Review Article

Peroxisome Proliferator-Activated Receptor Modulation during Metabolic Diseases and Cancers: Master and Minions

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The prevalence of obesity and metabolic diseases (such as type 2 diabetes mellitus, dyslipidaemia, and cardiovascular diseases) has increased in the last decade, in both industrialized and developing countries. This also coincided with our observation of a similar increase in the prevalence of cancers. The aetiology of these diseases is very complex and involves genetic, nutritional, and environmental factors. Much evidence indicates the central role undertaken by peroxisome proliferator-activated receptors (PPARs) in the development of these disorders. Due to the fact that their ligands could become crucial in future target-therapies, PPARs have therefore become the focal point of much research. Based on this evidence, this narrative review was written with the purpose of outlining the effects of PPARs, their actions, and their prospective uses in metabolic diseases and cancers.

1. Introduction

The prevalence of obesity and metabolic diseases (for example, type 2 diabetes mellitus (T2DM), dyslipidaemia, and cardiovascular diseases) has increased in the last decade, in both industrialized and developing countries. At the same time, we have observed similar increase in the prevalence of cancers. The aetiology of these disorders is very complex and involves genetic, nutritional, and environmental factors. There is much evidence that peroxisome proliferator-activated receptors (PPARs) play a significant part in the progression of these diseases [1, 2].

Peroxisome proliferator-activated receptors (PPARs) are a group of ligand-activated nuclear hormone receptors (NRs), existing within the steroid receptor superfamily, which includes the receptors for thyroid hormones, retinoids, 1,25-dihydroxyvitamin D_3, and steroid hormones [3]. After binding with their agonists (natural or synthetic) in cytoplasm, PPARs heterodimerize with the retinoid acid receptor (RNR or NR2B) and translocate to the nucleus, subsequently binding to specific DNA regions termed peroxisome proliferator response elements (PPREs). Here they activate the transcription of numerous genes that play a role in mechanisms associated with glucose and lipid metabolism, body energy production, inflammation, cell cycle arrest, apoptosis, and DNA damage response [4, 5].

Currently, we know of three different types of PPARs (PPARα, PPARβ/δ, and PPARγ), which present many different features, such as tissue distribution, ligand specificities, and effects. The principal differences among PPARs are due

to their structure; despite the DNA-binding domains being 80% identical, the ligand-binding domains are different. The biological effects of PPARs depend on their different ligand and the presence of several proteins that operate as coactivators or corepressors and whose presence may alter the expression of genes [6]. About this point, recent evidence suggests that the E6-associated protein (E6-AP) is an E3 ubiquitin ligase that affects the activity of other NRs: in particular, E6-AP is able to inhibit the ligand-independent transcriptional activity of PPARα and PPARβ, with marginal effects on PPARγ, and decreased basal mRNA levels of PPARα target genes [7]. Similarly, Murine Double Minute 2 (MDM2), an E3 ubiquitin ligase, was identified as a PPARα-interacting protein that regulates the transcriptional activity of PPARα and PPARβ/δ, but not PPARγ [8].

2. PPARα Role in Metabolic Diseases

PPARα is expressed in large amounts in the liver, skeletal muscles, heart, intestinal mucosa, and brown adipose tissue, where it undertakes an important role in fatty acid metabolism, as well as glucose and lipid metabolism [9] PPARα activation induces the expression of genes involved in lipid and lipoprotein metabolism (apolipoprotein genes A1, A2, and A5), in fatty acid oxidation (acyl-coenzyme A oxidase and carnitine palmitoyltransferases I and II), in the desaturation of fatty acyl-CoA (delta-6-desaturase), in High Density Lipoprotein (HDL) metabolism (Phospholipid Transfer Protein), and in ketone synthesis (3-Hydroxy-3-Methylglutaryl-CoA Synthase 2) [10]. Activated PPARα also stimulates the expression of the fibroblast growth factor gene 21 (FGF21) and the angiopoietin-like protein gene 4 (ANGPLT4). In response to PPARα activation, production of FGF21 in the liver begins, activating white adipose tissue lipolysis in order to provide nonadipose tissue with fatty acids as well as controlling ketogenesis in the liver with the purpose of procuring energy from fatty acids [11]. In partial agreement with these data, it was found that increased FGF21 expression was observed in the livers of PPARβ/δ-null mice and in mouse primary hepatocytes when this receptor was knocked down by small interfering RNA (siRNA) and that this increase was associated with enhanced protein levels in the heme-regulated eukaryotic translation initiation factor 2α (eIF2α) kinase (HRI) [12]. Recent studies indicate that the physiological fluctuations in lipoproteins lipase (LPL) activity are mediated by ANGPLT4 as well as the decrease in adipose LPL activity observed during intervals of fasting [13]. The natural and pharmacological ligands for PPARα are, respectively, omega-3 fatty acids resulting from diet (such as linolenic, α-linolenic, γ-linolenic, and arachidonic acids) and fibrate, normally used as potent hypolipidemic agents [14]. In the liver, PPARα plays the role of lipid sensor, normally undergoing activation due to fatty acids and resulting in the increased burning of energy, the reduction of fat storage, and the prevention of steatosis; conversely, when PPARα sensing is not efficient or when fatty acid concentration is decreased (for genetic, toxic, or metabolic causes), this causes a reduction in energy burning and the resulting lipotoxicity promotes hepatic steatosis and steatohepatitis [15].

These data were confirmed when liver and whole-body fatty acid homeostasis impairment was recently demonstrated in a hepatocyte-specific PPARα knockout mouse model. Results included hepatic lipid accumulation (nonalcoholic fatty liver disease, NAFLD) and hypercholesterolemia during ageing [16]. In addition, mice conditionally expressing human PPARδ demonstrated pronounced weight loss and promoted hepatic steatosis when treated with GW501516 (PPARδ-agonist) when compared to wild type mice [17]. Fibrates are weak PPARα ligands; they reduce triglyceride (30–50%) and very low-density lipoprotein (VLDL) levels through an increased rate of lipid uptake, lipoprotein lipase-mediated lipolysis, and β- oxidation; in addition, fibrates also induce a modest increase in HDL cholesterol levels (5–20%), secondary to the transcriptional induction of apolipoprotein A-I/A-II synthesis found in the liver [18]. In this way, they decrease the systemic availability of fatty acids as well as fatty acid uptake in muscles [19], consequently leading to fibrates reducing arteriosclerosis progression and cardiovascular events. They also increase insulin sensitization and reduce plasma glucose levels.

PPARα activation by omega-3 fatty acids results in an anti-inflammatory effect, caused in all probability by the inhibition of their own oxidation due to the activation of the nuclear factor kappa-light-chain-enhancers of activated B cells (NF-κB). PPARα also plays a key role in the mediation of the anti-inflammatory actions of palmitoylethanolamide, the natural amide of palmitic acid, and ethanolamide [20]. Recently, a PPARα agonist (K-877) displaying high levels of potency and selectivity demonstrated optimal effects on atherogenic dyslipidemia [21]. In addition, a recent study indicated that statins, which are normally employed as cholesterol-lowering drugs, induce an increase in neurotrophin expression in the brain, as a result of their binding to a specific PPARα domain independent of the mevalonate pathway. In a mouse model with Alzheimer's disease, the use of Simvastatin led to an increase in neutrophin expression, as well as an improvement in memory and learning [22].

3. The Role of PPARβ/δ in Metabolic Diseases

PPARβ/δ is expressed ubiquitously, particularly in tissue which is metabolically active, such as the liver, skeletal and cardiac muscle, adipose tissue, and macrophages. Its involvement in the oxidation of fatty acids is crucial, and it improves lipid and cholesterol profiles. It plays a central role in the oxidation of fatty acids as well as improving lipid and cholesterol profiles, which reduces adiposity and prevents the development of obesity [23, 24]. It also regulates glucose blood levels. In several animal studies, PPARβ/δ acted as regulator of fat consumption; the deficiency of this receptor leads to obesity, while the activation of PPARβ/δ conversely results in resistance to this condition [25]. In the heart, in the presence of high-level dietary fat, PPARβ/δ lowers lipid accumulation and increases glucose metabolism and consequently seems to be useful in diabetic cardiomyopathy, as it protects the heart against ischemia-reperfusion injury [26]. For all these reasons, PPARβ/δ agonists (GW501516, GW0742, and L-165041) could become a potential target

in the treatment of metabolic disorders. However, adverse effects, particularly for PPARγ agonists, are also observed with the use of investigational PPAR agonists and even some approved drugs [27].

Recently, it was found that GW501516 significantly increased fatty acid oxidation and reduced the triglyceride amount in VLDL-loaded foam cells, suggesting a key role of PPARβ/δ in modulating macrophage lipid overload [28]. Intriguingly, PPAR-δ agonist GW501516 decreases uptake of VLDL and expression of VLDL receptor at mRNA and protein levels through the regulation of miRNA-100 in Human Umbilical Vein Endothelial Cells [29]. Confirming the human findings, clear data from mouse model showed that PPARβ/δ-deficient mice fed with fructose exacerbated glucose intolerance and this led to macrophage infiltration, inflammation, enhanced mRNA and protein levels of CD36, and activation of the c-Jun N-terminal kinase pathway in white adipose tissue; fascinatingly, these effects were partially prevented by the PPARβ/δ activator GW501516 [30]. In addition, topical application of polymer-encapsulated GW501516 was found to have therapeutic wound healing activity, through stimulation of glutathione peroxidase 1 (GPx1) and catalase expression in fibroblasts: indeed, GPx1 and catalase are known to scavenge excessive H_2O_2 accumulation in diabetic wound beds, preventing H_2O_2-induced extracellular matrix modification and facilitating keratinocyte migration [31]. Furthermore, PPARδ plays pivotal roles in wound healing by promoting fibroblast-to-myofibroblast differentiation via transforming growth factor (TGF)-β/Smad3 signalling: according to recent findings [32], GW501516-activated PPARδ increases the migration and contractile properties of human dermal fibroblasts and upregulates the expression of myofibroblast markers such as collagen I and fibronectin, with a concomitant reduction in expression of the epithelial marker E-cadherin.

Regarding GW0742, it was recently demonstrated that it can reverse the lung tissue damage induced by elastase in emphysema-model mice and improves respiratory function in mouse model: in particular, GW0742 increases the in vivo expression of surfactant proteins A and D, which are known alveolar type II epithelial cell markers, reduces the average distance between alveolar walls in the lungs, and improves tissue elastance, as well as the ratio of the forced expiratory volume in the first 0.05 s to the forced vital capacity [33]. In addition, recent evidence suggests that GW0742 administration to mice fed in high-fat diet prevented the gain of body weight, heart and kidney hypertrophy, and fat accumulation: namely, it prevents the increase of in plasma levels of fasting glucose, glucose tolerance test, homeostatic model assessment of insulin resistance, and triglyceride; from the molecular point of view, it increases both protein kinase B (Akt) and endothelial nitric oxide synthase phosphorylation and inhibits the increase in caveolin-1/endothelial nitric oxide synthase interaction, ethidium fluorescence, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1, Toll-like receptor 4, tumor necrosis factor-α, and interleukin-6 expression, and IκBα phosphorylation [34].

Regarding the PPARβ agonist L-165041, it was demonstrated that it induces vascular endothelial growth factor (VEGF) (121), VEGF(165), and VEGF(189) expression in HPV (Human Papillomavirus) positive HeLa cells: considering the intrinsic connection between HPV-related cancer of uterine cervix and VEGF levels, it is possible that PPARβ-mediated pathway may play a key role in the development of this type of cancer [35]. Confirming these data, L-165041 was found to inhibit VEGF-stimulated angiogenesis by suppressing the cell cycle progression independently of PPARδ: in particular, it reduces the number of endothelial cells in the S phase and the expression levels of cell cycle regulatory proteins such as cyclin A, cyclin E, cyclin-dependent kinase (CDK) 2, and CDK4 [36]. Furthermore, a recent in vitro study found that L-165041 significantly inhibits high glucose-induced interleukin-6 and TNF-α production, receptor for advanced glycation end products expression, and NF-κB translocation in human embryonic kidney 293 (HEK) cells; in addition, it increases superoxide dismutase expression and attenuates apoptosis in HEK and mesangial cells [37].

4. PPARα/δ Role in Metabolic Diseases

The dual PPARα/δ agonist (GFT-505-Elafibranor) seems to have potentially beneficial effects in the treatment of NAFLD. In 2013, Staels et al. [38] showed in a mouse model that GFT505 protects liver from steatosis, inflammation, and fibrosis. This agonist also improves liver markers, decreases hepatic lipid accumulation, and inhibits proinflammatory (IL-1, TNFα) and profibrotic (transforming growth factor beta, tissue inhibitor of metalloproteinase 2, collagen type I, alpha 1, and collagen type I, alpha 2) gene expression with a PPARα dependent and independent mechanism [38]. In partial agreement with these data, it was recently found that Biliverdin reductase A protects against hepatic steatosis by inhibiting glycogen synthase kinase 3β (GSK3β) by enhancing serine 9 phosphorylation, which inhibits its activity: in particular, GSK3β phosphorylates serine 73 of the PPARα, which in turn increased ubiquitination and protein turnover, as well as decreasing activity [39].

In phase 2a trials (duration 8 weeks) involving twenty-two obese males with dyslipidemia, prediabetes, or T2DM, GFT505 reduced fasting plasma triglycerides, low-density lipoprotein (LDL) cholesterol, and liver enzyme concentrations improving peripheral insulin sensitivity and hepatic insulin sensitivity [40]. The liver-specific action of GFT505 was suggested by the fact that neither PPARα nor PPARδ target genes were induced in skeletal muscle. Recently, it was demonstrated that Elafibranor was capable of improving the histological features of severe and moderate nonalcoholic steatohepatitis (NASH) and presents a favorable safety profile [41].

5. PPARγ Role in Metabolic Diseases

PPARγ was the first to be cloned and studied in depth, due to its being the target of a class of antidiabetic drugs called thiazolidinediones (TZD). Currently, we know of three isoforms of PPARγ: PPARγ_1 and PPARγ_3, which are expressed in the liver, intestine, and spleen; PPARγ_2 is present only in white and brown adipose tissue. Activated PPARγ induces the

expression of many genes, essential for adipogenesis, energy balance, insulin sensitivity, lipid and glucose metabolism, and inflammation [42]. In adipocytes, PPARγ is necessary in order for adipose tissue to develop. PPARγ_2 is a potent transcription activator and is triggered as a response to nutrient intake and obesity [43]. Indeed, mice deprived of PPARγ_2 (obese POKO mice) presented higher levels of fat accumulation in adipocytes in comparison with normally obese mice fed an identical diet [44]. According to these data, PPARγ_2 is essential for preventing lipotoxicity by promoting the expansion of adipose tissue and an increased lipid-buffering capacity in liver, muscle, and pancreatic beta cells. A proliferative response of β-cells to insulin resistance is also promoted by PPARγ [45]. In adipocytes, activated PPARγ causes a both balanced and adequate adipocytokine secretion (adiponectin and leptin), which regulates the behavior of insulin when introduced to peripheral tissues (such as the liver, skeletal muscle). As a consequence, PPARγ leads to improved insulin sensitivity in the entire body, additionally protecting the nonadipose tissue against excessive lipid levels [46]. Activated PPARγ induces the expression of genes that regulate the release, transport, and storage of fatty acid, such as the gene of LPL and fatty acid transporter CD36 [44]. PPARγ is also found in endothelial cells and vascular smooth muscle cells, where it seems to be an important factor in inflammation and atherosclerosis [47]. Polyunsaturated fatty acids are the natural ligand of PPARγ; they increase glucose uptake and insulin sensitivity, but they do not have many effects on adipocytes differentiation [48]. As already mentioned, TZDs (pioglitazone, rosiglitazone) are synthetic agonists of PPARγ and are widely used for the treatment of type 2 diabetes. TZDs are also described as insulin sensitizing, as they indirectly induce a higher insulin-stimulated glucose uptake in adipocytes, hepatocytes, and skeletal muscle; they also reduce free fatty acids levels and increase lipid storage in adipocytes. In the liver, TZDs decrease fasting plasma glucose levels through the increase of insulin sensitivity and the inhibition of gluconeogenesis [34]. In the muscles, TZDs reduces postprandial glucose levels [49]. A typical effect of TZDs is weight gain, due (at least in part) to fat being redistributed from visceral depot to subcutaneous depot [49].

In diabetic patients, the two principal types of TZDs (rosiglitazone e pioglitazone) have different effects on cardiovascular outcomes. According to the data of a PROactive study, pioglitazone reduced 16% of cardiovascular complications compared to a placebo [50]. Conversely, rosiglitazone was linked with a significantly increased death rate due to cardiovascular causes; consequently, in 2010 the European Medicines Agency withdrew the usage of this molecule [51]. These existing differences between pio- and rosiglitazone are most likely due to their differing effects on lipid levels; in fact, pioglitazone leads to an increased level of HDL cholesterol whilst lowering levels of triglycerides and fasting fatty acids. Rosiglitazone increases total and HDL cholesterol but also LDL cholesterol, which is negatively associated with cardiovascular diseases [52].

Recently, a new synthetic antidiabetic drug (SR1664) was proposed: when compared to TZDs, it does not induce weight gain. SR1664, with respect to the classic agonist of PPARγ,

blocks only the phosphorylation of serine 273 by CDK5. In a recent study, CDK5 deficient mice (CDK5 KO) demonstrated a paradoxical augmentation of PPARγ phosphorylation at serine 273 by a protein kinase (extracellular signal-regulated kinase, ERK), normally suppressed by CDK5 [53], suggesting a key role in the modulation of the abovementioned pathways. Finally, as extensively summarized elsewhere [54, 55], it was showed that natural PPARγ ligands have different binding modalities to the receptor with respect to the full TZD agonists and can activate also PPARα (as it occurs for genistein, biochanin A, sargaquinoic acid, sargahydroquinoic acid, resveratrol, and amorphastilbol) or the PPARγ-dimer partner retinoid X receptor (RXR; as it occurs for the neolignans, magnolol, and honokiol).

6. PPARα and Tumorigenesis

To date, many studies have analysed the role played by PPARs in the complex mechanism of tumorigenesis. Not all data are clear and PPARs seem to possess both positive and negative effects, depending on the type of tumor. In particular, it leads to negatively regulated colonic inflammation and proliferation. In an animal model of IL-10 $-/-$ mice, the inhibition of colitis was mediated by fenofibrate, increasing the PPARα expression of lymphocytes, macrophages, and colonic epithelial cells and resulting in proinflammatory cytokine production, such as interleukin-17, interferon-γ, and chemokine (C-C motif) ligand 20 (CCL20), being inhibited [56]. In partial agreement with these results in the mouse model, it was recently found that activation of PPARα through fenofibrate suppressed migration of oral cancer cells: in particular, differential protein profiling demonstrated that expressions of genes related to mitochondrial energy metabolism were either upregulated (Atp5g3, Cyc1, Ndufa5, Ndufa10, and Sdhd) or downregulated (Cox5b, Ndufa1, Ndufb7, and Uqcrh), conforming the key role of PPARα activation and response in mitochondrial energy metabolism [57]. In addition, recent data suggests that the selective activation of PPARα by palmitoylethanolamide inhibits colitis-associated angiogenesis, decreasing VEGF release and new vessels formation, via the phosphatidylinositol 3-kinase/Akt/mammalian-target-of-rapamycin (mTOR) signalling pathway [58].

In breast cancer, the data are still not clear. In some studies, PPARα inhibits breast cancer progression, promoting apoptosis of cancer cells through NFκB signalling. Recently, it was demonstrated that clofibrate presents a high chemosensitivity towards breast cancer cells, in all likelihood through the inhibition of NF-κB and ERK1/2 activation, which lowers cyclin D1, cyclin A, and cyclin E and induces proapoptotic P21 levels [59]. In contrast, in other studies PPARα promoted breast cancer progression by releasing leukotriene B4 that activates PPARα in B cells, inducing the differentiation of B cells and metastasis [60].

Despite the fact that PPARα clearly acts in a tumor-dependent fashion [61], recent evidence suggests that its overexpression enhances cancer cell chemotherapy sensitivity, whereas silenced PPARα decreased this event. In this regard, it is possible that it induces cell apoptosis by destructing

B-cell lymphoma 2 (Bcl2): as summarized elsewhere [62], PPARα serves as an E3 ubiquitin ligase to govern Bcl2 protein stability; PPARα binds to BH3 domain of Bcl2 and, subsequently, transfers K48-linked polyubiquitin to lysine-22 site of Bcl2 resulting in its ubiquitination and proteasome-dependent degradation. Confirming these results, it was found that ectopic expression of PPARα in hepatocarcinoma cells significantly suppressed cell proliferation and induced apoptosis by inhibition of NF-κB promoter activity, diminution of phosphor-p65, phosphor-p50, and BCL2 levels, and enhancing IkBα protein [63].

7. PPARγ and Tumorigenesis

PPARγ or dual PPAR α/γ agonists, in rodent carcinogenicity studies, were frequently associated with the development of hemangioma or hemangiosarcoma, fibrosarcoma, bladder, and hepatic tumors [64], suggesting that these types of cancer are drug specific [65].

Recently, a hypothetical mechanism was proposed that could clarify the induction of liposarcoma by differing PPAR agonists: in this model, the first stage of tumor development is initiation, during which DNA damage ensues independent of PPAR activation. The second step, promotion, relies on PPAR and is defined by tumor cell recruitment, proliferation, and differentiation [44]. A multitude of in vitro and in vivo studies have demonstrated much evidence for the antitumor effects of natural and synthetic PPARγ, since it seems to be upregulated in several human cancer lines. Indeed, recent data suggest that PPARγ ligands have an antitumorigenic effect in prostate cancer as a result of antiproliferative and prodifferentiation effects [66]. It would appear that TZDs possess protective effects in the development of pancreatic ductal adenocarcinoma, through improvement in insulin sensitivity and inflammation [67]. Interestingly, it was recently found that PPARβ/δ plays a role in regulating pancreatic cancer cell invasion through regulation of genes via ligand-dependent release of B-cell lymphoma-6 and that activation of the receptor may provide an alternative therapeutic method for controlling migration and metastasis [68].

Despite the fact that data are still elusive, recent evidence from human follicular thyroid carcinoma seems to underlie a key role for paired box gene 8 (PAX8)/PPARγ fusion protein in enhancing in vivo angiogenesis through VEGF expression [69]. PPARγ has positive effects on breast cell cancer: it downregulates the expression of the C-X-C chemokine receptor type 4 (CXCR-4) gene, which is crucial in the growth and progression of cancer, as well as in the development of metastasis. This mechanism seems to be PPARγ dependent, because it could be reversed by GW9662, that is, a PPARγ antagonist [70]. In partial agreement with these results, it was recently found that γ-tocopherol-rich tocopherol decreased tumor volume and multiplicity in estrogen-induced breast cancer female rats, increasing the expression of PPARγ and its downstream genes, phosphatase and tensin homolog (PTEN), and p27 [71]. In addition, it was found that in vivo PPARγ expression in mammary stromal adipocytes attenuates breast tumorigenesis through breast cancer 1 (BRCA1) upregulation and decreased leptin

secretion, and that 7,12-dimethylbenz[a]anthracene (DMBA) plus Rosiglitazone is able to reduce average mammary tumor volumes by 50% [72]. Conversely, heterozygous or homozygous intestinal-specific PPARγ deficiency enhanced small intestine and colon tumorigenesis in Apc(Min/+) mice [73]. Last but not least, robust data from myeloid-specific bitransgenic mouse model allow us to hypothesize that anti-inflammatory PPARγ in myeloid-lineage cells plays a key role in controlling proinflammatory cytokine synthesis, myeloid-derived suppressor cell expansion, immunosuppression, and the development of cancer [74]. Finally, recent evidence suggests that PPARγ is able to induce apoptosis in lung cancer, although it can be inhibited by NR0B1, an orphan nuclear receptor whose knockdown reduces tumorigenic and antiapoptotic potential [75].

8. PPARδ and Tumorigenesis

The role of PPARδ in carcinogenesis is uncertain and seems to be context-dependent. In particular, PPARδ, through its anti-inflammatory effects, seems to prevent cancer before its development; conversely, after the development of cancer, the activation of PPARδ promotes angiogenesis and cancer growth [76]. Clinical data suggest a strong association between PPARδ and aggressive cancer; in particular, inverse correlation of PPARδ expression with survival in gastrointestinal cancer has been noted [77]. In addition, PPARδ is required for chronic colonic inflammation and colitis-associated carcinogenesis: specifically, the cyclooxygenase (COX)-2-derived prostaglandin E2 (PGE2) signalling mediates crosstalk between tumor epithelial cells and macrophages to promote chronic inflammation and colitis-associated tumor genesis [78]. In agreement with what reported in the previous chapters, high-fat diet is associated with increased colorectal cancer incidence, probably because many of its effects on stem and progenitor cell compartment are driven by a robust PPAR-δ program and contribute to the early steps of intestinal tumorigenesis [79]. In addition, recent evidence suggests that high-fat diet modifies the PPARγ pathway leading to disruption of microbial and physiological ecosystem in murine small intestine [80].

Recently, the expression of PPARδ in breast cancer has been negatively linked with patient survival. In 2016, Wang et al. [81] showed that PPARδ upregulation increases the expression of catalase and Akt in breast cancer cells and in this way cells are able to survive in harsh conditions (including in the presence of chemotherapies), promoting progression and metastasis. Not surprisingly, both the proinflammatory PGE2 and the BRCA1 tumor-suppressor gene were found to regulate aromatase expression [82] and, furthermore, pioglitazone is able to inhibit aromatase expression by inhibition of PGE2 signalling and upregulation of BRCA [83]. Finally, recent evidence suggests that PPARδ modulates the migration and invasion of melanoma cells by upregulating Snail expression: in an elegant in vitro study, it was found that activation of PPARδ by GW501516 significantly increased the migration and invasion of highly metastatic A375SM cells, but not that of low metastatic A375P cells, by upregulating Snail expression [84]. Despite the promising results, further

studies are necessary in order to clarify the role of PPAR pathway modulation during cancer, also taking into account their paramount importance in regulating pro- and anti-inflammatory activities [85, 86] as well as possible interaction with the immune system [87–89] and other metabolic determinants [90–93].

9. Conclusion

The fact that a link between PPAR signalling, metabolism, and cancer exists currently represents one of the most active research fields in the literature. As discussed in this review, PPARs have many important functions. PPARs could be considered the crossroads of obesity, diabetes, inflammation, and cancer. These molecules are extremely interesting and are capable of treating numerous metabolic and nonmetabolic diseases. Currently, not all the effects of PPARs are known or fully explained, especially those related to tumorigenesis. Further research is necessary to identify a high-affinity and high-specificity agonist in order to counteract the abovementioned diseases.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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