Antineoplastic Effects of PPAR γ Agonists, with a Special Focus on Thyroid Cancer.

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Running Title: PPARγ agonists antineoplastic effects in cancer.

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Abstract

Peroxisome Proliferator-Activated Receptor-γ (PPARγ) is a ligand-activated nuclear hormone receptor that functions as transcription factor and plays an important role in lipid metabolism and insulin sensitization. Recent studies have shown that PPARγ is over-expressed in many tumor types, including cancers of breast, lung, pancreas, colon, glioblastoma, prostate and thyroid differentiated/anaplastic cancers. These data suggest a role of PPARγ in tumor development and/or progression. PPARγ is emerging as a growth-limiting and differentiation-promoting factor, and it exerts a tumor suppressor role.

Moreover, naturally-occurring and synthetic PPARγ agonists promote growth inhibition and apoptosis. Thiazolidinediones (TZDs) are synthetic agonists of PPARγ that were developed to treat type II diabetes. These compounds also display anticancer effects which appear mainly to be independent of their PPARγ agonist activity. Various preclinical and clinical studies strongly suggest a role for TZDs both alone and in combination with existing chemotherapeutic agents, for the treatment of cancer.

Differentiation therapy involves the use of agents with the ability to induce differentiation in cells that have lost this ability, i.e. cancer cells, targeting pathways capable of re-activating blocked terminal differentiation programs. PPARγ agonists have been shown to induce differentiation in solid tumors such as thyroid differentiated/anaplastic cancers and sarcomas.

However, emerging data suggest that chronic use of TZDs is associated with increased risk of adverse cardiovascular events. The exploration of newer PPARγ agonists can help in unveiling the underlying mechanisms of these drugs, providing new molecules that are able to treat cancer, without increasing the cardiovascular risk of neoplastic patients.

Keywords: Peroxisome Proliferator-Activated Receptor-γ; Thiazolidinediones; PPARγ agonists; Antineoplastic effects; Thyroid cancer; Differentiated thyroid cancer; Anaplastic thyroid cancer.

1. INTRODUCTION

In humans Peroxisome Proliferator-Activated Receptor-γ (PPARγ) is a type II nuclear receptor, encoded by the *PPARg* gene [1]. Its endogenous ligands are free fatty acids and eicosanoids. Once activated, the receptor binds to DNA in complex with the retinoid X nuclear receptor (RXR), increasing or decreasing the transcription of specific genes. PPAR-α, PPAR-δ, and PPAR-γ are the known three PPARs subtypes. PPAR-γ regulates glucose metabolism and fatty acid storage, stimulates lipid uptake and adipogenesis by fat cells, and is a regulator of adipocyte differentiation [2]. In humans and mice, two isoforms of PPAR-γ are detected: PPAR-γ1 (present in almost all tissues, except muscle) and PPAR-γ2 (in adipose tissue and intestine) [3]. PPAR-γ is involved in the pathogenesis of different diseases: obesity, diabetes, atherosclerosis, and cancer. Its agonists are implicated in the treatment of hyperlipidaemia and hyperglycemia [4]. PPAR-γ decreases the inflammatory response of many cardiovascular cells, mainly endothelial cells [5], reduces atherosclerosis, activating the *PON1* gene, that increases the synthesis and release of paraoxonase 1 from the liver [6].
PPAR-γ are also involved in autoimmune disorders [7] and in cancerogenesis [8], too.
The PAX8-PPAR-γ1 fusion is present in approximately one-third of follicular thyroid carcinomas, that show the chromosomal translocation of t(2;3)(q13;p25), by juxtaposition of portions of both genes [9]. Furthermore, PPAR-γ is the target of various insulin sensitizing drugs involved in the treatment of diabetes.

1.1. Thiazolidinediones (TZDs) and "partial agonists of PPAR-γ"

TZDs (or glitazones) are drugs implicated in the treatment of diabetes mellitus type 2. TZDs activate PPARs, with greatest specificity for PPAR-γ. Once activated, the PPAR/RXR heterodimer binds to peroxisome proliferator hormone response elements upstream of target genes, complexed with coactivators, as nuclear receptor coactivator 1 and CREB binding protein, upregulating the target genes. The activation of PPAR-γ causes: 1) decrease of insulin resistance; 2) change in insulin secretion in β-cells [10]; 3) modification in adipocyte differentiation; 4) fall of certain cytokines/chemokines levels [11,12]; 5) antiproliferative action. Moreover, TZDs increase the synthesis of particular proteins implicated in fat metabolism, decrease triglycerides and increase high-density cholesterol. The "partial agonists of PPAR-γ" are other classes of compounds able to activate PPAR-γ, but weaker than TZDs. At the present, these compounds are studied, hoping that they could be effective hypoglycemic agents but with fewer side effects [13,14].

1.2. Epidemiologic evidence of TZD anti-cancer activity

Different epidemiological studies have demonstrated the TZDs antineoplastic effect. Pancreatic cancer cases decreased significantly in patients administered with rosiglitazone (RGZ) with respect to controls, as evidenced by a survey trial conducted in patients with diabetes [15].
A meta-analysis conducted in 30,000 patients showed a reduced incidence of cancer in diabetic patients administered with RGZ [16], and another meta-analysis [17] suggested that the treatment with TZDs was associated with a slight significantly decrease of risk of lung and breast cancers. This has been confirmed by a 6-years population-based cohort study, showing a decrease in different cancer risk in diabetic patients treated with TZDs, and that the association was dose-dependent [18]. Though encouraging preclinical results, favourable effects were not always been shown by clinical trials. Anyway, troglitazone (TGZ) stabilized the prostate-specific antigen (PSA) serum levels in advanced prostate cancer in a phase II trial [19].

1.3. PPARγ-dependent and -independent antitumor effects of TZDs

Different human cancer cell lines exhibit high levels of PPARγ expression, and their *in vitro* exposure to elevated doses (≥ 10 μM) of TZDs, particularly TGZ and ciglitazone (CGZ), led to cell cycle arrest, apoptosis and/or redifferentiation [20-24], suggesting a putative link between PPARγ signaling and TZD's antitumor activities. The *in vivo* anticancer effect of TGZ was shown in a few clinical cases in patients with liposarcomas [25] or prostate cancer [26]. Until now, the specific target genes contributing to the antiproliferative effects of PPARγ agonists are not clear, as the genomic responses to PPARγ are complex and depend on the cellular context in the different types of cancer [21]. In colorectal cancer cells PPARγ-specific target genes included those associated with growth regulatory pathways, colon epithelial cell maturation, immune modulation, and intercellular adhesion [27]. Even the functional role of the PPARγ-specific target genes in modulating TZDs' antiproliferative effects in cancer cells is still not clear.

On the other hand, not all authors agree on the fact that the antitumor effect of TZDs depends on PPARγ activation, as: 1) TZDs' antitumor effects seem to be structure-specific regardless of the potency in PPARγ activation [TGZ and CGZ are more active in inducing apoptosis in cancer cells compared to RGZ and pioglitazone (PGZ)]; 2) A 3-orders-of-magnitude discrepancy is present between the necessary concentration to mediate antitumor effects and that for activating PPARγ; 3) A correlation between the susceptibility of tumor cells to TZDs and the PPARγ expression level does not exist, as for example, LNCaP prostate cancer and MCF-7 breast cancer cells, that have low PPARγ expression levels, were more sensitive to the effects of TGZ and CGZ on suppressing cell viability than PC-3 and MDA-MB-231 cells, that over-express PPARγ [28,29]; 4) the PPARγ-inactive analogues of TGZ and CGZ, Δ2-TG and Δ2-CG, were slightly more effective than their parent compounds in suppressing cell proliferation in cancer cells [28,29]; 5) Knocking down PPARγ by siRNA in PC-3 cells, the ability of TGZ or Δ2-TG to induce apoptotis was not affected [8].

1.4. The TZDs induction of apoptosis

In prostate cancer cells, the induction of cytochrome c release and DNA fragmentation was stronger with Δ2-TGZ and Δ2-CGZ than TGZ and CGZ while minor effects were shown with powerful PPARγ agonists, as RGZ and PGZ and their Δ2 derivatives [28]. The TZD-induced apoptosis depends on caspases via intrinsic and extrinsic pathways. As an example, the dual PPARα/PPARγ agonist TZD18 is able to inhibit cell proliferation indipendently from PPARγ, and to induce apoptosis in SD1 and BV173 leukemic cells, by cleavage of caspases-8 and -9. The pan-caspase inhibitor Z-VAD-FMK blocked this activity [30]. The cleavage of caspase-9, -8 and -3 was stimulated also by TGZ in a PPARγ-independent manner in bladder cancer T24 and RT4 cells, as the apoptosis, specifically blocked by certain caspase inhibitors [31]. The same data were shown in T24 bladder cancer cells with CGZ [32]. In MCF-7 and MDA-MB-231 breast cancer cells, the mitochondrial membrane potential was modified by Δ2-TGZ, that also induced the cleavage of PARP and caspase-7 (stopped by Z-VAD-FMK) [33]. The expression of Bcl-2 family members was modulated by TZDs, stimulating the intrinsic pathway of apoptosis. TZD18 up-regulated the proapoptotic protein Bax in human leukaemia cells but did not change the anti-apoptotic Bcl-2 expression [30], while in MCF-7 and MDA-MB-231 breast cancer cells it up-regulated Bax and Bak [34]. The Bax/Bcl2 mRNA ratio was increased by TGZ in renal carcinoma cells, while it did not change the Bcl-2 members expression in PC-3 prostate cancer cells [28, 35]. Anyway, TGZ, CGZ and their Δ2 derivatives blocked the heterodimerization of Bcl-2 and Bcl-XL with Bax, inhibited the anti-apoptotic action, and activated cytochrome c release and caspase-9 [28]. Bcl-XL over-expression protected the PPARγ-deficient LNCaP cells against the apoptosis induced by TGZ and its Δ2 counterpart [28]. It has been recently shown that TZD activates the membrane G protein-coupled receptor 40 [36], leading to osteocyte apoptosis recruiting Bax to the outer mitochondrial membrane.
The inactive PPARγ derivative of D2-CGZ, OSU-CG12, exhibited its anticancer effect in prostate and breast cancer cells inducing apoptosis, through the cleavage of PARP, and the proapoptotic proteins ATF3, Noxa and DAPK2 increased. PARP cleavage was shown in OSU-CG30- exposed LNCaP cells, too [37]. In MDA-MB-231 and MDA-MB-468 (breast cancer cell lines), OSU-53 induced apoptosis through PARP-cleavage and rises in the sub-G1 apoptotic population [38]. The cleavage of PARP was also shown *in vivo* in nude mice in OSU-53-treated MDA-MB-231 tumors, while it did not stimulate PARP cleavage in the control MCF-10A cells. TZD exerts its effects also combined with other treatments. For example, TZD sensitized cancer cells to the apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [31,39–42]. In lung cancer cells treated with the combination of TRAIL and TZD, the cleaved forms of PARP and caspase-8, -9 and -3 were evidenced much more easily with respect to the treatment with each of them alone [41]. TZD induces apoptosis via TRAIL increasing DR5 expression and down-regulating cellular Flice-like inhibitor protein (c-FLIP) [43] or survivin [31,40–42]. In lung cancer, the over-expression of c-FLIP and silencing of DR5 expression through RNA interference abolished the induction of apoptosis by TRAIL by PPARγ ligand [41]. Furthermore, TGZ and CGZ up-regulated TRAIL expression in TRAIL-resistant T24 bladder cancer cells and increased apoptosis by TRAIL activating death receptor signaling pathways [31,32].

1.5. The TZDs induction of autophagy

TGZ induced autophagy in HeLa cells, evidenced by AMPK phosphorylation, LC3-II increase and degradation of sequestome 1 (SQSTM1/p62; a selective substrate of autophagy), participating in the apoptosis via caspases [44]. TGZ supported autophagosome creation and an increase in LC3-II in porcine aortic endothelial cells, too [45], related to AMPK phosphorylation and independently from PPARγ. Moreover, RGZ and TGZ induced autophagy activating PPARγ in MDA-MB-231 breast cancer cells [46]. RGZ inhibited cell proliferation

independently or not from PPARγ and provoked an autophagic process, increasing p-AMPK and the expression of beclin-1, in H295R adrenocortical cancer cells [47]. RGZ-induced autophagy depends on the cellular context, as this was not shown in SW13 adrenocortical cancer cells. In H295R cancer cells it was associated with the production of reactive oxygen species (ROS) and the disruption of the mitochondrial membrane potential [47]. Nutrient-deprivation autophagy factor-1 (NAF-1) and CDGSH iron sulfur domain 1 protein (mitoNEET) (members of NEET protein family) are determinant in maintaining the mitochondrial integrity, cellular iron and ROS homeostasis. NAF-1 and mitoNEET increase in MCF-7, MDA-MB-468 and HCC-70 human epithelial breast cancer cells with respect to the control MCF-10A. Knocking-down these proteins by small hairpin (sh)RNA in MCF-7 and MDA-MB-231 breast cancer cells decreases significantly cell proliferation and tumor growth, the mitochondrial membrane potential, and causes the increase of ROS in mitochondria and autophagy [48]. For these reasons, NAF-1 and mitoNEET could be considered TZDs mitochondrial targets [49–51].
OSU-CG12 induced autophagy in LNCaP prostate cancer cells, as shown by the increase of LC3-II in autophagic vacuoles, inducing AMPK phosphorylation upon 10min from exposure, down-regulation of mTOR and p70S6K phosphorylation. The expression of a dominant-negative form or the use of pharmacological agents inhibited the AMPK function, preventing the conversion from LC3-I to LC3-II and autophagy. This process decreased the action of OSU-CG12 on cell viability in LNCaP cells, but it did not have effects on PARP cleavage. OSU-53 stimulated a protective autophagy that weakened its antiproliferative effect [38]. If MDA-MB-231 cells expressed an AMK dominant-negative form, OSU-53 had effects on cell viability to a lesser extent. Its combination with the autophagy inhibitor chloroquine induced the *in vitro* antiproliferative effect and the *in vivo* tumor-suppressive effects of this compound [38].

1.6. TZDs as energy restriction mimetic agents (ERMAs)

Some TZDs behave as ERMAs, and this was confirmed for OSU-CG12 in LNCaP cells, that were protected from the cell death induced by this compound by elevated levels of supplemental glucose. OSU-CG12 provoked cellular responses characteristic of energy restriction in LNCaP and MCF-7 cells at 5 μM with respect to 5 mM for 2-DG. OSU-CG12 reduced glycolytic rate and intracellular lactate and NADH, and in this way the different ATP/AMP ratio induced AMPK activation. A slight fall in [3H]2-DG uptake can be seen after less than 20 min of OSU-CG12 exposure. After 24 h of treatment with OSU-CG12, RT-PCR analyses showed a fall in mRNA levels of the first 2 enzymes of the glycolytic pathway, hexokinase 2 and phosphofructokinase-1. In these cells OSU-CG5 suppressed [3H]-2DG uptake more strongly (IC50 = 6 μM) than OSU-CG12 (IC50 = 9 μM). The OSU-CG5-optimized OSU-CG30 was able to block glucose uptake into LNCaP cells (IC50 = 2.5 μM) [37], thanks to its capacity of binding to the GLUT1 channel at a different site than glucose [37].
In C-26 colon adenocarcinoma cells, OSU-53 stimulated AMPK phosphorylation and decreased p70S6K [52]. OSU-53 induced kinase activity with an EC50 of 0.3 μM with respect to 8 μM for AMP, as shown by radiometric kinase assays conducted using a recombinant AMPK α1β1γ2 [38]. In breast cancer, OSU-53 decreased viability and clonogenic growth of MDA-MB-468 (LKB1 positive) and MDA-MB-231 (LKB1 negative) with a similar strenght, while it did not have effects in nonmalignant MCF-10A cells. This data confirmed a direct activation of AMPK and not a LKB1-mediated process. Multiple AMPK downstream pathways are OSU-53 targets [38]. The temporary induction of Sirt1, proteolysis and endoplasmic reticulum (ER) stress are the key starvation-associated responses to these compounds. Each of them modulates a different signaling pathway linked to the anti-proliferative effects.

1.7. Sirt1/β-TrCP-dependent proteolytic events induced by TZDs

As after 2-DG-exposure, the temporary increase of Sirt1 expression in OSU-CG12-treated cells was determinant for the induction of apoptosis, as it increased β-TrCP through its stabilization, down-regulating β-TrCP-specific E3 ligase Skp2 expression. This resulted in an inferior ubiquitin-dependent β-TrCP degradation, that led to proteasomal degradation of different cell cycle and apoptosis regulatory proteins, as β-catenin, cyclin D1 and Sp1 [53,54]. The down-regulated Sp1 induced the transcriptional repression of histone deacetylases and H3K4 demethylases leading to an epigenetic effect of the tumor suppressor KLF6, important for the induction of apoptosis.
OSU-CG5 up-regulated “DNA methylation-silenced tumor suppressor genes” and down-regulated “methylated tumor/invasion-promoting genes”, owing to transcriptional repression of DNMT-1. Also OSU-CG30 led to apoptosis, inducing cellular responses dependent on ERMAs, as β-TrCP-mediated protein degradation [cyclinD1, Sp1] and epigenetic activation of KLF6 [37].

1.8. ER stress induction

As after 2-DG-exposure, also OSU-CG12 induced ER stress. Upon 6 h of exposure to OSU-CG12 10 μM, phosphorylation of eIF2α at Ser51 occurred, and after 48 h to 5 μM, an up-regulation of IRE-1α and the chaperone GRP78 were shown in LNCaP cells. Also up-regulation of C/Ebp-Homologous Protein (CHOP) was observed, that seemed to appear only in the case of treatment with higher doses (10–20 μM), and whose silencing did not affect the susceptibility to the antiproliferative effect of OSU-CG12 and PARP cleavage. OSU-CG12 was more potent in its anti-proliferative effect than 2-DG and resveratrol, as its energy restriction-associated responses were reached at 5 μM with respect to 5 mM and 100 μM for 2-DG and resveratrol, respectively. Furthermore, it had low toxicity against nonmalignant prostate epithelial cells where neither effect could be shown on β-TrCP or Sp1. The apoptosis induced by OSU-CG12 did not seem to be mediated by ER stress [43].
In colorectal cancer HCT-116 and Caco-2 cells, the ER stress response proteins GRP78 and GADD153/CHOP levels were increased by OSU-CG5 [55].
The major part of the TZDs anticancer effects are PPARγ-independent, and for this reason different derivatives belonging to the D2 family were synthesized, with a double bound next to the terminal thiazolidine-2,4-dione ring, lacking PPARγ agonist activity, but still displaying anticancer effects. For example, D2-TGZ affected breast cancer cells viability [56]. Most of D2-TGZ-derivatives were functionalized on the terminal hydroxyl group of the chromane moiety, and showed a stronger activity on breast cancer cell viability [57]. Some of them had good antiproliferative effects in breast cancer cells and low toxicity in human hepatocytes [58]. D2-TGZ and D2-CGZ inhibited prostate cancer cells proliferation more strongly than their parent compounds, in PPARγ-expressing PC-3 and PPARγ-deficient LNCaP cells [28]. The permutational rearrangement of the OSU-CG12 terminal methylcyclohexylmethyl moiety caused the formation of an inverted molecule, with the TZD ring in the middle, and in which the phenyl ring was functionalized by a trifluoroacetate group [59]. Upon oral administration to male transgenic adenocarcinoma of the mouse prostate (TRAMP) mice, OSU-CG5 blocked prostate epithelial growth and preneoplastic lesions [60].

1.9. Therapeutic efficacy of TZDs in specific cancers

CGZ, TGZ, RGZ, and PGZ induce a decrease of cell proliferation, cytotoxicity, and proapoptotic effects in different cell lines [sarcoma, melanoma, glioblastoma, breast carcinoma, colorectal cancer, gastric cancer, pancreatic cancer, prostate, bladder cancer, hepatic cancer, thyroid cancer (TC), ovarian cancer, endometrial cancer, and lung cancer cells, etc.]. Thanks to the good results obtained *in vitro*, animal experiments and clinical trials have been conducted.
In some of these cancer types, efatutazone (EFA), developed as a chemostatic rather than an antidiabetic drug, has been evaluated. EFA is a PPARγ activator 500 times more potent than TGZ and 50 times than RGZ. It was studied in a preclinical murine model for breast cancer based on BRCA1 (BReast CAncer 1) deficiency. In the Mouse Mammary Tumor Virus (MMTV)-Cr BRCA1flox/flox p53+/− model, exon 11 of the BRCA1 gene is deleted by MMTV-Cre transgene, causing a loss of one germline copy of TP53. EFA reduced the incidence of non-invasive and well-differentiated tumors in this model [61]. Administration of EFA reduced cell proliferation and xenograft size of pancreatic, anaplastic thyroid (ATC), and colorectal cancer [62].

1.9.1. Liposarcoma

Phase I trials were then started as monotherapy or combined with other compounds.
Stable disease (SD) was induced in 10/22 patients with advanced liposarcoma after monotherapy [63].
A phase I study evaluating the combination of bexarotene with EFA in solid tumors has been conducted (NCT01504490).
The first trial evaluating the antitumor effects of the antidiabetic TZDs was conducted in 3 liposarcoma patients, and TGZ led to a reduced proliferation [25], while there were no beneficial effects in a trial with RGZ in 9 liposarcoma patients [64]. Though the negative results obtained from this trial, another phase II trial on RGZ is ongoing (NCT00004180; http://www.cancer.gov/clinicaltrials/).

1.9.2. Colorectal Cancer

PPARγ expression shows protective effects in colorectal cancer, as evidenced by studies on human tumor samples [65]. Patients with PPARγ expression usually showed a better prognosis, in fact the reduction of β-catenin and PPARγ was correlated with elevated numbers of tumor-associated macrophages, increased metastasis, and poor survival [66]. Loss of function point mutations of the PPARγ gene and polymorphisms were reported in 8% of colorectal carcinoma patients. However, some studies on PPARγ expression in colorectal samples did not find any relation between PPARγ immunoreactivity and tumor aggressiveness [67,68].
TZDs showed variable effects *in vivo*. In mice the activation of PPARγ inhibited xenograft growth and its agonists reduced the number of aberrant cryptal foci in chemically induced inflammatory bowel disease [69,70]. PGZ induced increased polyp numbers in mice with APC mutation, susceptible to colon adenoma (APCmin), but not in wild-type mice, leading to hypothesize that TZDs could also promote colon cancer development [71]. These dissimilar results might be explained by *in vitro* studies in colon cancer cell lines, which evidenced that PPARγ expression correlated to cells' sensitivity to proliferation inhibition [72]. A phase II trial with TGZ did not increase progression-free survival in 25 colorectal cancer patients [73].

1.9.3. Lung Cancer

As PPARγ expression in well-differentiated lung adenocarcinoma was higher than in poorly differentiated tumors, it was hypothesized that it promotes tumor formation, even if it is not a marker for aggressive growth [74]. However, in another paper it was shown the opposite trend, as the expression was linked to poor prognosis [75]. RGZ decreased progression of chemically induced murine cancer model [76].

1.9.4. Breast Cancer

In breast cancer cells PPARγ mRNA levels did not correlate with nodal involvement and tumor grade, but significantly lower PPARγ levels were shown in large metastatic tumors, patients with local recurrence and poor survival [77]. TZDs had moderate positive effects in breast cancer models. RGZ decreased tumor growth in a chemically induced rat and in a syngenic murine tumor model [78,79]. Treating with TZDs patients with advanced breast carcinoma and with early mammary cancer did not lead to therapeutic effects [80,81].

1.9.5. Prostate Cancer

Immunoreactivity and PPARγ expression correlated inversely with tumor size and PSA levels in most of prostate cancers (73%) [82]. Data obtained in prostate cancer xenografts as well as results from a phase II trial and a case report showed efficacy of PGZ and TGZ [19,26,83].

1.9.6. Glioblastoma

Gliomas did not show any correlation with PPARγ expression [84]. However, patients with diabetes mellitus administered with TZD showed lower incidence of high-grade glioma than controls (patients with hip fractures), while survival of patients with glioma was similar in both groups [85]. The efficacy of PGZ has been shown in glioma xenografts and in a phase II trial [86,87].

1.9.7. Melanoma

No correlation of PPARγ expression and melanoma prognosis was evidenced [88]. In a cohort study conducted in patients with diabetes mellitus under PGZ therapy, an increased hazard ratio for melanoma (1.3) was shown [89]. It is not clear whether these data represent an increased incidence of tumors because the maximum duration of follow-up was < 6 years after the initiation of PGZ. Studies on monotherapy with TZDs in melanoma are restricted, as only CGZ inhibited growth of melanoma xenografts [90].
PPARγ seems to have a protective effect in tumor development, as elevated mRNA or protein expression in well-differentiated tumors compared to poorly differentiated tumors and tumors with poor prognosis has been shown [63].

1.10. TZDs in Differentiated Thyroid Carcinoma (DTC)

Follicular thyroid cancer (FTC) is the only known neoplasm associated with a PPARγ fusion gene product [91], PAX8/PPARγ, that is expressed in 30–35% of FTC and 2–13% of follicular adenomas [92]. This chimeric protein derives from a genetic translocation between chromosomes 2 and 3 and is able to activate the PPARγ response element inducing proliferation. It functions as a gain and loss of function mutant determining thyroid tumor differentiation; in more aggressive tumors gain of function predominates [91].
In the last decades, TC incidence in the United States has increased [93].
The increasing diagnosis of TC is related to the use of neck ultrasonography for the diagnosis of thyroid nodules, but also to ionizing radiations [94], the exposure to fall-out of nuclear accidents [95], the exposure to iodine deficiency that increases frequency of FTC [96]. Furthermore, autoimmune thyroiditis has been shown to be a risk factor for papillary thyroid caner (PTC) [97,98], and new risk factors are emerging [99-101].
DTC (mainly PTC) is the most common type of thyroid carcinoma, accounting for 80–90% of all TCs. FTCs is the 2nd most common, with 10–15% incidence. The prognosis of DTC is frequently good, with a 10-year survival rate of 85% [102]. Approximately 10–20% of patients develop distant metastases [103], showing a 10-year survival rate of 40%. Recurrence in DTC occurs in not less than a third of patients and only 30% of patients with distant metastases respond to radioiodine (RAI) therapy with complete remission [104,105]. DTC first-line therapy is total or near total thyroidectomy and lymph node dissection (if necessary). RAI treatment commonly follows, for thyroid remnant ablation and elimination of metastases. In case of inefficacy of these treatments, doxorubicin follows [106]. As doxorubicin is not strongly efficient, in the future differentiating therapies will play a determinant role in cancer treatment. Redifferentiating compounds include retinoids, histone deacetylase inhibitors, DNA methyltransferase inhibitors, and TZDs. Somatostatin analogues (for example, 68Ga-DOTATOC) are additional options for RAI-negative TC [107].
PGZ and CGZ did not increase differentiation in the human PTC cell line NPA [108], while TGZ, RGZ, and PGZ showed antiproliferative, proapoptotic, and differentiating effects on DTC cells in another paper [63,109]. TGZ increased expression of sodium-iodide symporter in DTC lines [110] and restored RAI-uptake *in vitro* [111].
PGZ reduced metastatic disease in a tumor model where the effect of PAX8/PPARγ fusion protein is mimicked [112]. RGZ reduced thyrocyte growth by 40% in a murine knock-in model of thyroid hormone receptor γ [113].
TZDs modulate chemokine secretion in TC. In fact, a dysregulation of chemokine CXCL10 secretion has been shown in PTCs. A CXCL10 secretion more than ten times higher has been induced by IFNγ+TNFα in PTCs with respect to control thyroid follicular cells (TFC). Moreover, TZDs inhibited CXCL10 secretion in control TFC while stimulated it in PTCs. The effect of TZDs on CXCL10 was unrelated to the significant antiproliferative effect in PTCs [114,115].
TZDs were also evaluated in patients with TC. In 5 patients treated with PGZ for 6 months, no increase in RAI-uptake was observed [116]. An effective induction of RAI-uptake after RGZ therapy was reported by 2 case reports, in patients with non-iodide avid metastases of DTC [117,118]. The results of treatment showed reduced thyroglobulin levels and tumor size. An increased RAI-uptake after RGZ treatment was shown in 1/5 patients enrolled in a pilot study [119], while another paper reported positive RAI scans in 4/10 patients after RGZ treatment [120]. A clinical trial showed increased RAI-uptake in therapeutic 131I scans in 5/23 patients [121]. In another phase II trial, though reinduction of RAI-uptake in 5/20 patients, none had a complete or partial response (PR) to RGZ after 3 months [122] by RECIST criteria [123]. A current trial (NCT00098852) with RGZ for reinduction of RAI-uptake is still ongoing (http://www.clinicaltrial.gov/). The redifferentiating action of PGZ is being reassessed in a trial focused on follicular variants of PTC (NCT01655719; http://www.clinicaltrial.gov/). The restricted accuracy of the 131I scans technique, the unknown status of receptor expression of the treated tumors, too low levels of expression by the target cells, inhomogeneity of RAI-uptake into the tumor, and the generally poor correlation between RAI-uptake and clinical remission, make the interpretation of the obtained data quite difficult. Moreover, an observation time shorter than 1 year could not be enough to monitor effects in slow-growing DTC.
Recently epidemiologic, clinical, and preclinical studies suggest that another antidiabetic drug (metformin) may lower cancer risk and improve outcomes of cancer in diabetics [124]. Moreover, metformin treatment was associated with low recurrence in diabetic patients with cervical lymph node metastasis of DTC [125].
The molecular mechanisms at the base of the antineoplastic effect of metformin remain controversial. Different mechanisms have been suggested, in fact metformin: a-can act on mitochondria, inhibiting complex I; b-can activate AMPK and Redd1 proteins, inhibiting the mTOR pathway cell cycle arrest, inducing autophagy, apoptosis and cell death; c-alters the methionine and folate cycles, with a decrease in nucleotide synthesis [126].

CXCL8 is a chemokine previously shown to play relevant tumor promoting effects in TC microenvironment [127,128]. For this reason, pharmacological strategies aimed at modulating the concentration of this chemokine were tested. PGZ was demonstrated to inhibit the TNF-α induced CXCL8 secretion in endometriotic stromal cells [129] and to suppress CXCL8 mRNA expression in pancreatic cancer cell lines [130]. As far as TC is concerned, it was recently demonstrated that metformin, among its anti-tumor effects [131], is able to inhibit the TNF-α-induced CXCL8 secretion in primary cultures of normal and PTC cells [132]. The demonstration that metformin and PGZ besides an overall similar efficacy in the control of hyperglycemia display some differences in their anti-inflammatory activity could make it worth to evaluate the combined effects of these two compounds also in terms of CXCL8 secretion [133].

In ATC, Hayashi *et al.* showed the expression of both PPARγ gene and protein in 5 human cell lines [134] than in PTC cells. Cell proliferation was reduced by PPARγ agonists inducing apoptosis. Moreover, PPARγ agonists decreased the invasive potential of the 5 ATC cell lines [134].

Aiello *et al.* [135] studied the biologic effects of CGZ and RGZ in ATC cell lines, and demonstrated that RGZ increased the expression of thyroid-specific markers of differentiation.

Marlow *et al.* [136] showed that, the high-affinity PPARγ agonist RS5444, reactivating suppressed RhoB, induced the cyclin-dependent kinase inhibitor p21 and inhibited ATC cells proliferation.

Recently, Antonelli *et al.* have shown that PGZ and RGZ can reduce cell growth and proliferation in human ATC primary cultured cells, from different patients [137]. Moreover, in another *in vitro* study it was shown that the results of chemosensitivity tests with PPARγ agonists in primary ATC cells obtained directly from fine-needle aspiration are similar to those obtained from biopsies [138,139].

A recent paper showed that TZDs are able to modulate chemokine secretion also in ATC. In fact, ATC cells produced CXCL10 basally and stimulated by cytokines. However, the pattern of modulation by IFN-γ, TNF-α or TZDs was extremely variable, suggesting that the intracellular pathways involved in the chemokine modulation in ATC have different types of deregulation with respect to DTC and control TFC [140].

More recently a phase I study [141] was conducted on 15 ATC patients, to determine the potential effectiveness of paclitaxel and EFA at different doses (7 of them received 0.15 mg, 6 received 0.3 mg, 2 received 0.5 mg of EFA). One subject, treated with 0.3 mg of EFA, had a PR; 7 patients had SD. The median times to progression in patients treated with 0.15 mg and 0.3 mg of EFA, were 48 and 68 days, while the median survival were 98 *versus* 138 days, respectively. Adverse events grade 3 or greater related to the treatment were observed in 10 subjects. This study suggested that the combination between EFA and paclitaxel was safe and tolerated and had biologic activity [141].

Conclusion

Recent studies have shown that PPARγ is over-expressed in many tumor types, including those from breast, lung, pancreas, colon, glioblastoma, prostate, and DTCs and ATCs. These data suggest a role of PPARγ in tumor development and/or progression. PPARγ is emerging as a growth-limiting and differentiation-promoting factor, and it exerts a tumor suppressor role.

Moreover, naturally-occurring and synthetic PPARγ agonists promote growth inhibition and apoptosis. TZDs are synthetic agonists of PPARγ that were developed to treat type II diabetes. These compounds also display anticancer effects which appear mainly to be independent of their PPARγ agonist activity. Various preclinical and clinical studies strongly suggest a role for TZDs both alone and in combination with existing chemotherapeutic agents, for the treatment of cancer.

Differentiation therapy involves the use of agents with the ability to induce differentiation in cells that have lost this ability, i.e. cancer cells, targeting pathways capable of re-activating blocked terminal differentiation programs. PPARγ agonists have been shown to induce differentiation in solid tumors such as TCs and sarcomas.

However, emerging data suggest that chronic use of TZDs is associated with increased risk of adverse cardiovascular events. The exploration of newer PPARγ agonists can help in unveiling the underlying mechanisms of these drugs, providing new molecules that are able to treat cancer, without increasing the cardiovascular risk of neoplastic patients.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

[1] 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*(7220), 350-356.

[2] Jones, J.R.; Barrick, C.; Kim, K.A.; Lindner, J.; Blondeau, B.; Fujimoto, Y.; Shiota, M.; Kesterson, R.A.; Kahn, B.B.; Magnuson, M.A. Deletion of PPARgamma in adipose tissues of mice protects against high fat diet-induced obesity and insulin resistance. *Proc. Natl. Acad. Sci.USA,* **2005**, *102*(17), 6207-6212.

[3] Fajas, L.; Auboeuf, D.; Raspé, E.; Schoonjans, K.; Lefebvre, A.M.; Saladin, R.; Najib, J.; Laville, M.; Fruchart, J.C.; Deeb, S.; Vidal-Puig, A.; Flier, J.; Briggs, M.R.; Staels, B.; Vidal, H.; Auwerx, J. The organization, promoter analysis, and expression of the human PPARgamma gene. *J. Biol. Chem.,* **1997**, *272*(30), 18779-18789.

[4] Li, Y.; Qi, Y.; Huang, T.H.; Yamahara, J.; Roufogalis, B.D. Pomegranate flower: a unique traditional antidiabetic medicine with dual PPAR-alpha/-gamma activator properties. *Diabetes. Obes. Metab.*, **2008**, *10*(1), 10-17.

[5] Hamblin, M.; Chang, L.; Fan, Y.; Zhang, J.; Chen, Y.E. PPARs and the cardiovascular system. *Antioxid. Redox. Signal.*, **2009**, *11*(6), 1415-1452.

[6] Khateeb, J.; Gantman, A.; Kreitenberg, A.J.; Aviram, M.; Fuhrman, B. Paraoxonase 1 (PON1) expression in hepatocytes is upregulated by pomegranate polyphenols: a role for PPAR-gamma pathway. *Atherosclerosis*, **2010**, *208*(1), 119-125.

[7] Ferrari, S.M.; Fallahi, P.; Vita, R.; Antonelli, A.; Benvenga, S. Peroxisome Proliferator-Activated Receptor- γ in Thyroid Autoimmunity. *PPAR. Res.*, **2015**, *2015*, 232818.

[8] Wei, S.; Yang, J.; Lee, S.L.; Kulp, S.K.; Chen, C.S. PPARgamma-independent antitumor effects of thiazolidinediones. *Cancer Lett*., **2009**, *276*(2), 119-124.

[9] Kroll, T.G.; Sarraf, P.; Pecciarini, L.; Chen, C.J.; Mueller, E.; Spiegelman, B.M.; Fletcher, J.A. PAX8-PPARgamma1 fusion oncogene in human thyroid carcinoma [corrected]. *Science*, **2000**, *289*(5483), 1357-1360.

[10] Santini, E.; Fallahi, P.; Ferrari, S.M.; Masoni, A.; Antonelli, A.; Ferrannini, E. Effect of PPAR-gamma activation and inhibition on glucose-stimulated insulin release in INS-1e cells. *Diabetes*, **2004**, *53* Suppl 3:S79-83.

[11] Antonelli, A.; Ferrari, S.M.; Frascerra, S.; Pupilli, C.; Mancusi, C.; Metelli, M.R.; Orlando, C.; Ferrannini, E.; Fallahi, P. CXCL9 and CXCL11 chemokines modulation by peroxisome proliferator-activated receptor-alpha agonists secretion in Graves' and normal thyrocytes. *J. Clin. Endocrinol. Metab.*, **2010**, *95*(12), E413-420.

[12] Antonelli, A.; Ferrari, S.M.; Fallahi, P.; Ghiri, E.; Crescioli, C.; Romagnani, P.; Vitti, P.; Serio, M.; Ferrannini, E. Interferon-alpha, -beta and -gamma induce CXCL9 and CXCL10 secretion by human thyrocytes: modulation by peroxisome proliferator-activated receptor-gamma agonists. *Cytokine*, **2010**, *50*(3), 260-267.

[13] Atanasov, A.G.; Wang, J.N.; Gu, S.P.; Bu, J.; Kramer, M.P.; Baumgartner, L.; Fakhrudin, N.; Ladurner, A.; Malainer, C.; Vuorinen, A.; Noha, S.M.; Schwaiger, S.; Rollinger, J.M.; Schuster, D.; Stuppner, H.; Dirsch, V.M.; Heiss, E.H. Honokiol: a non-adipogenic PPARγ agonist from nature. *Biochim. Biophys. Acta.,* **2013**, *1830*(10), 4813-4819.

[14] Atanasov, A.G.; Blunder, M.; Fakhrudin, N.; Liu, X.; Noha, S.M.; Malainer, C.; Kramer, M.P.; Cocic, A.; Kunert, O.; Schinkovitz, A.; Heiss, E.H.; Schuster, D.; Dirsch, V.M.; Bauer, R. Polyacetylenes from Notopterygium incisum--new selective partial agonists of peroxisome proliferator-activated receptor-gamma. *PLoS One*, **2013**, *8*(4), e61755.

[15] Home, P.D.; Pocock, S.J.; Beck-Nielsen, H.; Curtis, P.S.; Gomis, R.; Hanefeld, M.; Jones, N.P.; Komajda, M.; McMurray, J.J.; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*, **2009**, *373*(9681), 2125-2135.

[16] Monami, M.; Lamanna, C.; Marchionni, N.; Mannucci, E. Rosiglitazone and risk of cancer: a meta-analysis of randomized clinical trials. *Diabetes Care,* **2008**, *31*(7), 1455-1460.

[17] Colmers, I.N.; Bowker, S.L.; Johnson, J.A. Thiazolidinedione use and cancer incidence in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Metab.*, **2012**, *38*(6), 475-484.

[18] Lin, H.C.; Hsu, Y.T.; Kachingwe, B.H.; Hsu, C.Y.; Uang, Y.S.; Wang, L.H. Dose effect of thiazolidinedione on cancer risk in type 2 diabetes mellitus patients: a six-year population-based cohort study. *J. Clin. Pharm. Ther.,* **2014**, *39*(4), 354-360.
[19] Mueller, E.; Smith, M.; Sarraf, P.; Kroll, T.; Aiyer, A.; Kaufman, D.S.; Oh, W.; Demetri, G.; Figg, W.D.; Zhou, X.P.; Eng, C.; Spiegelman, B.M.; Kantoff, P.W. Effects of ligand activation of peroxisome proliferator-activated receptor gamma in human prostate cancer. *Proc. Natl. Acad. Sci. USA,* **2000**, *97*(20), 10990-10995.
[20] Kopelovich, L.; Fay, J.R.; Glazer, R.I.; Crowell, J.A. Peroxisome proliferator-activated receptor modulators as potential chemopreventive agents. *Mol. Cancer Ther.,* **2002**, *1*(5), 357-363.
[21] Koeffler, H.P. Peroxisome proliferator-activated receptor gamma and cancers. *Clin. Cancer Res.,* **2003**, *9*(1), 1-9.
[22] Grommes, C.; Landreth, G.E.; Heneka, M.T. Antineoplastic effects of peroxisome proliferator-activated receptor gamma agonists. *Lancet Oncol.,* **2004**, *5*(7), 419-429.
[23] Jiang, M.; Shappell, S.B.; Hayward, S.W. Approaches to understanding the importance and clinical implications of peroxisome proliferator-activated receptor gamma (PPARgamma) signaling in prostate cancer. *J. Cell. Biochem.,* **2004**, *91*(3), 513-527.
[24] Weng, J.R.; Chen, C.Y.; Pinzone, J.J.; Ringel, M.D.; Chen C.S. Beyond peroxisome proliferator-activated receptor gamma signaling: the multi-facets of the antitumor effect of thiazolidinediones. *Endocr. Relat. Cancer,* **2006**, *13*(2), 401-413.
[25] Demetri, G.D.; Fletcher, C.D.; Mueller, E.; Sarraf, P.; Naujoks, R.; Campbell, N.; Spiegelman, B.M.; Singer, S. Induction of solid tumor differentiation by the peroxisome proliferator-activated receptor-gamma ligand troglitazone in patients with liposarcoma. *Proc. Natl. Acad. Sci. U S A,* **1999**, *96*(7), 3951-3956.
[26] Hisatake, J.I.; Ikezoe, T.; Carey, M.; Holden, S.; Tomoyasu, S.; Koeffler, H.P. Down-Regulation of prostate-specific antigen expression by ligands for peroxisome proliferator-activated receptor gamma in human prostate cancer. *Cancer Res.,* **2000**, *60*(19), 5494-5498.
[27] Gupta, R.A.; Brockman, J.A.; Sarraf, P.; Willson, T.M.; DuBois, R.N. Target genes of peroxisome proliferator-activated receptor gamma in colorectal cancer cells. *J. Biol. Chem.*, **2001**; *276*(32), 29681-29687.
[28] Shiau, C.W.; Yang, C.C.; Kulp, S.K.; Chen, K.F.; Chen, C.S.; Huang, J.W.; Chen, C.S. Thiazolidenediones mediate apoptosis in prostate cancer cells in part through inhibition of Bcl-xL/Bcl-2 functions independently of PPARgamma. *Cancer Res.*, **2005**, *65*(4), 1561-1569.
[29] Huang, J.W.; Shiau, C.W.; Yang, Y.T.; Kulp, S.K.; Chen, K.F.; Brueggemeier, R.W.; Shapiro, C.L.; Chen, C.S. Peroxisome proliferator-activated receptor gamma-independent ablation of cyclin D1 by thiazolidinediones and their derivatives in breast cancer cells. *Mol. Pharmacol.,* **2005**, *67*(4), 1342-1348.
[30] Liu, H.; Zang, C.; Fenner, M.H.; Liu, D.; Possinger, K.; Koeffler, H.P.; Elstner, E. Growth inhibition and apoptosis in human Philadelphia chromosome-positive lymphoblastic leukemia cell lines by treatment with the dual PPARalpha/gamma ligand TZD18. *Blood*, **2006**, *107*(9), 3683-3692.
[31] Plissonnier, M.L.; Fauconnet, S.; Bittard, H.; Lascombe, I. Insights on distinct pathways of thiazolidinediones (PPARgamma ligand)-promoted apoptosis in TRAIL- sensitive or -resistant malignant urothelial cells. *Int. J. Cancer*, **2010**, *127*(8), 1769-1784.
[32] Plissonnier, M.L.; Fauconnet, S.; Bittard, H.; Lascombe, I. The antidiabetic drug ciglitazone induces high grade bladder cancer cells apoptosis through the up-regulation of TRAIL. *PLoS. One*, **2011**, *6*(12), e28354.
[33] Colin-Cassin, C.; Yao, X.; Cerella, C.; Chbicheb, S.; Kuntz, S.; Mazerbourg, S.; Boisbrun, M.; Chapleur, Y.; Diederich, M.; Flament, S.; Grillier-Vuissoz, I. PPARgamma-inactive Δ2-troglitazone independently triggers ER stress and apoptosis in breast cancer cells. *Mol. Carcinog.,* **2013**, *54*(5), 393-404.
[34] Zang, C.; Liu, H.; Bertz, J.; Possinger, K.; Koeffler, H.P.; Elstner, E.; Eucker, J. Induction of endoplasmic reticulum stress response by TZD18, a novel dual ligand for peroxisome proliferator-activated receptor alpha/gamma, in human breast cancer cells. *Mol. Cancer. Ther.,* **2009**, *8*(8), 2296-2307.
[35] Fujita, M.; Yagami, T.; Fujio, M.; Tohji, C.; Takase, K.; Yamamoto, Y.; Sawada, K.; Yamamori, M.; Okamura, N. Cytotoxicity of troglitazone through PPARγ-independent pathway and p38 MAPK pathway in renal cell carcinoma. *Cancer Lett.,* **2011**, *312*(2), 219-227.
[36] Mieczkowska, A.; Baslé, M.F.; Chappard, D.; Mabilleau, G. Thiazolidinediones induce osteocyte apoptosis by a G protein-coupled receptor 40-dependent mechanism. *J. Biol. Chem.*, **2012**, *287*(28), 23517-23526.

[37] Wang, D.; Chu, P.C.; Yang, C.N.; Yan, R.; Chuang, Y.C.; Kulp, S.K.; Chen, C.S. Development of a novel

class of glucose transporter inhibitors. *J. Med. Chem.,* **2012**, *55*(8), 3827-3836.
[38] Lee, K.H.; Hsu, E.C.; Guh, J.H.; Yang, H.C.; Wang, D.; Kulp, S.K.; Shapiro, C.L.; Chen, C.S. Targeting energy metabolic and oncogenic signaling pathways in triple-negative breast cancer by a novel adenosine monophosphate-activated protein kinase (AMPK) activator. *J. Biol. Chem.*, **2011**, *286*(45), 39247-39258.
[39] Lu, M.; Kwan, T.; Yu, C.; Chen, F.; Freedman, B.; Schafer, J.M.; Lee, E.J.; Jameson, J.L.; Jordan, V.C.; Cryns, V.L. Peroxisome proliferator-activated receptor gamma agonists promote TRAIL-induced apoptosis by reducing survivin levels via cyclin D3 repression and cell cycle arrest. *J. Biol. Chem.*, **2005**, *280*(8), 6742-6751.
[40] Schultze, K.; Böck, B.; Eckert, A.; Oevermann, L.; Ramacher, D.; Wiestler, O.; Roth, W. Troglitazone sensitizes tumor cells to TRAIL-induced apoptosis via down-regulation of FLIP and Survivin. *Apoptosis,* **2006**, *11*(9), 1503-1512.
[41] 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*(1), 99-106.
[42] Kim, Y.H.; Jung, E.M.; Lee, T.J.; Kim, S.H.; Choi, Y.H.; Park, J.W.; Park, J.W.; Choi, K.S.; Kwon, T.K. Rosiglitazone promotes tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis by reactive oxygen species-mediated up-regulation of death receptor 5 and down-regulation of c-FLIP. *Free Radic. Biol. Med.,* **2008**, *44*(6), 1055-1068.
[43] Kuntz, S.; Mazerbourg, S.; Boisbrun, M.; Cerella, C.; Diederich, M.; Grillier-Vuissoz, I.; Flament, S. Energy restriction mimetic agents to target cancer cells: comparison between 2-deoxyglucose and thiazolidinediones. *Biochem. Pharmacol.,* **2014,** *92*(1), 102-111.
[44] Jin, X.; Yuan, D.; Chen, X.; Jiang, X. [AMP-activated protein kinase-alpha is involved in the autophagy and apoptosis caused by troglitazone]. *Wei Sheng Wu Xue Bao.*, **2012**, *52*(7), 840-849.
[45] Yan, J.; Yang, H.; Wang, G.; Sun, L.; Zhou, Y.; Guo, Y.; Xi, Z.; Jiang, X. Autophagy augmented by troglitazone is independent of EGFR transactivation and correlated with AMP-activated protein kinase signaling. *Autophagy,* **2010**, *6*(1), 67-73.
[46] Zhou, J.; Zhang, W.; Liang, B.; Casimiro, M.C.; Whitaker-Menezes, D.; Wang, M.; Lisanti, M.P.; Lanza-Jacoby, S.; Pestell, R.G.; Wang, C. PPARgamma activation induces autophagy in breast cancer cells. *Int. J. Biochem. Cell. Biol.*, **2009**, *41*(11), 2334-2342.
[47] Cerquetti, L.; Sampaoli, C.; Amendola, D.; Bucci, B.; Masuelli, L.; Marchese, R.; Misiti, S.; De Venanzi, A.; Poggi, M.; Toscano, V.; Stigliano, A. Rosiglitazone induces autophagy in H295R and cell cycle deregulation in SW13 adrenocortical cancer cells. *Exp. Cell. Res.,* **2011**, *317*(10), 1397-1410.
[48] Sohn, Y.S.; Tamir, S.; Song, L.; Michaeli, D.; Matouk, I.; Conlan, A.R.; Harir, Y.; Holt, S.H.; Shulaev, V.; Paddock, M.L.; Hochberg, A.; Cabanchick, I.Z.; Onuchic, J.N.; Jennings, P.A.; Nechushtai, R.; Mittler, R. NAF-1 and mitoNEET are central to human breast cancer proliferation by maintaining mitochondrial homeostasis and promoting tumor growth. *Proc. Natl. Acad. Sci. U S A*, **2013**, *110*(36), 14676-14681.
[49] Tamir, S.; Zuris, J.A.; Agranat, L.; Lipper, C.H.; Conlan, A.R.; Michaeli, D.; Harir, Y.; Paddock, M.L.; Mittler, R.; Cabantchik, Z.I.; Jennings, P.A.; Nechushtai, R. Nutrient-deprivation autophagy factor-1 (NAF-1): biochemical properties of a novel cellular target for anti-diabetic drugs. *PLoS. One*, **2013**, *8*(5), e61202.
[50] Geldenhuys, W.J.; Funk, M.O.; Awale, P.S.; Lin, L.; Carroll, R.T. A novel binding assay identifies high affinity ligands to the rosiglitazone binding site of mitoNEET. *Bioorg. Med. Chem. Lett.,* **2011**, *21*(18), 5498-5501.
[51] Wiley, S.E.; Murphy, A.N.; Ross, S.A.; van der Geer, P.; Dixon, J.E. MitoNEET is an iron-containing outer mitochondrial membrane protein that regulates oxidative capacity. *Proc. Natl. Acad. Sci. U S A,* **2007**, *104*(13), 5318-5323.
[52] Guh, J.H.; Chang, W.L.; Yang, J.; Lee, S.L.; Wei, S.; Wang, D.; Kulp, S.K.; Chen, C.S. Development of novel adenosine monophosphate-activated protein kinase activators. *J. Med. Chem.,* **2010**, *53*(6), 2552-2561.
[53] Wei, S.; Yang, H.C.; Chuang, H.C.; Yang, J.; Kulp, S.K.; Lu, P.J.; Lai, M.D.; Chen, C.S. A novel mechanism by which thiazolidinediones facilitate the proteasomal degradation of cyclin D1 in cancer cells. *J. Biol. Chem.*, **2008**, *283*(39), 26759-26770.
[54] Wei, S.; Lin, L.F.; Yang, C.C.; Wang, Y.C.; Chang, G.D.; Chen, H.; Chen, C.S. Thiazolidinediones modulate the expression of beta-catenin and other cell-cycle regulatory proteins by targeting the F-box proteins of Skp1-Cul1-F-box protein E3 ubiquitin ligase independently of peroxisome proliferator-activated receptor gamma. *Mol. Pharmacol.,* **2007**, *72*(3), 725-733.

[55] Arafa, el-S.A.; Abdelazeem, A.H.; Arab, H.H.; Omar, H.A. OSU-CG5, a novel energy restriction mimetic agent, targets human colorectal cancer cells in vitro. *Acta. Pharmacol. Sin.,* **2014**, *35*(3), 394-400.
[56] Lecomte, J.; Flament, S.; Salamone, S.; Boisbrun, M.; Mazerbourg, S.; Chapleur, Y.; Grillier-Vuissoz, I. Disruption of ERalpha signalling pathway by PPARgamma agonists: evidences of PPARgamma-independent events in two hormone-dependent breast cancer cell lines. *Breast Cancer Res. Treat.*, **2008**, *112*(3), 437-451.
[57] Colin, C.; Salamone, S.; Grillier-Vuissoz, I.; Boisbrun, M.; Kuntz, S.; Lecomte, J.; Chapleur, Y.; Flament, S. New troglitazone derivatives devoid of PPARγ agonist activity display an increased antiproliferative effect in both hormone-dependent and hormone-independent breast cancer cell lines. *Breast Cancer Res. Treat.*, **2010**, *124*(1), 101-110.
[58] Salamone, S.; Colin, C.; Grillier-Vuissoz, I.; Kuntz, S.; Mazerbourg, S.; Flament, S.; Martin, H.; Richert, L.; Chapleur, Y.; Boisbrun, M. Synthesis of new troglitazone derivatives: anti-proliferative activity in breast cancer cell lines and preliminary toxicological study. *Eur. J. Med. Chem.,* **2012**, *51*, 206-215.
[59] Yang, J.; Wei, S.; Wang, D.S.; Wang, Y.C.; Kulp, S.K.; Chen, C.S. Pharmacological exploitation of the peroxisome proliferator-activated receptor gamma agonist ciglitazone to develop a novel class of androgen receptor-ablative agents. *J. Med. Chem.*, **2008**, *51*(7), 2100-2107.
[60] Berman-Booty, L.D.; Chu, P.C.; Thomas-Ahner, J.M.; Bolon, B.; Wang, D.; Yang, T.; Clinton, S.K.; Kulp, S.K.; Chen, C.S. Suppression of prostate epithelial proliferation and intraprostatic progrowth signaling in transgenic mice by a new energy restriction-mimetic agent. *Cancer Prev. Res. (Phila).,* **2013**, *6*(3), 232-241.
[61] Nakles, R.E.; Kallakury, B.V.; Furth, P.A. The PPAR-γ agonist efatutazone increases the spectrum of well-differentiated mammary cancer subtypes initiated by loss of full-length BRCA1 in association with TP53 haploinsufficiency. *Am. J. Pathol.*, **2013**, *182*(6), 1976-1985.
[62] Shimazaki, N.; Togashi, N.; Hanai, M.; Isoyama, T.; Wada, K.; Fujita, T.; Fujiwara, K.; Kurakata, S. Anti-tumour activity of CS-7017, a selective peroxisome proliferator-activated receptor gamma agonist of thiazolidinedione class, in human tumour xenografts and a syngeneic tumour implant model. *Eur. J. Cancer*, **2008**, *44*(12), 1734-1743.
[63] Fröhlich, E.; Wahl, R. Chemotherapy and chemoprevention by thiazolidinediones. *Biomed. Res. Int.*, **2015**, *2015*:845340.
[64] Debrock, G.; Vanhentenrijk, V.; Sciot, R.; Debiec-Rychter, M.; Oyen, R.; Van Oosterom, A. A phase II trial with rosiglitazone in liposarcoma patients. *Br. J. Cancer*, **2003**, *89*(8), 1409-1412.
[65] Dai, Y.; Wang, W.H. Peroxisome proliferator-activated receptor γ and colorectal cancer. *World J. Gastrointest. Oncol.*, **2010**, *2*(3), 159-164.
[66] Pancione, M.; Forte, N.; Sabatino, L.; Tomaselli, E.; Parente, D.; Febbraro, A.; Colantuoni, V. Reduced beta-catenin and peroxisome proliferator-activated receptor-gamma expression levels are associated with colorectal cancer metastatic progression: correlation with tumor-associated macrophages, cyclooxygenase 2, and patient outcome. *Hum. Pathol.*, **2009**, *40*(5), 714-725.
[67] Theocharis, S.; Giaginis, C.; Parasi, A.; Margeli, A.; Kakisis, J.; Agapitos, E.; Kouraklis, G. Expression of peroxisome proliferator-activated receptor-gamma in colon cancer: correlation with histopathological parameters, cell cycle-related molecules, and patients' survival. *Dig. Dis. Sci.*, **2007**, *52*(9), 2305-2311.
[68] Gustafsson, A.; Hansson, E.; Kressner, U.; Nordgren, S.; Andersson, M.; Wang, W.; Lönnroth, C.; Lundholm, K. EP1-4 subtype, COX and PPAR gamma receptor expression in colorectal cancer in prediction of disease-specific mortality. *Int. J. Cancer*, **2007**, *121*(2), 232-240.
[69] Osawa, E.; Nakajima, A.; Wada, K.; Ishimine, S.; Fujisawa, N.; Kawamori, T.; Matsuhashi, N.; Kadowaki, T.; Ochiai, M.; Sekihara, H.; Nakagama, H. Peroxisome proliferator-activated receptor gamma ligands suppress colon carcinogenesis induced by azoxymethane in mice. *Gastroenterology*, **2003**, *124*(2), 361-367.
[70] Yoshizumi, T.; Ohta, T.; Ninomiya, I.; Terada, I.; Fushida, S.; Fujimura, T.; Nishimura, G.; Shimizu, K.; Yi, S.; Miwa, K. Thiazolidinedione, a peroxisome proliferator-activated receptor-gamma ligand, inhibits growth and metastasis of HT-29 human colon cancer cells through differentiation-promoting effects. *Int. J. Oncol.*, **2004**, *25*(3), 631-639.
[71] Choi, I.K.; Kim, Y.H.; Kim, J.S.; Seo, J.H. PPAR-gamma ligand promotes the growth of APC-mutated HT-29 human colon cancer cells in vitro and in vivo. *Invest. New Drugs*, **2008**, *26*(3), 283-288.
[72] Tsukahara, T.; Haniu, H. Peroxisome proliferator-activated receptor gamma overexpression suppresses proliferation of human colon cancer cells. *Biochem. Biophys. Res. Commun.*, **2012**, *424*(3), 524-529.
[73] Kulke, M.H.; Demetri, G.D.; Sharpless, N.E.; Ryan, D.P.; Shivdasani, R.; Clark, J.S.; Spiegelman, B.M.; Kim, H.; Mayer, R.J.; Fuchs, C.S. A phase II study of troglitazone, an activator of the PPARgamma

receptor, in patients with chemotherapy-resistant metastatic colorectal cancer. *Cancer J.*, **2002**, *8*(5), 395-399.
[74] Theocharis, S.; Kanelli, H.; Politi, E.; Margeli, A.; Karkandaris, C.; Philippides, T.; Koutselinis, A. Expression of peroxisome proliferator activated receptor-gamma in non-small cell lung carcinoma: correlation with histological type and grade. *Lung Cancer*, **2002**, *36*(3), 249-255.
[75] Sasaki, H.; Tanahashi, M.; Yukiue, H.; Moiriyama, S.; Kobayashi, Y.; Nakashima, Y.; Kaji, M.; Kiriyama, M.; Fukai, I.; Yamakawa, Y.; Fujii, Y. Decreased perioxisome proliferator-activated receptor gamma gene expression was correlated with poor prognosis in patients with lung cancer. *Lung Cancer*, **2002**, *36*(1), 71-76.
[76] Lyon, C.M.; Klinge, D.M.; Do, K.C.; Grimes, M.J.; Thomas, C.L.; Damiani, L.A.; March, T.H.; Stidley, C.A.; Belinsky, S.A. Rosiglitazone prevents the progression of preinvasive lung cancer in a murine model. *Carcinogenesis*, **2009**, 30(12), 2095-2099.
[77] Jiang, W.G.; Douglas-Jones, A.; Mansel, R.E. Expression of peroxisome-proliferator activated receptor-gamma (PPARgamma) and the PPARgamma co-activator, PGC-1, in human breast cancer correlates with clinical outcomes. *Int. J. Cancer*, **2003**, *106*(5), 752-757.
[78] Magenta, G.; Borenstein, X.; Rolando, R.; Jasnis, M.A. Rosiglitazone inhibits metastasis development of a murine mammary tumor cell line LMM3. *BMC Cancer,* **2008**, *8*, 47.
[79] Bojková, B.; Garajová, M.; Kajo, K.; Péc, M.; Kubatka, P.; Kassayová, M.; Kisková, T., Orendás, P.; Ahlersová, E.; Ahlers, I. Pioglitazone in chemically induced mammary carcinogenesis in rats. *Eur. J. Cancer Prev.*, **2010**, *19*(5), 379-384.
[80] Burstein, H.J.; Demetri, G.D.; Mueller, E.; Sarraf, P.; Spiegelman, B.M.; Winer, E.P. Use of the peroxisome proliferator-activated receptor (PPAR) gamma ligand troglitazone as treatment for refractory breast cancer: a phase II study. *Breast Cancer Res. Treat.*, **2003**, *79*(3), 391-397.
[81] Yee, L.D.; Williams, N.; Wen, P.; Young, D.C.; Lester, J.; Johnson, M.V.; Farrar, W.B.; Walker, M.J.; Povoski, S.P.; Suster, S.; Eng, C. Pilot study of rosiglitazone therapy in women with breast cancer: effects of short-term therapy on tumor tissue and serum markers. *Clin. Cancer Res.*, **2007**, *13*(1), 246-252.
[82] Nakamura, Y.; Suzuki, T.; Sugawara, A.; Arai, Y.; Sasano, H. Peroxisome proliferator-activated receptor gamma in human prostate carcinoma. *Pathol. Int.*, **2009**, *59*(5), 288-293.
[83] Annicotte, J.S.; Iankova, I.; Miard, S.; Fritz, V.; Sarruf, D.; Abella, A.; Berthe, M.L.; Noël, D.; Pillon, A.; Iborra, F.; Dubus, P.; Maudelonde, T.; Culine, S.; Fajas, L. 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.
[84] Kato, M.; Nagaya, T.; Fujieda, M.; Saito, K.; Yoshida, J.; Seo, H. Expression of PPARgamma and its ligand-dependent growth inhibition in human brain tumor cell lines. *Jpn. J. Cancer Res.*, **2002**, *93*(6), 660-666.
[85] Grommes, C.; Conway, D.S.; Alshekhlee, A.; Barnholtz-Sloan, J.S. Inverse association of PPARγ agonists use and high grade glioma development. *J. Neurooncol.*, **2010**, *100*(2), 233-239.
[86] Grommes, C.; Karlo, J.C.; Caprariello, A.; Blankenship, D.; Dechant, A.; Landreth, G.E. The PPARγ agonist pioglitazone crosses the blood-brain barrier and reduces tumor growth in a human xenograft model. *Cancer Chemother. Pharmacol.*, **2013**, *71*(4), 929-936.
[87] Hau, P.; Kunz-Schughart, L.; Bogdahn, U.; Baumgart, U.; Hirschmann, B.; Weimann, E,.; Muhleisen, H.; Ruemmele, P.; Steinbrecher, A.; Reichle, A. Low-dose chemotherapy in combination with COX-2 inhibitors and PPAR-gamma agonists in recurrent high-grade gliomas - a phase II study. *Oncology*, **2007**, *73*(1-2), 21-25.
[88] Meyer, S.; Vogt, T.; Landthaler, M.; Berand, A.; Reichle, A.; Bataille, F.; Marx, A.H.; Menz, A.; Hartmann, A.; Kunz-Schughart, L.A.; Wild, P.J. Cyclooxygenase 2 (COX2) and Peroxisome Proliferator-Activated Receptor Gamma (PPARG) Are Stage-Dependent Prognostic Markers of Malignant Melanoma. *PPAR. Res.*, **2009**, *2009*, 848645.
[89] Ferrara, A.; Lewis, J.D.; Quesenberry, C.P. Jr.; Peng, T.; Strom, B.L.; Van Den Eeden, S.K.; Ehrlich, S.F.; Habel, L.A. Cohort study of pioglitazone and cancer incidence in patients with diabetes. *Diabetes Care*, **2011**, *34*(4), 923-929.
[90] Botton, T.; Puissant, A.; Bahadoran, P.; Annicotte, J.S.; Fajas, L.; Ortonne, J.P.; Gozzerino, G.; Zamoum, T.; Tartare-Deckert, S.; Bertolotto, C.; Ballotti, R.; Rocchi, S. In vitro and in vivo anti-melanoma effects of ciglitazone. *J. Invest. Dermatol.,* **2009**, *129*(5), 1208-1218.
[91] Ondrey, F. Peroxisome proliferator-activated receptor gamma pathway targeting in carcinogenesis: implications for chemoprevention. *Clin. Cancer Res.*, **2009**, *15*(1), 2-8.

[92] Omur, O.; Baran, Y. An update on molecular biology of thyroid cancers. *Crit. Rev. Oncol. Hematol.,* **2014**, *90*(3), 233-252.
[93] Li, N.; Du, X.L.; Reitzel, L.R.; Xu, L.; Sturgis, E.M. Impact of enhanced detection on the increase in thyroid cancer incidence in the United States: review of incidence trends by socioeconomic status within the surveillance, epidemiology, and end results registry, 1980-2008. *Thyroid*, **2013**, *23*(1), 103-110.
[94] Schlumberger, M.; Chevillard, S.; Ory, K.; Dupuy, C.; Le Guen, B.; de Vathaire, F. [Thyroid cancer following exposure to ionising radiation]. *Cancer Radiother.,* **2011**, *15*(5), 394-399.
[95] Antonelli, A.; Miccoli, P.; Derzhitski, V.E.; Panasiuk, G.; Solovieva, N.; Baschieri, L. Epidemiologic and clinical evaluation of thyroid cancer in children from the Gomel region (Belarus). *World J. Surg.,* **1996**, *20*(7), 867-871.
[96] Zimmermann, M.B.; Boelaert, K. Iodine deficiency and thyroid disorders. *Lancet Diabetes Endocrinol.,* **2015**, *3*(4), 286-295.
[97] Jankovic, B.; Le, K.T.; Hershman, J.M. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? *J. Clin. Endocrinol. Metab.,* **2013**, *98*(2), 474-482.
[98] Antonelli, A.; Delle Sedie, A.; Fallahi, P.; Ferrari, S.M., Maccheroni, M.; Ferrannini, E.; Bombardieri, S.; Riente, L. High prevalence of thyroid autoimmunity and hypothyroidism in patients with psoriatic arthritis. *J. Rheumatol.,* **2006**, *33*(10), 2026-2028.
[99] Antonelli, A.; Ferri, C.; Fallahi, P.; Pampana, A.; Ferrari, S.M.; Barani, L.; Marchi, S.; Ferrannini, E. Thyroid cancer in HCV-related chronic hepatitis patients: a case-control study. *Thyroid,* **2007**, *17*(5), 447-451.
[100] Antonelli, A.; Ferri, C.; Fallahi, P.; Nesti, C.; Zignego, A.L.; Maccheroni, M. Thyroid cancer in HCV-related mixed cryoglobulinemia patients. *Clin. Exp. Rheumatol.,* **2002**, *20*(5), 693-696.
[101] Antonelli, A.; Ferri, C.; Fallahi, P.; Cazzato, M.; Ferrari, S.M.; Sebastiani, M.; Ferrannini, E. Clinical and subclinical autoimmune thyroid disorders in systemic sclerosis. *Eur. J. Endocrinol.,* **2007**, *156*(4), 431-437.
[102] Eustatia-Rutten, C.F.; Corssmit, E.P.; Biermasz, N.R.; Pereira, A.M.; Romijn, J.A.; Smit, J.W. Survival and death causes in differentiated thyroid carcinoma. *J. Clin. Endocrinol. Metab.,* **2006**, *91*(1), 313-319.
[103] Durante, C.; Haddy, N.; Baudin, E.; Leboulleux, S.; Hartl, D.; Travagli, J.P.; Caillou, B.; Ricard, M.; Lumbroso, J.D.; De Vathaire, F.; Schlumberger, M. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J. Clin. Endocrinol. Metab.*, **2006**, *91*(8), 2892-2899.
[104] Dohán, O.; De la Vieja, A.; Paroder, V.; Riedel, C.; Artani, M.; Reed, M.; Ginter, C.S.; Carrasco, N. The sodium/iodide Symporter (NIS): characterization, regulation, and medical significance. *Endocr. Rev.*, **2003**, *24*(1), 48-77.
[105] Schlumberger, M.J. Diagnostic follow-up of well-differentiated thyroid carcinoma: historical perspective and current status. *J. Endocrinol. Invest.*, **1999**, *22*(11), 3-7.
[106] Carling, T.; Udelsman, R. Thyroid Tumors. In: *Cancer: Principles and Practice of Oncology;* DeVita, V.T.; Hellman, S.; Rosenberg, S.A.; eds. DeVita, Hellman, and Rosenberg's. 9th ed.; Lippincott Williams & Wilkins: Philadelphia, **2011**.
[107] Versari, A.; Sollini, M.; Frasoldati, A.; Fraternali, A.; Filice, A.; Froio, A.; Asti, M.; Fioroni, F.; Cremonini, N.; Putzer, D.; Erba, P.A. Differentiated thyroid cancer: a new perspective with radiolabeled somatostatin analogues for imaging and treatment of patients. *Thyroid*, **2014**, *24*(4), 715-726.
[108] Martelli, M.L.; Iuliano, R.; Le Pera, I.; Sama', I.; Monaco, C.; Cammarota, S.; Kroll, T.; Chiariotti, L.; Santoro, M.; Fusco, A. Inhibitory effects of peroxisome proliferator-activated receptor gamma on thyroid carcinoma cell growth. *J. Clin. Endocrinol. Metab.* **2002**, *87*(10), 4728-4735.
[109] Fröhlich, E.; Brossart, P.; Wahl, R. Induction of iodide uptake in transformed thyrocytes: a compound screening in cell lines. *Eur. J. Nucl. Med. Mol. Imaging*, **2009,** *36*(5), 780-790.
[110] Park, J.W.; Zarnegar, R.; Kanauchi, H.; Wong, M.G.; Hyun, W.C.; Ginzinger, D.G.; Lobo, M.; Cotter, P.; Duh, Q.Y.; Clark, O.H. Troglitazone, the peroxisome proliferator-activated receptor-gamma agonist, induces antiproliferation and redifferentiation in human thyroid cancer cell lines. *Thyroid*, **2005**, *15*(3), 222-231.
[111] Fröhlich, E.; Machicao, F.; Wahl, R. Action of thiazolidinediones on differentiation, proliferation and apoptosis of normal and transformed thyrocytes in culture. *Endocr. Relat. Cancer*, **2005**, *12*(2), 291-303.
[112] Dobson, M.E.; Diallo-Krou, E.; Grachtchouk, V.; Yu, J.; Colby, L.A.; Wilkinson, J.E.; Giordano, T.J.; Koenig, R.J. Pioglitazone induces a proadipogenic antitumor response in mice with PAX8-PPARgamma fusion protein thyroid carcinoma. *Endocrinology*, **2011**, *152*(11), 4455-4465.
[113] Kato, Y.; Ying, H.; Zhao, Y.; Furuya, F.; Araki, O.; Willingham, M.C.; Cheng, S.Y. PPARgamma

insufficiency promotes follicular thyroid carcinogenesis via activation of the nuclear factor-kappaB signaling pathway. *Oncogene*, **2006**, *25*(19), 2736-2747.

[114] Antonelli, A.; Ferrari, S.M.; Fallahi, P.; Frascerra, S.; Piaggi, S.; Gelmini, S.; Lupi, C.; Minuto, M.; Berti, P.; Benvenga, S.; Basolo, F.; Orlando, C.; Miccoli, P. Dysregulation of secretion of CXC alpha-chemokine CXCL10 in papillary thyroid cancer: modulation by peroxisome proliferator-activated receptor-gamma agonists. *Endocr. Relat. Cancer.*, **2009**, *16*(4), 1299-1311.

[115] Antonelli, A.; Ferrari, S.M.; Corrado, A.; Di Domenicantonio, A.; Fallahi, P. Autoimmune thyroid disorders. *Autoimmun. Rev.,* **2015**, *14*(2), 174-180.

[116] Rosenbaum-Krumme, S.J.; Bockisch, A.; Nagarajah, J. Pioglitazone therapy in progressive differentiated thyroid carcinoma. *Nuklearmedizin*, **2012,** *51*(4), 111-115.

[117] Elola, M.; Yoldi, A.; Emparanza, J.I.; Matteucci, T.; Bilbao, I.; Goena, M. [Redifferentiation therapy with rosiglitazone in a case of differentiated thyroid cancer with pulmonary metastases and absence of radioiodine uptake]. *Rev. Esp. Med. Nucl.* **2011**, *30*(4), 241-243.

[118] Elias, A.N.; Lizotte, P. Enhanced radioiodine uptake in a patient with poorly differentiated papillary thyroid cancer after treatment with rosiglitazone. *Clin. Nucl. Med.*, **2006,** *31*(9), 517-519.

[119] Philips, J.C.; Petite, C.; Willi, J.P.; Buchegger, F.; Meier, C.A. Effect of peroxisome proliferator-activated receptor gamma agonist, rosiglitazone, on dedifferentiated thyroid cancers. *Nucl. Med. Commun.*, **2004**, *25*(12), 1183-1186.

[120] Kebebew, E.; Peng, M.; Reiff, E.; Treseler, P.; Woeber, K.A.; Clark, O.H.; Greenspan, F.S.; Lindsay, S.; Duh, Q.Y.; Morita, E. A phase II trial of rosiglitazone in patients with thyroglobulin-positive and radioiodine-negative differentiated thyroid cancer. *Surgery*, **2006**, *140*(6), 960-967.

[121] Tepmongkol, S.; Keelawat, S.; Honsawek S.; Ruangvejvorachai, P. Rosiglitazone effect on radioiodine uptake in thyroid carcinoma patients with high thyroglobulin but negative total body scan: a correlation with the expression of peroxisome proliferator-activated receptor-gamma. *Thyroid*, **2008**, *18*(7), 697-704.

[122] Kebebew, E.; Lindsay, S.; Clark, O.H.; Woeber, K.A.; Hawkins, R.; Greenspan, F.S. Results of rosiglitazone therapy in patients with thyroglobulin-positive and radioiodine-negative advanced differentiated thyroid cancer. *Thyroid*, **2009**, *19*(9), 953-956.

[123] Eisenhauer, E.A.; Therasse, P.; Bogaerts, J.; Schwartz, L.H.; Sargent, D.; Ford, R.; Dancey, J.; Arbuck, S.; Gwyther, S.; Mooney, M.; Rubinstein, L.; Shankar, L.; Dodd, L.; Kaplan, R.; Lacombe, D.; Verweij, J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer*, **2009**, *45*(2), 228-247.

[124] **Leone, A.; Di Gennaro, E.; Bruzzese, F.; Avallone, A.; Budillon, A. New perspective for an old antidiabetic drug: metformin as anticancer agent. *Cancer Treat. Res.*, 2014, *159*, 355-376.**

[125] **Jang, E.K.; Kim, W.G.; Kwon, H.; Choi, Y.M.; Jeon, M.J.; Kim, T.Y.; Shong, Y.K.; Kim, W.B.; Kim, E.Y. Metformin Is Associated with a Favorable Outcome in Diabetic Patients with Cervical Lymph Node Metastasis of Differentiated Thyroid Cancer. *Eur. Thyroid J.*, 2015, *4*(3), 181-188.**

[126] **Jara, J.A.; López-Muñoz, R. Metformin and cancer: Between the bioenergetic disturbances and the antifolate activity. *Pharmacol. Res.*, 2015, *101*, 102-108.**

[127] **Rotondi, M.; Coperchini, F.; Pignatti, P.; Sideri, R.; Groppelli, G.; Leporati, P.; La Manna, L.; Magri, F.; Mariotti, S.; Chiovato, L. Interferon-γ and Tumor Necrosis Factor-α Sustain Secretion of Specific CXC Chemokines in Human Thyrocytes: A First Step Toward a Differentiation between Autoimmune and Tumor-Related Inflammation? *J. Clin. Endocrinol. Metab.*, 2013, *98*(1), 308-313.**

[128] **Rotondi, M.; Coperchini, F.; Chiovato, L. CXCL8 in thyroid disease: From basic notions to potential applications in clinical practice. *Cytokine Growth Factor Rev.*, 2013, *24*(6), 539-546.**

[129] **Ohama, Y.; Harada, T.; Iwabe, T.; Taniguchi, F.; Takenaka, Y.; Terakawa, N. Peroxisome proliferator-activated receptor-gamma ligand reduced tumor necrosis factor-alpha-induced interleukin-8 production and growth in endometriotic stromal cells. *Fertil. Steril.*, 2008, *89*(2), 311-317.**

[130] **Ninomiya, I.; Yamazaki, K.; Oyama, K.; Hayashi, H.; Tajima, H.; Kitagawa, H.; Fushida, S.; Fujimura, T.; Ohta, T. Pioglitazone inhibits the proliferation and metastasis of human pancreatic cancer cells. *Oncol. Lett.*, 2014, *8*(6), 2709-2714.**

[131] **Coperchini, F.; Leporati, P.; Rotondi, M.; Chiovato, L. Expanding the therapeutic spectrum of metformin: from diabetes to cancer. *J. Endocrinol. Invest.*, 2015, *38*(10), 1047-1055.**

[132] **Rotondi, M.; Coperchini, F.; Pignatti, P.; Magri, F.; Chiovato, L. Metformin Reverts the Secretion of CXCL8 Induced by TNF-α in Primary Cultures of Human Thyroid Cells: An Additional Indirect Anti-Tumor Effect of the Drug. *J. Clin. Endocrinol. Metab.*, 2015, *100*(3), E427-**

32.

[133] **Esteghamati, A.; Rezvani, S.; Khajeh, E.; Ebadi, M.; Nakhjavani, M.; Noshad, S. Comparative effects of metformin and pioglitazone on YKL-40 in type 2 diabetes: a randomized clinical trial. *J. Endocrinol. Invest.*, 2014, *37*(12), 1211-1218.**

[134] Hayashi, N.; Nakamori, S.; Hiraoka, N.; Tsujie, M.; Xundi, X.; Takano, T.; Amino, N.; Sakon, M.; Monden, M. Antitumor effects of peroxisome proliferator activate receptor gamma ligands on anaplastic thyroid carcinoma. *Int. J. Oncol.,* **2004**, *24*(1), 89-95.

[135] Aiello, A.; Pandini, G.; Frasca, F.; Conte, E.; Murabito, A.; Sacco, A.; Genua, M.; Vigneri, R.; Belfiore, A. Peroxisomal proliferator-activated receptor-gamma agonists induce partial reversion of epithelial-mesenchymal transition in anaplastic thyroid cancer cells. *Endocrinology,* **2006**, *147*(9), 4463-4475.

[136] Marlow, L.A.; Reynolds, L.A.; Cleland, A.S.; Cooper, S.J.; Gumz, M.L.; Kurakata, S.; Fujiwara, K.; Zhang, Y.; Sebo, T.; Grant, C.; McIver, B.; Wadsworth, J.T.; Radisky, D.C.; Smallridge, R.C.; Copland, J.A. Reactivation of suppressed RhoB is a critical step for the inhibition of anaplastic thyroid cancer growth. *Cancer Res.,* **2009**, *69*(4), 1536-1544.

[137] Antonelli, A.; Ferrari, S.M.; Fallahi, P.; Berti, P.; Materazzi, G.; Minuto, M.; Giannini, R.; Marchetti, I.; Barani, L.; Basolo, F.; Ferrannini, E.; Miccoli, P. Thiazolidinediones and antiblastics in primary human anaplastic thyroid cancer cells. *Clin. Endocrinol. (Oxf).,* **2009**, *70*(6), 946-953.

[138] Antonelli, A.; Ferrari, S.M.; Fallahi, P.; Berti, P.; Materazzi, G.; Marchetti, I.; Ugolini, C.; Basolo, F.; Miccoli, P.; Ferrannini, E. Evaluation of the sensitivity to chemotherapeutics or thiazolidinediones of primary anaplastic thyroid cancer cells obtained by fine-needle aspiration. *Eur. J. Endocrinol.,* **2008**, *159*(3), 283-291.

[139] Antonelli, A.; Ferrari, S.M.; Fallahi, P.; Berti, P.; Materazzi, G.; Barani, L.; Marchetti, I.; Ferrannini, E.; Miccoli, P. Primary cell cultures from anaplastic thyroid cancer obtained by fine-needle aspiration used for chemosensitivity tests. *Clin. Endocrinol. (Oxf).,* **2008**, *69*(1), 148-152.

[140] Antonelli, A.; Ferrari, S.M.; Fallahi, P.; Piaggi, S.; Di Domenicantonio, A.; Galleri, D.; Santarpia, L.; Basolo, F.; Ferrannini, E.; Miccoli, P. Variable modulation by cytokines and thiazolidinediones of the prototype Th1 chemokine CXCL10 in anaplastic thyroid cancer. *Cytokine,* **2012**, *59*(2), 218-222.

[141] Smallridge, R.C.; Copland, J.A.; Brose, M.S.; Wadsworth, J.T.; Houvras, Y.; Menefee, M.E.; Bible, K.C.; Shah, M.H.; Gramza, A.W.; Klopper, J.P.; Marlow, L.A.; Heckman, M.G.; Von Roemeling, R. 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.