir. Cell Mol. Biol.* **2010**, *42*, 113–122. [[CrossRef](#)]
64. Liu, Y.; Tian, Y.; Cai, W.; Guo, Y.; Xue, C.; Wang, J. DHA/EPA-Enriched Phosphatidylcholine Suppresses Tumor Growth and Metastasis via Activating Peroxisome Proliferator-Activated Receptor γ in Lewis Lung Cancer Mice. *J. Agric. Food Chem.* **2021**, *69*, 676–685. [[CrossRef](#)]
65. Yue, H.; Tian, Y.; Zhao, Z.; Bo, Y.; Guo, Y.; Wang, J. Comparative Study of Docosahexaenoic Acid with Different Molecular Forms for Promoting Apoptosis of the 95D Non-Small-Cell Lung Cancer Cells in a PPAR γ -Dependent Manner. *Mar. Drugs* **2022**, *20*, 599. [[CrossRef](#)]
66. Kim, T.W.; Hong, D.W.; Kang, C.M.; Hong, S.H. A novel PPAR γ ligand, PPZ023, overcomes radioresistance via ER stress and cell death in human non-small-cell lung cancer cells. *Exp. Mol. Med.* **2020**, *52*, 1730–1743. [[CrossRef](#)]
67. Kim, T.W.; Hong, D.W.; Hong, S.H. CB13, a novel PPAR γ ligand, overcomes radio-resistance via ROS generation and ER stress in human non-small cell lung cancer. *Cell Death Dis.* **2020**, *11*, 848. [[CrossRef](#)]
68. Nazim, U.M.; Moon, J.H.; Lee, Y.J.; Seol, J.W.; Park, S.Y. PPAR γ activation by troglitazone enhances human lung cancer cells to TRAIL-induced apoptosis via autophagy flux. *Oncotarget* **2017**, *8*, 26819–26831. [[CrossRef](#)]
69. Kim, K.Y.; Ahn, J.H.; Cheon, H.G. Apoptotic action of peroxisome proliferator-activated receptor-gamma activation in human non small-cell lung cancer is mediated via proline oxidase-induced reactive oxygen species formation. *Mol. Pharmacol.* **2007**, *72*, 674–685. [[CrossRef](#)]
70. Li, M.; Lee, T.W.; Yim, A.P.; Mok, T.S.; Chen, G.G. Apoptosis induced by troglitazone is both peroxisome proliferator-activated receptor-gamma- and ERK-dependent in human non-small lung cancer cells. *J. Cell. Physiol.* **2006**, *209*, 428–438. [[CrossRef](#)]
71. Satoh, T.; Toyoda, M.; Hoshino, H.; Monden, T.; Yamada, M.; Shimizu, H.; Miyamoto, K.; Mori, M. Activation of peroxisome proliferator-activated receptor-gamma stimulates the growth arrest and DNA-damage inducible 153 gene in non-small cell lung carcinoma cells. *Oncogene* **2002**, *21*, 2171–2180. [[CrossRef](#)]
72. Ni, J.; Zhou, L.L.; Ding, L.; Zhao, X.; Cao, H.; Fan, F.; Li, H.; Lou, R.; Du, Y.; Dong, S.; et al. PPAR γ agonist efatutazone and gefitinib synergistically inhibit the proliferation of EGFR-TKI-resistant lung adenocarcinoma cells via the PPAR γ /PTEN/Akt pathway. *Exp. Cell Res.* **2017**, *361*, 246–256. [[CrossRef](#)]
73. Matthews, H.K.; Bertoli, C.; de Bruin, R.A.M. Cell cycle control in cancer. *Nat. Rev. Mol. Cell Biol.* **2022**, *23*, 74–88. [[CrossRef](#)]
74. Keshamouni, V.G.; Reddy, R.C.; Arenberg, D.A.; Joel, B.; Thannickal, V.J.; Kalemkerian, G.P.; Standiford, T.J. Peroxisome proliferator-activated receptor-gamma activation inhibits tumor progression in non-small-cell lung cancer. *Oncogene* **2004**, *23*, 100–108. [[CrossRef](#)]
75. Han, S.; Sidell, N.; Fisher, P.B.; Roman, J. Up-regulation of p21 gene expression by peroxisome proliferator-activated receptor gamma in human lung carcinoma cells. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2004**, *10*, 1911–1919. [[CrossRef](#)]
76. Mehlen, P.; Puisieux, A. Metastasis: A question of life or death. *Nat. Rev. Cancer* **2006**, *6*, 449–458. [[CrossRef](#)] [[PubMed](#)]
77. Castaneda, M.; den Hollander, P.; Kuburich, N.A.; Rosen, J.M.; Mani, S.A. Mechanisms of cancer metastasis. *Semin. Cancer Biol.* **2022**, *87*, 17–31. [[CrossRef](#)] [[PubMed](#)]
78. Fares, J.; Fares, M.Y.; Khachfe, H.H.; Salhab, H.A.; Fares, Y. Molecular principles of metastasis: A hallmark of cancer revisited. *Signal Transduct. Target. Ther.* **2020**, *5*, 28. [[CrossRef](#)]
79. Reka, A.K.; Kurapati, H.; Narala, V.R.; Bommer, G.; Chen, J.; Standiford, T.J.; Keshamouni, V.G. Peroxisome proliferator-activated receptor-gamma activation inhibits tumor metastasis by antagonizing Smad3-mediated epithelial-mesenchymal transition. *Mol. Cancer Ther.* **2010**, *9*, 3221–3232. [[CrossRef](#)]
80. Li, J.; Chen, L.; Yu, P.; Liu, B.; Zhu, J.; Yang, Y. Telmisartan exerts anti-tumor effects by activating peroxisome proliferator-activated receptor- γ in human lung adenocarcinoma A549 cells. *Molecules* **2014**, *19*, 2862–2876. [[CrossRef](#)]

81. Yin, H.; Liu, Y.; Yue, H.; Tian, Y.; Dong, P.; Xue, C.; Zhao, Y.T.; Zhao, Z.; Wang, J. DHA- and EPA-Enriched Phosphatidylcholine Suppress Human Lung Carcinoma 95D Cells Metastasis via Activating the Peroxisome Proliferator-Activated Receptor γ . *Nutrients* **2022**, *14*, 4675. [[CrossRef](#)]
82. Choudhary, R.; Li, H.; Winn, R.A.; Sorenson, A.L.; Weiser-Evans, M.C.; Nemenoff, R.A. Peroxisome proliferator-activated receptor-gamma inhibits transformed growth of non-small cell lung cancer cells through selective suppression of Snail. *Neoplasia* **2010**, *12*, 224–234. [[CrossRef](#)]
83. Han, S.; Ritzenthaler, J.D.; Rivera, H.N.; Roman, J. Peroxisome proliferator-activated receptor-gamma ligands suppress fibronectin gene expression in human lung carcinoma cells: Involvement of both CRE and Sp1. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2005**, *289*, L419–L428. [[CrossRef](#)]
84. Lugano, R.; Ramachandran, M.; Dimberg, A. Tumor angiogenesis: Causes, consequences, challenges and opportunities. *Cell. Mol. Life Sci.* **2020**, *77*, 1745–1770. [[CrossRef](#)]
85. Keshamouni, V.G.; Arenberg, D.A.; Reddy, R.C.; Newstead, M.J.; Anthwal, S.; Standiford, T.J. PPAR-gamma activation inhibits angiogenesis by blocking ELR+CXC chemokine production in non-small cell lung cancer. *Neoplasia* **2005**, *7*, 294–301. [[CrossRef](#)]
86. Jin, M.Z.; Jin, W.L. The updated landscape of tumor microenvironment and drug repurposing. *Signal Transduct. Target. Ther.* **2020**, *5*, 166. [[CrossRef](#)]
87. Li, H.; Sorenson, A.L.; Poczbott, J.; Amin, J.; Joyal, T.; Sullivan, T.; Crossno, J.T., Jr.; Weiser-Evans, M.C.; Nemenoff, R.A. Activation of PPAR γ in myeloid cells promotes lung cancer progression and metastasis. *PLoS ONE* **2011**, *6*, e28133. [[CrossRef](#)]
88. Cheng, H.S.; Yip, Y.S.; Lim, E.K.Y.; Wahli, W.; Tan, N.S. PPARs and Tumor Microenvironment: The Emerging Roles of the Metabolic Master Regulators in Tumor Stromal-Epithelial Crosstalk and Carcinogenesis. *Cancers* **2021**, *13*, 2153. [[CrossRef](#)]
89. Gou, Q.; Che, S.; Chen, M.; Chen, H.; Shi, J.; Hou, Y. PPAR γ inhibited tumor immune escape by inducing PD-L1 autophagic degradation. *Cancer Sci.* **2023**, *114*, 2871–2881. [[CrossRef](#)]
90. Fujita, T.; Sugiyama, Y.; Taketomi, S.; Sohda, T.; Kawamatsu, Y.; Iwatsuka, H.; Suzuoki, Z. Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (ADD-3878, U-63,287, ciglitazone), a new antidiabetic agent. *Diabetes* **1983**, *32*, 804–810. [[CrossRef](#)]
91. Lehmann, J.M.; Moore, L.B.; Smith-Oliver, T.A.; Wilkison, W.O.; Willson, T.M.; Kliewer, S.A. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J. Biol. Chem.* **1995**, *270*, 12953–12956. [[CrossRef](#)] [[PubMed](#)]
92. Kohloser, J.; Mathai, J.; Reichheld, J.; Banner, B.F.; Bonkovsky, H.L. Hepatotoxicity due to troglitazone: Report of two cases and review of adverse events reported to the United States Food and Drug Administration. *Am. J. Gastroenterol.* **2000**, *95*, 272–276. [[CrossRef](#)] [[PubMed](#)]
93. Nissen, S.E.; Wolski, K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N. Engl. J. Med.* **2007**, *356*, 2457–2471. [[CrossRef](#)] [[PubMed](#)]
94. Lewis, J.D.; Ferrara, A.; Peng, T.; Hedderson, M.; Bilker, W.B.; Quesenberry, C.P., Jr.; Vaughn, D.J.; Nessel, L.; Selby, J.; Strom, B.L. Risk of bladder cancer among diabetic patients treated with pioglitazone: Interim report of a longitudinal cohort study. *Diabetes Care* **2011**, *34*, 916–922. [[CrossRef](#)] [[PubMed](#)]
95. Han, S.; Roman, J. Rosiglitazone suppresses human lung carcinoma cell growth through PPARgamma-dependent and PPARgamma-independent signal pathways. *Mol. Cancer Ther.* **2006**, *5*, 430–437. [[CrossRef](#)] [[PubMed](#)]
96. Sun, X.; Ritzenthaler, J.D.; Zheng, Y.; Roman, J.; Han, S. Rosiglitazone inhibits alpha4 nicotinic acetylcholine receptor expression in human lung carcinoma cells through peroxisome proliferator-activated receptor gamma-independent signals. *Mol. Cancer Ther.* **2009**, *8*, 110–118. [[CrossRef](#)] [[PubMed](#)]
97. Zou, W.; Liu, X.; Yue, P.; Khuri, F.R.; Sun, S.Y. PPARgamma ligands enhance TRAIL-induced apoptosis through DR5 upregulation and c-FLIP downregulation in human lung cancer cells. *Cancer Biol. Ther.* **2007**, *6*, 99–106. [[CrossRef](#)] [[PubMed](#)]
98. Hann, S.S.; Tang, Q.; Zheng, F.; Zhao, S.; Chen, J.; Wang, Z. Repression of phosphoinositide-dependent protein kinase 1 expression by ciglitazone via Egr-1 represents a new approach for inhibition of lung cancer cell growth. *Mol. Cancer* **2014**, *13*, 149. [[CrossRef](#)]
99. Yuan, H.; Li, M.Y.; Ma, L.T.; Hsin, M.K.; Mok, T.S.; Underwood, M.J.; Chen, G.G. 15-Lipoxygenases and its metabolites 15(S)-HETE and 13(S)-HODE in the development of non-small cell lung cancer. *Thorax* **2010**, *65*, 321–326. [[CrossRef](#)]
100. Li, M.Y.; Yuan, H.L.; Ko, F.W.; Wu, B.; Long, X.; Du, J.; Wu, J.; Ng, C.S.; Wan, I.Y.; Mok, T.S.; et al. Antineoplastic effects of 15(S)-hydroxyeicosatetraenoic acid and 13-S-hydroxyoctadecadienoic acid in non-small cell lung cancer. *Cancer* **2015**, *121* (Suppl. S17), 3130–3145. [[CrossRef](#)]
101. Chopra, B.; Dhingra, A.K.; Dhar, K.L. *Psoralea corylifolia* L. (Buguchi)—Folklore to modern evidence: Review. *Fitoterapia* **2013**, *90*, 44–56. [[CrossRef](#)] [[PubMed](#)]
102. Kim, T.W.; Hong, D.W.; Park, J.W.; Hong, S.H. CB11, a novel purine-based PPAR γ ligand, overcomes radio-resistance by regulating ATM signalling and EMT in human non-small-cell lung cancer cells. *Br. J. Cancer* **2020**, *123*, 1737–1748. [[CrossRef](#)] [[PubMed](#)]
103. Vasan, N.; Baselga, J.; Hyman, D.M. A view on drug resistance in cancer. *Nature* **2019**, *575*, 299–309. [[CrossRef](#)] [[PubMed](#)]
104. Osmani, L.; Askin, F.; Gabrielson, E.; Li, Q.K. Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): Moving from targeted therapy to immunotherapy. *Semin. Cancer Biol.* **2018**, *52*, 103–109. [[CrossRef](#)] [[PubMed](#)]

105. Singh, S.; Sadhukhan, S.; Sonawane, A. 20 years since the approval of first EGFR-TKI, gefitinib: Insight and foresight. *Biochim. Biophys. Acta Rev. Cancer* **2023**, *1878*, 188967. [[CrossRef](#)] [[PubMed](#)]
106. Lee, S.Y.; Hur, G.Y.; Jung, K.H.; Jung, H.C.; Lee, S.Y.; Kim, J.H.; Shin, C.; Shim, J.J.; In, K.H.; Kang, K.H.; et al. PPAR-gamma agonist increase gefitinib's antitumor activity through PTEN expression. *Lung Cancer* **2006**, *51*, 297–301. [[CrossRef](#)] [[PubMed](#)]
107. Serizawa, M.; Murakami, H.; Watanabe, M.; Takahashi, T.; Yamamoto, N.; Koh, Y. Peroxisome proliferator-activated receptor γ agonist efatutazone impairs transforming growth factor β 2-induced motility of epidermal growth factor receptor tyrosine kinase inhibitor-resistant lung cancer cells. *Cancer Sci.* **2014**, *105*, 683–689. [[CrossRef](#)]
108. To, K.K.W.; Wu, W.K.K.; Loong, H.H.F. PPARgamma agonists sensitize PTEN-deficient resistant lung cancer cells to EGFR tyrosine kinase inhibitors by inducing autophagy. *Eur. J. Pharmacol.* **2018**, *823*, 19–26. [[CrossRef](#)]
109. Reddy, R.C.; Srirangam, A.; Reddy, K.; Chen, J.; Gangireddy, S.; Kalemkerian, G.P.; Standiford, T.J.; Keshamouni, V.G. Chemotherapeutic drugs induce PPAR-gamma expression and show sequence-specific synergy with PPAR-gamma ligands in inhibition of non-small cell lung cancer. *Neoplasia* **2008**, *10*, 597–603. [[CrossRef](#)]
110. Girnun, G.D.; Chen, L.; Silvaggi, J.; Drapkin, R.; Chirieac, L.R.; Padera, R.F.; Upadhyay, R.; Vafai, S.B.; Weissleder, R.; Mahmood, U.; et al. Regression of drug-resistant lung cancer by the combination of rosiglitazone and carboplatin. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2008**, *14*, 6478–6486. [[CrossRef](#)]
111. Han, E.J.; Im, C.N.; Park, S.H.; Moon, E.Y.; Hong, S.H. 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*, e239–e248. [[CrossRef](#)]
112. Govindarajan, R.; Ratnasinghe, L.; Simmons, D.L.; Siegel, E.R.; Midathada, M.V.; Kim, L.; Kim, P.J.; Owens, R.J.; Lang, N.P. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2007**, *25*, 1476–1481. [[CrossRef](#)] [[PubMed](#)]
113. Wigle, D.A.; Mandrekar, S.J.; Allen-Ziegler, K.; Gesthalter, Y.; Holland, P.; Aubry, M.-C.; Limburg, P.J.; Avi, S.; Szabo, E. Pioglitazone as a candidate chemoprevention agent for lung cancer: A pilot window trial in early stage NSCLC. *J. Clin. Oncol.* **2014**, *32*, 1581. [[CrossRef](#)]
114. Keith, R.L.; Blatchford, P.J.; Merrick, D.T.; Bunn, P.A., Jr.; Bagwell, B.; Dwyer-Nield, L.D.; Jackson, M.K.; Geraci, M.W.; Miller, Y.E. A Randomized Phase II Trial of Pioglitazone for Lung Cancer Chemoprevention in High-Risk Current and Former Smokers. *Cancer Prev. Res.* **2019**, *12*, 721–730. [[CrossRef](#)] [[PubMed](#)]
115. Jones, J.D.; Comer, S.D.; Metz, V.E.; Manubay, J.M.; Mogali, S.; Ciccocioppo, R.; Martinez, S.; Mumtaz, M.; Bisaga, A. Pioglitazone, a PPAR γ agonist, reduces nicotine craving in humans, with marginal effects on abuse potential. *Pharmacol. Biochem. Behav.* **2017**, *163*, 90–100. [[CrossRef](#)] [[PubMed](#)]
116. Domi, E.; Caputi, F.F.; Romualdi, P.; Domi, A.; Scuppa, G.; Candeletti, S.; Atkins, A.; Heilig, M.; Demopulos, G.; Gaitanaris, G.; et al. Activation of PPAR γ Attenuates the Expression of Physical and Affective Nicotine Withdrawal Symptoms through Mechanisms Involving Amygdala and Hippocampus Neurotransmission. *J. Neurosci. Off. J. Soc. Neurosci.* **2019**, *39*, 9864–9875. [[CrossRef](#)]
117. Yin, Y.; Hou, G.; Li, E.; Wang, Q.; Kang, J. PPAR γ agonists regulate tobacco smoke-induced Toll like receptor 4 expression in alveolar macrophages. *Respir. Res.* **2014**, *15*, 28. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.