PPARs and the Hallmarks of Cancer

Subjects: Pathology

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Peroxisome proliferator-activated receptors (PPARs) function as nuclear transcription factors upon the binding of physiological or pharmacological ligands and heterodimerization with retinoic X receptors. Physiological ligands include fatty acids and fatty-acid-derived compounds with low specificity for the different PPAR subtypes (alpha, beta/delta, and gamma). For each of the PPAR subtypes, specific pharmacological agonists and antagonists, as well as pan-agonists, are available. In agreement with their natural ligands, PPARs are mainly focused on as targets for the treatment of metabolic syndrome and its associated complications. Nevertheless, many publications are available that implicate PPARs in malignancies. In several instances, they are controversial for very similar models.

Keywords: PPAR ; cell proliferation ; angiogenesis ; cellular metabolism ; immune surveillance

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1. Introduction

In addition to receptors for steroid and thyroid hormones, vitamin D and retinoids, and several orphan receptors, peroxisome proliferator-activated receptors (PPARs) belong to the group of nuclear receptors [1][2]. Although peroxisome proliferation in response to hypolipidemic fibrate drugs (PPAR alpha agonist) was described already in 1970s [3][4], it took nearly 20 years for PPAR alpha (PPARα), PPAR beta/delta (PPARβ/δ), and PPAR gamma (PPARγ) to be identified [5][6][7]. On the molecular level, PPARs activate/repress target genes as heterodimers with retinoic X receptors (RxR), which exist in three different isoforms. Liver X receptor α (LxRα) and retinoic acid receptors (RAR)s also form heterodimers with RxR. Thus, depending on the level of expression of the different receptors, the outcome of PPAR activation might differ between cell types [1]. In addition to the classical PPAR/RxR transcriptional complexes [8], PPARs might also interact with glucocorticoid receptors, photoreceptor-specific nuclear receptors, and estrogen-related receptors, which could additionally modify the responses of PPAR activation [9]. As a general PPAR response element, a direct repeat of the sequence AGGTCA, spaced by a single nucleotide, has been originally identified (DR1); in fact for PPAR alpha only [10]. Binding exclusively to this element would not explain the specificity of the identified PPAR alpha, beta/delta, and gamma target genes. Furthermore, thousands of these elements are found in the genome, mostly far away from the gene promoter regions. Experimental evidence suggests a higher heterogeneity of binding elements for PPARs [1][11]. The ligand-dependent and ligand-independent effects, posttranscriptional modifications, co-activators, and co-repressors of PPARs have been extensively researched [1][12][13].

Endogenous ligands for PPARs include unsaturated fatty acids, eicosanoids, prostaglandins, and prostacyclins [1][14]. Synthetic activators and inhibitors for all PPARs are available. Until now, only PPARα agonists (e.g., fibrates) have been in clinical use for lipid lowering, the prevention of atherosclerosis, and cardiovascular disease [15][16], while PPARγ agonists (e.g., thiazolidinediones) lower glucose by increasing insulin sensitivity, mainly in skeletal muscle and adipose tissue [17]. In addition to these "classical" applications for the treatment of metabolism-related diseases and metabolic syndrome, PPARs might be involved in a variety of diseases [18] and PPAR modulators might become interesting candidates for neurodegenerative disorders [19], addiction [20], psychiatric disorders [21][22], hepatic and kidney diseases [12][23][24][25], and autoimmune and inflammatory diseases [16][26][27][28][29]. Importantly, PPARs are also critically involved in cancer. The expression of PPARs has been detected in various cancer types and cancer cell lines, but PPARs also play important roles in the tumor stroma, i.e., cancer-associated fibroblasts, mesenchymal cells, endothelial cells, and macrophages [30]. In addition to cancer cell growth, angiogenesis, and the antitumor immune response play an important role in cancer progression and metastasis [31].

2. PPARs and Cell Proliferation

2.1. PPARα

PPARα expression has been demonstrated in human breast cancer cell lines, which showed increased proliferation upon PPARα activation [32]. Leptin and glucose treatment stimulated breast cancer proliferation, which was accompanied by an

upregulation of PPARα, suggesting the involvement of PPARα in this process [33]. Similarly, arachidonic acid (AA) has been found to promote breast cancer cell proliferation through the activation of PPARα [34]. However, contrasting results were obtained by another group [35]. The PPAR agonist fenofibrate reduced the proliferation of triple-negative breast cancer cells [36]. Similar results were obtained with clofibrate in inflammatory breast cancer cell lines [37]. Different outcomes on breast cancer cell proliferation may be explained by the different types of breast cancer cell lines used, but also by the different concentrations of fibrates. Tauber and colleagues reported stimulation of the proliferation of MCF-7 breast cancer cells with low fibrate concentrations, and suppression with high doses [38]. Dose-dependent effects of fibrates on cell proliferation have also been reported for human liver cancer cells [39]. The sustained activation of PPARα leads to liver tumorigenesis in rodents. However, in a PPARα humanized model, sustained PPARα activation very rarely provoked liver cancers, which suggests that structural differences between human and mouse PPARα are responsible for the differential susceptibility to peroxisome proliferator-induced hepatocarcinogenesis [40]. In an excellent study, Tanaka and colleagues provided evidence that the hepatitis C virus (HCV) core protein induces heterogeneous activation of PPARα in transgenic mice. The stabilization of PPARα through interaction with the Hepatitis C virus (HCV) core protein and an increase in non-esterified fatty acids, serving as endogenous PPARα ligands, were suggested to contribute to the age-dependent and multicentric hepatocarcinogenesis mediated by the core protein [41]. Interestingly, the hepatocyte restricted the constitutive activation of the PPARα-induced proliferation of hepatocytes, but not carcinogenesis, indicating that the PPARα activation of other cell types than hepatocytes is responsible for the carcinogenic effect of PPARα activation [42]. The existence of an alternatively spliced transcript variant (PPARA-tr) in humans, but not in rodents, with a deficient ligand-binding domain that is unable to bind to peroxisome proliferator-responsive DNA elements (PPREs) could partially explain the species differences in hepatocarcinogenesis [43][44]. A later study suggested a higher susceptibility of PPARα-knockout mice to diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) [45]. However, Kaipainen and colleagues evidenced a tumor-suppressive phenotype in PPARα-deficient mice. The absence of PPARα switches tumor-associated inflammation into tumor-suppressive inflammatory infiltrates, which inhibit tumor angiogenesis and tumor progression independently of the cellular tumor type [46]. Later, PPARα deficiency was also proposed to impair regulatory T-cell functions, leading to the inhibition of melanoma growth [47]. These studies confirm the importance of the molecular properties of stromal host cells for cancer progression, which also explains the differential outcomes of analyses in pure in vitro studies, leading to potential false therapeutic deductions. The PPARα agonist fenofibrate, for example, decreased endometrial cancer cell proliferation in vitro but failed to improve outcomes in vivo [48]. Yokoyama and co-workers reported an inhibition of proliferation in ovarian cancer cell lines in vitro, as well as a reduction in ovarian cancer cell tumor growth in vivo via the activation of PPARα with clofibrate [49]. PPARα is expressed in medulloblastoma cells, and PPARα activation with fenofibrate inhibited cell proliferation in medulloblastoma cell lines [50]. Similar results were proposed using fenofibrate treatment in a glioblastoma cell line [51] and neuroblastoma cells [52]. However, the overexpression of PPARα in glioma stem cells (GSCs) has been observed. GSCs are responsible for tumor initiation, treatment resistance, and recurrence. The knockdown (KD) of PPARα reduced the proliferative and tumor-forming capacities of GSCs, and xenografts failed to establish viable intracranial tumors [53]. PPARα was found to induce carnitine palmitoyltransferase 1C (CPT1C) in a breast and a pancreatic cancer cell line, leading to the activation of cell proliferation [54]. Using syngenic implantation of B16 melanoma, LLC1 lung carcinoma, and SKOV-3 ovarian cancer xenograft models, the efficiency of the tumor growth-inhibiting properties of the PPARα antagonist NXT629 has been demonstrated [55]. Li and colleagues showed that the level of PPARα and its activity were increased in 4-(methylnitrosamino)-l-(3-pyridyl)-lbutanone (NNK)-induced mouse-lung tumors. An increase in PPARα occurred before the formation of lung tumors, indicating that the molecular changes play a role in lung carcinogenesis [56]. In contrast, in two lung cancer cell lines, fenofibrate reduced cell proliferation [57]. PPARα activation in vivo using Wy-14,643 or bezafibrate reduced non-small-cell lung cancer (NSCLC) growth through the inhibition of a proangiogenic epoxygenase. Epoxygenases oxidize arachidonic acid to epoxyeicosatrienoic acids (EET), pro-angiogenic lipids which support tumor growth [58]. Although PPARα activation by Wy-14,643 did not alter proliferation of cancer cell lines in vitro, it reduced tumorigenesis in vivo through the inhibition of angiogenesis [59]. The PPARα agonist fenofibrate has further been demonstrated to suppress B cell lymphoma in mice through the modulation of lipid metabolism. B cell tumors trigger systemic lipid mobilization from white adipose tissue to the liver and increase very-low-density lipoprotein (VLDL)/low-density lipoprotein (LDL) release from the liver to promote tumor growth. B cell lymphoma cells express extremely low levels of PPARα; therefore, fenofibrate did not increase lipid utilization in the tumors but enhanced the clearance of lipids and blocked hepatic lipid release, leading to reduced tumor growth [60]. Fenofibrate has also been proposed to suppress colon cancer cell proliferation in vitro and in in vivo xenograft models through epigenetic modifications involving the inhibition of DNA Methyltransferase 1 (DNMT1) [61]. To summarize, given the highly controversial results regarding the tumor-suppressing or -promoting effects of therapeutic PPARα modulation, especially activation, this intervention seems to be inadequate in the context of cancer. To the best of the knowledge, no clinical trials for the use of PPARα agonists in cancer therapy exist. One trial with the PPARα antagonist TPST-1120 as a monotherapy, and in combination with Nivolumab, Docetaxel or Cetuximab, in subjects with advanced cancers (NCT03829436) is ongoing.

2.2. PPARβ/δ

PPARβ/δ expression has been reported in a variety of cancer tissues and cell lines. The effects of PPARβ/δ on cell proliferation and tumor growth are highly controversial, and have been researched recently; summarizing tables are provided [62]. Many studies focused on colon cancer. The discrepancy between the observed effects of PPARβ/δ activation can only lead to the conclusion that any therapeutical use of PPARβ/δ modulation has to be avoided. Most studies report a colon cancer-enhancing effect of PPARβ/δ. Examination of PPARβ/δ in human multistage carcinogenesis of the colorectum revealed that its expression increased from normal mucosa to adenomatous polyps to colorectal cancer. The most elevated PPARβ/δ levels were observed in colon cancer cells with a highly malignant morphology [63]. PPARβ/δ expression in human colon cancer tissues was associated with poor prognosis and a higher metastatic risk [64]. An opposite report has been published for human and mouse colon cancer samples; however, no histomorphological detection analysis of PPARβ/δ has been performed to allow for the correlation of PPARβ/δ with expression in malignant cancer cells [65]. It has been demonstrated that PPARβ/δ mediates mitogenic vascular endothelial growth factor (VEGF) release in colon cancer [66][67][68], although one report also claimed that a loss of PPARβ/δ would enhance vascular endothelial growth factor (VEGF) release [69]. PPARβ/δ has been shown to promote [66][70][71][72][73][74][75] or to inhibit [69][76] [77] colon cancer in vivo. In line with a pro-tumorigenic role, PPARβ/δ activation via a high-fat diet (HFD) or PPARβ/δ agonist treatment allowed stem and progenitor cells to initiate tumorigenesis in the setting of a loss of the adenomatous polyposis coli (APC) tumor-suppressor gene [78]. PPARβ/δ-mediated epithelial hyperproliferation, which increases the risk for gastric adenocarcinoma, was further found to be induced by Helicobacter pylori infection [79]. Regarding breast cancer, most studies suggest a pro-tumorigenic function of PPARβ/δ. Only two in vitro studies from the same group using the same breast cancer cell line suggest a reduction in cell proliferation upon PPARβ/δ activation [80][81]. The same group published two very similar studies, one using neuroblastoma cell lines, and the other testicular embryonal carcinoma cells, in which PPARβ/δ overexpression and/or activation had beneficial tumor-cell proliferation- or growth-inhibiting effects [82] [83]. In contrast, by applying a variety of different molecular tools as either overexpression or knockout models, or conducting pharmacological activation or inhibition of PPARβ/δ, it has been shown, in vivo, that PPARβ/δ favors mammary tumorigenesis [84][85][86][87]. 3-phosphoinositide-dependent kinase-1 (DK1) favors these tumorigenic properties of PPARβ/δ in breast cancer [85][86]. Fatty-acid-binding protein 5 (FABP5), which shuttles ligands from the cytosol to PPARβ/δ, underlines the importance of endogenous PPARβ/δ ligands for cancer growth, as knockout of FABP5 was sufficient to reduce mammary tumorigenesis [88]. In line with this, FABP5 has been shown to convert the strong anticarcinogenic properties of retinoic acid (RA) into tumor-promoting functions as it delivers RA to the mitogenic and anti-apoptotic PPARβ/δ receptor [89]. Similar to the effects observed in mammary carcinomas, activation of the FABP5/PPARβ/δ pathway was shown to promote cell survival, proliferation, and anchorage-independent growth in prostate cancer cells [90]. The oncogenic redirection of transforming growth factor (TGF)-β1 signaling via the activation of PPARβ/δ was also identified to promote prostate cancer growth [91]. One study, however, suggested the inhibition of prostate cancer growth by PPARβ/δ through a noncanonical and ligand-independent pathway [92]. The activation of PPARβ/δ has been proposed to inhibit liver tumorigenesis in hepatitis B transgenic mice [93]; however, in different human hepatocellular carcinoma cell lines, the activation of PPARβ/δ enhanced the growth of these cancer cells through the activation of cyclooxygenase (COX)-2 [94]. PPARβ/δ activation has been shown to inhibit melanoma skin cancer cell proliferation through repression of the Wilms tumor suppressor (WT)1 [95], which favors human melanoma progression [96]. PPARβ/δ-knockout animals were more susceptible to skin carcinogenesis as their wildtype counterparts and PPARβ/δ agonists inhibited keratinocyte proliferation [97], as well as proliferation in a human squamous-cell carcinoma cell line [98]. In line with these finding, the researchers proposed a protective effect of PPARβ/δ activation, coupled with the inhibition of COX-2 activity, to increase the efficacy of chemoprevention in skin tumorigenesis [99][100]. However, a later report from this group showed that PPARβ/δ is not involved in the suppression of skin carcinogenesis by non-steroidal anti-inflammatory drugs (NSAID) which inhibit COX-2 [101]. In contrast to an inhibitory function of PPARβ/ δ in the tumorigenesis of non-melanoma skin cancers, one study clearly evidenced the pro-tumorigenic role of PPARβ/δ involving the direct activation of proto-oncogene tyrosine-protein kinase Src, which promotes the development of ultraviolet (UV)-induced skin cancer in mice [102]. An elegant study focused on the importance of fibroblast PPARβ/ δ expression in non-melanoma skin tumorigenesis. Although the chemically induced skin tumors of animals with the conditional deletion of PPARβ/ δ in fibroblasts showed increased proliferation, the tumor burden was smaller and the tumor onset delayed; this indicates the role of fibroblast PPARβ/δ in epithelial–mesenchymal communication, which further influences tumor growth [103]. Regarding lung cancer, high expression of PPARβ/δ limited to cancer cells has been demonstrated in human cancer samples. In lung cancer cell lines, the activation of PPARβ/δ stimulated proliferation and inhibited apoptosis [104][105]. Nicotine increases PPARβ/δ expression in lung carcinoma cells, which contributes to increased proliferation [106]. In contrast, one study using the activation of PPARβ/δ in two lung cancer cell lines in vitro did not find differences for proliferation upon stimulation of PPARβ/δ [107]. In transgenic mice lacking one or both PPARβ/δ alleles, the growth of RAF-induced lung adenomas was decreased [108]. Although cell proliferation in mouse LLC1 lung cancer cells was decreased upon activation of PPARβ/δ, LLC1 tumor

growth in vivo was enhanced in mice with conditional vascular overexpression of PPARβ/δ, underlining the importance of crosstalk between the tumor stroma and cancer cells for tumor growth [11]. One study reported that PPARβ/δ activation promoted apoptosis and reduced the tumor growth of nasopharyngeal carcinoma cells [109]. PPARβ/δ was found to be highly expressed in liposarcoma compared to benign lipoma, and PPARβ/δ activation increased liposarcoma cell proliferation, which was mediated via the direct transcriptional repression of leptin by PPARβ/δ [110]. Additionally, in thyroid tumors, PPARβ/δ was increased and correlated with the expression of the proliferation marker Ki67. PPARβ/δ activation increased the cell proliferation of thyroid cells [111]. PPARβ/δ was highly expressed in epithelial ovarian cancer cell lines and the inhibition of PPARβ/δ reduced their proliferation and tumor growth in vivo. Interestingly, aspirin, a NSAID that preferentially inhibits COX-1, compromised PPARβ/δ function and cell growth by inhibiting extracellular signal-regulated kinases 1/2 [112]. PPARβ/δ promoted the survival and proliferation of chronic lymphocytic leukemia cells [113] and changed the outcome of signaling from cytokines such as interferons (IFNs) [114]. A detailed table on the effects of PPARβ/δ on cell proliferation and tumor growth can be found in [62]. In conclusion, most studies identified PPARβ/δ as a tumor-promoting factor which increases cell proliferation and cancer growth. Although some studies report the inhibition of cancer cell proliferation upon PPARβ/δ activation, the therapeutic modulation of PPARβ/δ appears dangerous. Consequently, no cancer-related clinical trials are reported.

2.3. PPARγ

PPARγ expression is found in a variety of cancer tissues and cell lines. The activation of PPARγ by different agonists increased the frequency and size of colon tumors in C57BL/6J-APCMin/+ mice [115][116]. However, in human colon cancer cell lines, PPARγ inhibited tumor-cell proliferation [117][118][119][120]. Prostate cancers were found to overexpress PPARγ. The PPARγ agonist troglitazone inhibited the proliferation of PC-3 prostate cancer cells in vitro and in xenograft models in vivo [121], which was confirmed by others in later studies [122][123]. Similarly, growth inhibition via PPARγ activation has been described for liposarcoma [124], gastric cancer [125][126], bladder carcinoma [123][127], renal cell carcinoma [123], neuroblastoma [128][129], glioblastoma [130][131], melanoma [132][133][134][135], NSCLC [136][137], adrenocortical cancer [138][139], hepatocellular carcinoma [140], endometrial carcinoma [141], ovarian cancer [142][143], multiple myeloma [144], B cell lymphoma [145], mesothelioma [146], and esophageal squamous-cell carcinoma [147]. Most of these studies used cancer cell lines and PPARγ agonist treatment in vitro. Exciting results for therapeutic effects of PPARγ activation have been obtained in chronic myeloid leukemia (CML). With standard therapies, mainly tyrosine kinase inhibitors (TKIs), only 10% of patients achieve a complete molecular response/remission (CMR). This is mainly due to a pool of quiescent CML leukemia stem cells (LSCs), which are not completely eradicated by TKIs. Prost and colleagues demonstrated that thiazolidinediones target this pool of LSCs through the decreased transcription of signal transducer and activator of transcription (STAT) 5, leading to sustained CMR in a small group of patients [148]. A proof-of-concept study including 24 patients yielded positive outcomes with a combined therapy of pioglitazone and imatinib (TKI) [149]. A phase 2 trial is ongoing (EudraCT 2009-011675-79). PPARγ has been identified as a critical modifier in thyroid carcinogenesis using transgenic animals harboring a knock-in dominant-negative mutant thyroid hormone receptor beta (TRbetaPV/PV mouse), which spontaneously develop follicular thyroid carcinoma. TRbetaPV/PV mice were crossed with PPARγ +/− mice, and it was shown that thyroid carcinogenesis progressed faster in animals with PPARγ haplo-insufficiency. Reduced PPARγ led to the activation of the nuclear factor-kappaB signaling pathway, resulting in the repression of apoptosis. Furthermore, the treatment of TRbetaPV/PV mice with rosiglitazone delayed the progression of thyroid carcinogenesis by decreasing cell proliferation [150]. Wu and colleagues showed that the inhibition of PPARγ via the overexpression of dominant negative PPARγ (dnPPARγ) in the myeloid cell lineage provokes systemic inflammation and an increase in myeloid-derived suppressor cells (MDSC), which led to immunosuppression and the appearance of multiple cancers [151]. In breast cancer [152][153] and uterine leiomyomas [154], the growth-inhibiting effect of PPARγ activation was attributed to the inhibition of estrogen-receptor signaling. This seems to be partially mediated through the repression of leptin's stimulatory effects on estrogen signaling by PPARγ [155]. However, later, it was shown that the PPARγ agonist prostaglandin 15-deoxy-$\Delta^{12,14}$-PGJ2 (15d-PGJ2) inhibits the transcriptional activity of estrogen receptor alpha via PPARγ-independent covalent modification of its DNA-binding domain [156]. Methylene-substituted diindolylmethanes (C-DIMs) are PPARγ-activating agents. They reduce the proliferation of breast cancer cell lines. However, the decrease in cell growth was not inhibited by PPARγ antagonists, indicating that the observed effect might be PPARγ-independent [157]. An elegant study used transgenic mice prone to mammary-gland cancer crossed with mice expressing a constitutively active form of PPARγ in the mammary gland. The resulting PyV/VpPPARγ females developed tumors with accelerated kinetics. Even before reaching maturity at around 30 days of age, female mice displayed palpable tumor masses. These results indicate that once an initiating event has taken place, increased PPARγ signaling exacerbates mammary-gland tumor development [158]; this is similar to the observed situation of accelerated colon cancer formation in APCMin/+ mice treated with thiazolidinediones described before [115][116]. Avena and colleagues focused on the importance of the tumor stroma for cancer growth. They demonstrated that the overexpression of PPARγ in breast cancer cells reduced tumor growth in a

xenograft model and demonstrated increased autophagy in the tumor cells. However, when breast cancer cells were co-injected with PPARγ-overexpressing fibroblasts, tumor growth was significantly increased. Stromal cells with overexpression of PPARγ displayed metabolic features of cancer-associated fibroblasts, with increased autophagy, glycolysis, and senescence; this supports a catabolic pro-inflammatory microenvironment that metabolically enhances cancer growth. The activation of an autophagic program, therefore, have pro- or antitumorigenic effects, depending on the cellular context [159]. The mammary secretory-epithelial-cell-specific knockout of PPARγ enhanced tumor growth in a 7,12-dimethylbenz[a]anthracene (DMBA)-induced breast cancer model [160]. A small clinical trial in patients with early-stage breast cancer did not evidence differences in breast tumor-cell proliferation upon treatment with rosiglitazone, administered between the time of diagnostic biopsy and definitive surgery [161]. PPARγ ligands did not prevent chemically or UV-induced skin tumors, although they significantly inhibited basal-level keratinocyte proliferation [162].

It is important to note that the anti-cancer effects of thiazolidinediones (rosiglitazone, pioglitazone, and troglitazone) might be independent of PPARγ activation, as it has been demonstrated that they are mediated by translation inhibition [163]. In osteosarcoma cell lines, troglitazone enhanced proliferation in one study [164], and inhibited proliferation in another [165]. Srivastava and colleagues demonstrated, in a lung cancer model, that treatment with the PPARγ agonist pioglitazone triggers a metabolic switch that inhibits pyruvate oxidation and reduces glutathione levels. These metabolic changes increase reactive oxygen species (ROS) levels, which leads to the rapid hypophosphorylation of the retinoblastoma protein (RB) and cell-cycle arrest [166]. In a very recent study, Musicant and colleagues demonstrated that the inhibition of PPARγ might be beneficial in mucoepidermoid carcinoma (MEC), a salivary-gland cancer that is driven primarily by a transcriptional coactivator fusion composed of cyclic AMP-regulated transcriptional coactivator 1 (CRTC1) and mastermind-like 2 (MAML2). The chimeric CRTC1/MAML2 (C1/M2) oncoprotein induces transcriptional activation of the non-canonical peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) splice variant PGC-1α4, which regulates PPARγ-mediated insulin-like growth factor (IGF) 1 expression. The inhibition of PPARγ by inverse agonists inhibits MEC cell proliferation and tumor growth in xenograft models [167]. Besides the clinical trials already mentioned, one trial (NCT00408434) of efatutazone in patients with advanced solid malignancies and no curative therapeutic options reported evidence of disease control [168]. In other clinical trials investigating the effects of efatutazone in combination with carboplatin/paclitazel in NSCLC (NCT01199055), or in combination with erlotinib (NCT01199068), partial responses were around 40%. However, in a clinical trial for liposarcoma (NCT02249949), efatutazone resulted in neither complete nor partial responses. The development of efatutazone has been discontinued. Clinical trials for pioglitazone in the treatment of leukoplakia in head and neck cancer (NCT00099021) resulted in partial responses of 70%, and in another trial for oral leukoplakia (NCT00951379), partial responses of 46% were achieved. Over twenty years ago, a very small clinical trial in three patients with liposarcoma treated with troglitazone already provided some evidence for adipocytic differentiation and decreased proliferation [169]. However, no results are available for later trials with a higher number of patients enrolled (NCT00003058 and NCT00004180). A table with detailed information regarding clinical trials using PPARγ agonists for cancer treatment is given in [170]. Although a large body of evidence suggests that PPARγ functions as a tumor suppressor, the role of PPARγ in tumorigenesis remains controversial. The predominant use of in vitro cell culture studies is limited in its elucidation of the biological relevance of PPARγ in cancer, as complex gene–gene and gene–environment interactions are not considered. It can be concluded that the role of PPARγ in cancer depends on the specific cancer type, the tumor stage, and the tumor environment, which implies that the therapeutical modulation of PPARγ must be considered with caution.

3. PPARs and Cell Death

3.1. PPARα

The PPARα activator fenofibrate has been shown to induce apoptosis in a human hepatocellular carcinoma cell line through an increase in reactive oxygen species (ROS) [171]. As another molecular mechanism of PPARα-dependent apoptosis, it has been proposed that PPARα serves as an E3 ubiquitin ligase to induce Bcl2 ubiquitination and degradation, leading to apoptosis [172]. Additionally in endometrial cancer [173], breast cancer [174], glioblastoma [175], colon cancer [61][176], ovarian cancer [49], medulloblastoma [50], neuroblastoma [52], pancreatic cancer [177], and NSCLC [178], the activation of PPARα induced apoptosis. These studies were mainly performed using a cancer cell line in in vitro assays. Conjugated linoleic acids induced apoptosis in a variety of human cancer cell lines, which was accompanied by a strong increase in PPARα [179]. The synergistic pro-apoptotic anticancer activity of clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) and docosahexaenoic acid (DHA) in human cancer cells has also been suggested to be mediated by PPARα signaling [180]. Zang and colleagues reported that the dual PPARα/γ agonist TZD18 provoked apoptosis in human leukemia, glioblastoma, and breast cancer cell lines through the induction of the endoplasmic reticulum stress response [181]. Later, the same observations were made in gastric cancer cell lines [182]. However, it is not clear if these actions were mediated through combined PPARα/γ signaling or solely through PPARα or PPARγ signaling. Crowe and colleagues evidenced that

combined therapy using PPAR and RXR ligands for breast cancer treatment resulted in growth inhibition. This was due to apoptosis when PPARα ligands were used. In contrast, PPARγ agonists provoked decreased growth characterized by S-phase inhibition [174]. In mantle-cell lymphoma (MCL), a type of aggressive B cell non-Hodgkin's lymphoma, which is frequently resistant to conventional chemotherapies, fenofibrate efficiently induced apoptosis through the downregulation of tumor necrosis factor (TNF) α. The addition of recombinant TNFα partially rescued fenofibrate-induced apoptosis, whereas the PPARα antagonist GW6471 did not affect the fenofibrate effects. Therefore, it might be possible that fenofibrate induced apoptosis through other mechanisms than the activation of PPARα [183]. In retinoblastoma cells, apoptosis was induced by fatty acid synthase, which led to the downregulation of PPARα; however, the relationship between these molecular events has not been investigated [184]. Similarly, in hepatic carcinoma cells, apoptosis was induced by the flavonoid quercetin, which downregulated PPARα expression [185]. The cause–effect relationship remains to be elucidated. Fenofibrate was found to induce apoptosis in triple-negative breast cancer cell lines, which involved the activation of the nuclear factor 'kappa-light-chain-enhancer' of activated B-cell (NF-κB) pathways, as the effect could be almost totally blocked by an NF-κB-specific inhibitor. The induction of apoptosis by fenofibrate was, however, independent of PPARα expression status, as the PPARα antagonist GW6471 did not change apoptosis induction by fenofibrate [36]. In contrast, the induction of apoptosis in hepatocellular carcinoma cells via the overexpression of PPARα was dependent on NF-κB signaling, as PPARα was found to directly interact with IκBα (nuclear factor kappa-light-polypeptide-gene-enhancer in B-cells inhibitor alpha) [45]. In contrast to most studies suggesting a pro-apoptotic function of PPARα activation, Li and coworkers reported that the PPARα inhibitor MT886 induced apoptosis in hepatocarcinoma cell lines, and the agonist fenofibrate significantly increased proliferation, the expression of cell-cycle-related protein (CyclinD1, CDK2), and cell-proliferation-related proteins (PCNA) [39]. Similarly, Abu Aboud and colleagues demonstrated enhanced apoptosis in renal-cell carcinoma upon PPARα inhibition in vitro [186] and in vivo through a decrease in enhanced fatty-acid oxidation and oxidative phosphorylation, and further cancer-cell-specific glycolysis inhibition [187]. The induction of apoptosis via PPARα inhibition has also been described in head and neck paragangliomas (HNPGLs); in one case, the researchers described the inhibition of the PI3K/GSK3β/β-catenin signaling pathway as the underlying molecular mechanism [188]. In conclusion, most of the studies suggest that PPARα activation induces apoptosis in cancer cells. However, given that a substantial number of research works also propose the opposite, and advise the use of PPARα inhibition to provoke apoptosis in tumor cells, no clear recommendation for therapeutic PPARα modulation in cancer treatment can be postulated.

3.2. PPARβ/δ

The function of PPARβ/δ in cancer-cell death was researched in detail in [62]. Most studies support the cell-death-preventing role of PPARβ/δ in tumor cells. In 1999, it was already demonstrated that PPARβ/δ was overexpressed in colorectal cancers (CRC) with adenomatous polyposis coli (APC)/β-catenin mutations, leading to the prevention of apoptosis in colon cancer cells. NSAIDs could compensate for this defect by suppressing PPARβ/δ and promoting apoptosis [189]. Cyclooxygenase-derived prostaglandin E$_2$ (PGE$_2$), which is overexpressed in most CRCs, was further found to indirectly transactivate PPARβ/δ to inhibit colon cancer-cell apoptosis [190]. Interestingly, it has been demonstrated that fibroblasts isolated from the mucosa of hereditary non-polyposis colorectal cancer (HNPCC) patients produced 50 times more PGE$_2$ than normal fibroblasts. Stromal overproduction of PGE$_2$ in HNPCC patients is likely to prevent the apoptosis of neoplastic lesions through the activation of PPARβ/δ, thereby facilitating progression into a malignant state [191]. Studies using HCT116 colon cancer cells confirmed that treatment with the PPARβ/δ agonist GW501516 diminished serum-withdrawal-induced apoptosis, which was not the case in PPARβ/δ-deficient HCT116 cells; this indicates the specificity of the apoptosis-preventing effect for PPARβ/δ [70]. Other mechanisms for the PPARβ/δ-mediated prevention of apoptosis in colon cancer have been suggested, such as the activation of the 14-3-3ε protein [192], or survivin [193] expression by PPARβ/δ. In contrast to these studies, one report suggested a pro-apoptotic function of PPARβ/δ in colon carcinoma. GW0742 agonist treatment induced apoptosis in wildtype, but not in PPARβ/δ-knockout animals with chemically induced colon carcinoma. Apoptosis was quantified via TdT-mediated dUTP-biotin nick-end labeling (TUNEL) staining of colon sections and subsequent cell counting; however, as no images were provided, it is difficult to assume TUNEL-specific positivity for cancer cells [76]. A study from the same group using different human colon cancer cell lines treated with hydrogen peroxide to induce apoptosis, different concentrations of the PPARβ/δ agonist GW0742, and NSAIDs could not find evidence for a decrease in apoptosis upon PPARβ/δ activation [65]. Conjugated linoleic acids (CLAs) were found to reduce proliferation in different human cancer cell lines. In cancer cell lines in which the inhibition of cell proliferation was correlated with apoptosis induction, PPARβ/δ expression became strongly downregulated [179]. PPARβ/δ activation decreased human and mouse melanoma cell proliferation; however, no changes in apoptosis could be observed [95]. The activation of PPARβ/δ has been shown to inhibit cisplatin-induced apoptosis in human lung cancer cell lines [104], and the knockout of PPARβ/δ induced apoptosis in lung cancer cells [105]. In mouse LLC1 lung cancer cells, the modulation of PPARβ/δ activity did not influence apoptosis [11]. The inhibition of PPARβ/δ sensitized neuroblastoma cells to retinoic acid-induced cell death [194]. In contrast, in prostate cancer cell lines,

ginsenoside Rh2- [195] and telmisartan- [196] induced apoptosis were hampered by the inhibition of PPARβ/δ. In line with a pro-apoptotic function of PPARβ/δ, enhanced apoptosis in a bladder carcinoma cell line [197] as well as in nasopharyngeal tumor cells [109] and liver cancer cells [198] was reported upon PPARβ/δ activation.

3.3. PPARγ

Over twenty years ago, Padilla and colleagues already described that 15d-PGJ2 that binds to PPARγ exerts cytotoxicity in malignant B-cell lymphoma via apoptosis induction. Additionally, thiazolidinedione PPARγ agonists negatively affected B-lineage cells, indicating a specific PPARγ function of counteracting the stimulatory effects of prostaglandin E_2 (PGE$_2$) [199] [200]. Later, the inhibition of NFκB was shown to be the major mechanism of 15d-PGJ$_2$-induced apoptosis in aggressive B-cell malignancies. These effects were mimicked by the proteasome inhibitor MG-132, but not by troglitazone, suggesting that 15d-PGJ2-induced apoptosis is independent of PPARγ [201]. In multiple myeloma, the overexpression of PPARγ induced apoptosis through the inhibition of Interleukin-6 production [144]. Similarly, in acute myeloid leukemia (AML), the forced expression of PPARγ regulated the induction of apoptosis via caspase-8 activation [202]. The activation of PPARγ by 15d-PGJ2 has also been demonstrated to inhibit tyrosine phosphorylation of epidermal growth factor receptors ErbB-2 and ErbB-3 in a breast cancer cell line, leading to a dramatic increase in apoptosis [152]. A later study, however, showed that while 15d-PGJ2 activates PPRE-mediated transcription, PPARγ is not required for 15d-PGJ$_2$-induced apoptosis in breast cancer cells. As other possible mechanisms of apoptosis induction by 15d-PGJ2, the inhibition of NFκB-mediated survival pathways, the inhibition of transcriptional activation of COX-2, and the inhibition of the ubiquitin proteosome were proposed [203]. The PPARγ-independent induction of apoptosis by 15d-PGJ$_2$ has also been demonstrated in prostate and bladder carcinoma cells [204]. Additionally, 15d-PGJ$_2$ induced apoptosis in pancreatic cancer cells through the downregulation of human telomerase reverse transcriptase (hTERT) [205]. Thiazolidinediones sensitize breast cancer cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) therapy by reducing cyclin D3 levels, but not other D-type cyclins [206]. Later, combined treatment with TRAIL and PPARγ ligands, especially 15d-PGJ2, was proposed to overcome chemoresistance in ovarian cancers for successful apoptosis induction [207]. The simultaneous activation of PPARγ and RXR has been suggested to promote apoptosis, implicating the upregulation of p53 in breast cancer cell lines [208]. NSAIDs, considered in cancer prevention due to their inhibitory effect on cyclooxygenases (COX), have recently been proposed to exert their antineoplastic activity through the activation of PPARγ, which induces proline dehydrogenase/proline oxidase (PRODH/POX)-dependent apoptosis in breast cancer cells [209]. In many other studies PPARγ agonists induced apoptosis in bladder cancer [210], gastric carcinoma [126][211], lung cancer [212], esophageal adenocarcinoma [213], pancreatic cancer [214], hepatocellular carcinoma [215], neuroblastoma [216], melanoma [134][135], glioblastoma [217], leukemia [218], leiomyoma [219], mesothelioma [146], and colon carcinoma [220]. Nevertheless, it is not always clear if apoptosis induction is mediated via PPARγ activation. In colon carcinoma, increased PPARβ/δ expression and/or activation of PPARβ/δ antagonized the ability of PPARγ to induce cell death. The activation of PPARγ was found to decrease survivin expression and increase caspase-3 activity, whereas the activation of PPARβ/δ counteracted these effects [193]. A highly interesting study investigated the role of PPARγ coactivator-1 alpha (PGC-1α) in the induction of apoptosis in human epithelial ovarian cancer cells. The overexpression of PGC-1α in human epithelial ovarian cancer cells induced cell apoptosis through the coordinated regulation of Bcl-2 and Bax expression. The suppression of PPARγ expression via siRNA or PPARγ antagonist treatment inhibited PGC-1α-induced apoptosis, suggesting that PPARγ is required for apoptosis induction by PGC-1α [204]. Alternative promoter and mRNA splicing give rise to several PPARγ mRNA and protein isoforms [221]. Kim and coworkers identified a novel splice variant of human PPARγ 1 (hPPAR γ1) that exhibits dominant-negative activity in human tumor-derived cell lines and investigated the function of a truncated splice variant of hPPARγ 1 (hPPARγ1(tr)) in lung cancer. The overexpression of hPPARγ1(tr) rendered cancer cells more resistant to chemotherapeutic drug- and chemical-induced cell death [222]. PPARγ mediated apoptosis induction by n-3 polyunsaturated fatty acids (n-3 PUFA) in a breast cancer cell line, which might explain the beneficial effects of diets enriched in n-3 PUFA [223]. Like the results described above for breast cancer, in colon cancer, the anti-apoptotic activity of the PPARγ agonist troglitazone was also found to be independent of PPARγ. Instead of apoptosis induction through PPARγ, the activation of early growth response-1 (Egr-1) transcription factor was identified as the underlying molecular mechanism [224]. This has also been described for the apoptotic action of C-DIMs, PPARγ agonists, which decreased colon cancer cell survival through the PPARγ-independent activation of early growth response protein (Egr) 1 [120]. In contrast, Telmisartan, an angiotensin II receptor blocker (ARB), was found to inhibit cancer cell proliferation and induce apoptosis through the activation of PPARγ [225][226][227]. In contrast to these pro-apoptotic actions of PPARγ agonists, the PPARγ agonist troglitazone increased cell proliferation and inhibited staurosporine-induced apoptosis in several osteosarcoma cell lines through Akt activation [164]. Later, studies from the Kilgore lab provided evidence that the unreflected therapeutical use of PPARγ ligands in patients predisposed to or already diagnosed with cancer, especially breast cancer, could be dangerous. They identified Myc-associated zinc finger protein (MAZ) as a transcriptional mediator of PPARγ1 expression. The down-regulation of PPARγ1 expression led to reduced cellular proliferation and the induction

of apoptosis in breast cancer cells [228]. Interestingly, it has been demonstrated that PPARγ ligands can have distinct activities. One relates to the ability of ligands to act as canonical agonists of the nuclear receptor on peroxisome proliferator response elements, which leads to adipogenesis. The second relates to the allosteric inhibition of phosphorylation of the Ser273 residue of PPARγ. PPARγ is phosphorylated in response to DNA damage, and the inhibition of phosphorylation by novel noncanonical ligands can sensitize cancer cells to DNA-damaging agents. They might represent a safer approach in cancer therapies as the established canonical agonists, which are used less and less frequently due to reported severe side effects or contradictory therapeutical outcomes [229]. A good study by Schaefer and colleagues using hepatocellular carcinoma cells demonstrated that PPARγ antagonists prevented adhesion to the extracellular matrix followed by caspase-dependent apoptosis (anoikis). They found that PPARγ inhibitor T0070907 was significantly more efficient in causing cancer-cell death than the activators troglitazone and rosiglitazone, which had no effect on cell adhesion and caused cell death at much higher concentrations [230]. Later studies confirmed this mechanism of anoikis induction by PPARγ antagonists in squamous-cell carcinoma [171][231]. Some reports evidenced autophagy induction in cancer cells upon PPARγ activation [232][233][234]. Autophagy can either suppress or promote tumor growth [235], and deducing that the induction of autophagy in cancers via PPARγ modulation might be beneficial is, consequently, erroneous. The difficulty in categorizing PPARγ activation in cancer therapy as beneficial or disadvantageous is also well-illustrated in a study from Baron and colleagues, who investigated the effects of ciglitazone in two different colon cancer cell lines: HT29 and SW480 cells. Ciglitazone induced apoptosis in HT29 cells, but stimulated SW480 cell proliferation. The researchers concluded that the differential responses for growth regulation result from cell-specific protein synthesis and differences in protein regulation [236]. Based on the outcomes of all these studies, it is therefore impossible to recommend PPARγ modulation to induce cancer-cell death.

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