Review Article

Anticancer Properties of PPARα-Effects on Cellular Metabolism and Inflammation

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Peroxisome proliferator-activated receptors (PPARs) have lately attracted much attention as therapeutic targets. Previously, PPAR ligands were associated with the treatment of diabetes, hyperlipidemia and cardiovascular diseases, as they modulate the expression of genes regulating glucose and lipid metabolism. Recently, PPAR ligands have been also considered as potential anticancer agents, with relatively low systemic toxicity. The emerging evidence for antiproliferative, proapoptotic, antiinflammatory and potential antimetastatic properties of PPARα ligands prompted us to discuss possible roles of PPARα in tumor suppression. PPARα activation can target cancer cells energy balance by blocking fatty acid synthesis and by promoting fatty acid β-oxidation. In the state of limited nutrient availability, frequently presents in the tumor microenvironment, PPARα cooperates with AMP-dependent protein kinase in: (i) repressing oncogenic Akt activity, (ii) inhibiting cell proliferation, and (iii) forcing glycolysis-dependent cancer cells into "metabolic catastrophe." Other potential anticancer effects of PPARα include suppression of inflammation, and upregulation of uncoupling proteins (UCPs), which attenuates mitochondrial reactive oxygen species production and cell proliferation. In conclusion, there are strong premises that the low-toxic and well-tolerated PPAR ligands should be considered as new therapeutic agents to fight disseminating cancer, which represents the major challenge for modern medicine and basic research.

1. PPARα AND CANCER CELL ENERGY BALANCE

The concept that neoplastic transformation based on the failure of energy homeostasis is currently regaining considerable interest. This notion was associated with the hypothesis by Otto Warburg who indicated a distinctive dependence of tumor cell metabolism from glycolysis, even when there is sufficient amount of oxygen available for much more efficient oxidative phosphorylation [1, 2]. Only recently, it has been established that the inclination of tumor cells for glycolysis is mainly driven by mitochondrial dysfunction or oncogenic activity of Akt, Ras, or Myc [3, 4].

PPARα, which is a transcriptional activator of fatty acid β-oxidation machinery (e.g., acyl-CoA oxidase (ACO), acyl-CoA synthetase (ACS), carnitine palmitoyl transferase (CPT1), fatty acid binding protein (FABP), and fatty acid transporter (FAT)), can switch energy metabolism toward fatty acid degradation, and decrease glucose uptake by repressing glucose transporter GLUT4 [5, 6]. Interestingly, PPARα acts as a direct sensor for fatty acids, which are considered natural ligands for this nuclear receptor [7, 8]. According to fatty acid, glucose cycle paradigm increased rate of fatty acid and ketone bodies oxidation forces the decline in glucose utilization through the inhibition of glycolytic enzymes [9, 10]. This concept was supported by the results of animal studies, showing that during fasting-activated PPARα can divert energy metabolism from the glucose to fatty acid utilization as a primary source of energy.

Mitochondria are the main organelles that carry out fatty acid β-oxidation and produce ATP through oxidative phosphorylation [11]. Oncogenic transformation is frequently associated with mitochondrial dysfunction, however, it is still controversial if this is a result, cause, or contribution to the malignant phenotype [12]. A direct link between

aerobic respiration and carcinogenesis has been provided by the demonstration that the loss of p53, which is most commonly mutated gene in cancer, results in decrease of synthesis of cytochrome c oxidase (SCO2) gene expression [13]. SCO2 is crucial for the incorporation of mitochondrial DNA-encoded cytochrome c oxidase subunit (MTCO2) into the cytochrome c oxidase complex, and the proper assembly of this complex is essential for the mitochondrial respiration. Therefore, SCO2 downregulation in p53-deficient cells heavily inpairs oxidative phosphorylation and triggers the switch toward glycolysis [13].

Furthermore, loss of function mutations in the nuclear genes encoding the Krebs cycle enzymes (such as succinate dehydrogenase and fumarate hydratase) are frequently observed in uterine leiomyomas, renal carcinomas paragangliomas, and phaeochromocytomas [14]. The clinical data suggest that these proteins might have other functions besides energy metabolism and can be involved in the induction of apoptosis, similarly to mitochondrial apoptosis inducing factor (AIF) [15]. Nevertheless, it is likely that the glycolysis-promoting metabolism of cancer cells relieves the selection pressure and permits clonal growth of the cells with defective mitochondrial system. Such cells could be brought to the verge of metabolic catastrophe in the condition of limited glucose availability or when the oxidative metabolism is forced pharmacologically. This opens an opportunity for the use of PPARα ligands, as they should be selectively toxic for cancer cells and neutral for normal cells.

Energetic function of mitochondria is not restricted to ATP generation in the process of oxidative phosphorylation. Systemic thermal homeostasis maintained by mammals relies broadly on nonshivering thermogenesis carried on by brown adipocytes. In these cells, uncoupling protein (UCP1) is responsible for the "proton leak" of mitochondrial inner membrane, which separates respiration from ATP synthesis. The energy released through the proton flow in line with electric potential gradient is dissipated as heat.

Recently, several mammalian UCP homologues have been discovered, among which ubiquitously expressed UCP2 and muscle—specific UCP3 gained deep interest [16]. They share high degree of structural similarity with UCP1 though their primary function, which still remains elusive, is not limited to thermogenesis, but their mitochondrial uncoupling activity is connected with fatty acid anion transport. The expression of both UCP2 and UCP3 is regulated by PPARα [6, 17–19], and this notion provides an interesting link with cancer cell metabolism and behavior.

The recent report by Pecqueur and colleagues [20] has revealed that UCP2 controls proliferation through driving cellular metabolism to fatty acid oxidation and limiting glycolysis. UCP2- deficient cells proliferate significantly faster than wild-type cells and rely on glycolysis-derived pyruvate catabolism, like all rapidly normal and transformed dividing cells do. Remarkably, the higher proliferation rate in these cells is a result of cell cycle shrinkage and not the decrease in the quiescent (G0/G1) cell fraction, even though the proproliferative PI3K/Akt and MAPK signaling pathways are more activated in UCP −/− than wt cells [20]. Interestingly, UCP2 is also involved in cellular adhesion and invasive potential,

as was revealed in the studies on the THP1 monocytes with UCP2 overexpression, which showed impaired β2 integrin—mediated adhesion and transendothelial migration [21]. Taking together, these data suggest that PPARα- mediated UCP2 upregulation might have a negative impact on cancer progression.

Uncoupling proteins due to their ability to reduce ATP bisynthesis inhibit production of reactive oxygen species (ROS) during respiration. ROS and products of their activity, such as lipid peroxides, are not only toxic and mutagenic, but also stimulate inflammatory response, and therefore contribute to cancer development. PPARα regulates the expression of three proteins which govern the transport of fatty acids in and out of mitochondria. This includes CPT1 and UCP3 as well as mitochondrial thioesterase 1 (MTE-1) [17, 22]. This trio controls the mitochondrial pool of fatty acids in order to keep the danger of their peroxidation at minimal level. CPT1 supplies mitochondria with long chain fatty acid—CoA (LCFA-CoA) complexes, which undergo β-oxidation. At a high rate of β-oxidation, UCP3 in the conjunction with MTE-1 acts to prevent LCFA-CoA accumulation: MTE-1 releazes CoA-SH and enables its recycling, whereas UCP3 exports fatty acid anions outside the mitochondrial matrix, and therefore reduces the chance of their peroxidation by the superoxide generated in the complex I and III of mitochondrial electron chain [23–25]. Simultaneously, UCP2 and UCP3 due to their proton leak activity reduce the rate of ROS production, which is proportional to the protonmotive force [16, 26]. The hypothesis of protective role of PPARα in oxidative stress is supported by the results from in vivo studies showing that PPARα-deficient mice have higher level of oxidative damage in cardiac muscle, and that fenofibrate diminishes inflammatory response and oxidative stress in the neural tissue in rats subjected to traumatic brain injury [27, 28].

The above described evidence indicates that PPARα activation might metabolically target neoplastic cells through inhibition of glycolysis and promotion of fatty acid catabolism, but also might elicit chemopreventive effect through the decrease of respiratory ROS production.

Interestingly, the metabolic peculiarities of cancer cells are not restricted to aerobic glycolysis but paradoxically include also fatty acid synthesis. Some types of tumors, particularly of hormone responsive epithelial origin, are characterized by the abnormally high activity of fatty acid synthase (FAS), which is an enzyme with barely detectable levels in normal tissues. The FAS produces palmitate from the condensation of acetyl-CoA and malonyl-CoA. Interestingly, FAS overexpression correlates well with prostate cancer progression in which the highest levels of FAS activity have been observed in bone metastases [30]. For this reason, FAS has been named a "metabolic oncogene" [31]. FAS is also involved in biosynthesis of phospholipids, which are substrates for the new membrane synthesis in rapidly dividing cells, protein myristoylation, and lipid partitioning into membrane microdomains [31, 32]. FAS activity provides a significant growth advantage for transformed cells. Indeed, pharmacological inhibition of FAS induced apoptosis in cancer cell, possibly by the accumulation of
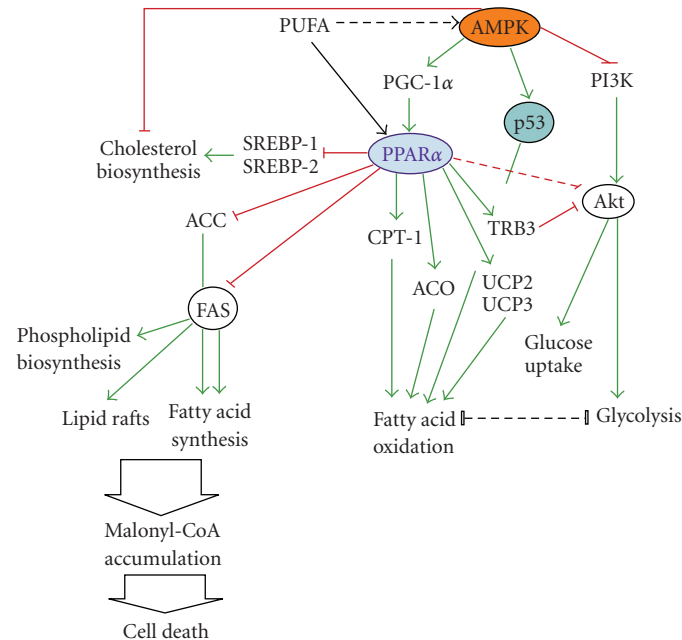
FIGURE 1: PPARα interferes with the metabolic pathways in the cancer cells. In the state of energy deprivation, AMPK activates fatty acid oxidation through PPARα- and p53-dependent pathways and blocks anabolic processes, for example, cholesterol biosynthesis. AMPK is a potent inhibitor of Akt-induced glycolysis. In response to nutrient deficiency, PGC-1α and PPARα upregulate expression of TRB3, which inactivates Akt via direct interaction [29]. PPARα promotes fatty acid β-oxidation as a transcriptional activator of fatty acid catabolic enzymes and transport proteins (e.g., ACO, CPT1, UCP2, and UCP3). Simulateneously, PPARα blocks lipid synthesis by repression of SREBP-1 and -2, ACC, and FAS. FAS inhibition in various cancer types results in toxic accumulation of malonyl-CoA and apoptosis. For more details, see the text. Arrowheads represent activation/upregulation, and blunted lines indicate inhibition/downregulation of the cellular proteins or processes. ACC—acetyl-coA carboxylase; ACO—acyl-coA oxidase; AMPK—AMP-dependent kinase; CTP-1—carnitine palmitoyltransferase-1; FAS—fatty acid synthase; PGC-1α—PPARγ coactivator 1α; PUFA—polyunsaturated fatty acids; SREBP—steroid response element binding protein; TRB3—mammalian homolog of *tribbles*; UCP2, UCP3—uncoupling proteins.

malonyl-CoA [33]. In addition, pharmacological or RNA silencing-mediated inhibition of FAS significantly reduced the expression of the oncogenic Her-2/neu (erbB-2) [34, 35], but it also induced a dramatic increase in VEGF expression by activating the Erk1/2 pathway [36].

Importantly, activation of PPARα has been shown to block FAS pathways through the transcriptional repression of genes, which are directly involved in its metabolic activity (FAS; acyl-CoA carboxylase (ACC); steroid response element binding proteins (SREBP1, SREBP2)) [37–41] (Figure 1). Simultaneously, PPARα blocks Erk1/2 activation [42]. Therefore, the possibility exists that PPARα agonists could block Her-2/neu expression without a danger of proangiogenic stimulation of VEGF expression. This might encourage new clinical applications for PPARα ligands against those cancer cells, which are characterized by the overactive FAS.

Lipid metabolism deregulation manifested by hiperlipidemia has been described as a significant risk factor for colorectal cancer development [43]. Increased serum trigliceride and cholesterol level were observed in patients with familial adenomatous polyposis coli. An interesting study by Niho and coworkers [44] showed that APC-deficient mice, the animal model for human adenomatous polyposis coli syndrome, when treated with PPARα ligand and lipid level normalizing drug—bezafibrate, develop

significantly fewer intestinal polyps. This protective action of PPARα agonists against colorectal carcinogenesis seems promising from the therapeutic point of view, suggesting that the patients might benefit not only from normolipidemic activity of PPARα, but also from its antineoplastic effects as well.

2. AMPK AND AUTOPHAGY

In the state of energy depletion, caused for instance by a limited glucose availability, normal cells can switch between energy metabolic pathways to support their survival. AMP-dependent protein kinase (AMPK) plays an integral role in the response to starvation by sensing the rise in AMP/ATP ratio and switching off the ATP-consuming anabolic processes, such as protein and lipid synthesis or DNA replication. AMPK can induce several rescue pathways, which enhance cell survival during glucose deprivation (Figures 1 and 2). One of them includes p53-dependent check point, which blocks cell cycle progression and promotes fatty acid oxidation and autophagy, as an alternative source of energy [45, 46]. Interestingly, p53-deficient cancer cells are very sensitive to the lack of glucose, and being incapable of autophagy, underwent massive apoptosis [46, 47]. It was demonstrated that PPARα acts downstream from AMPK and
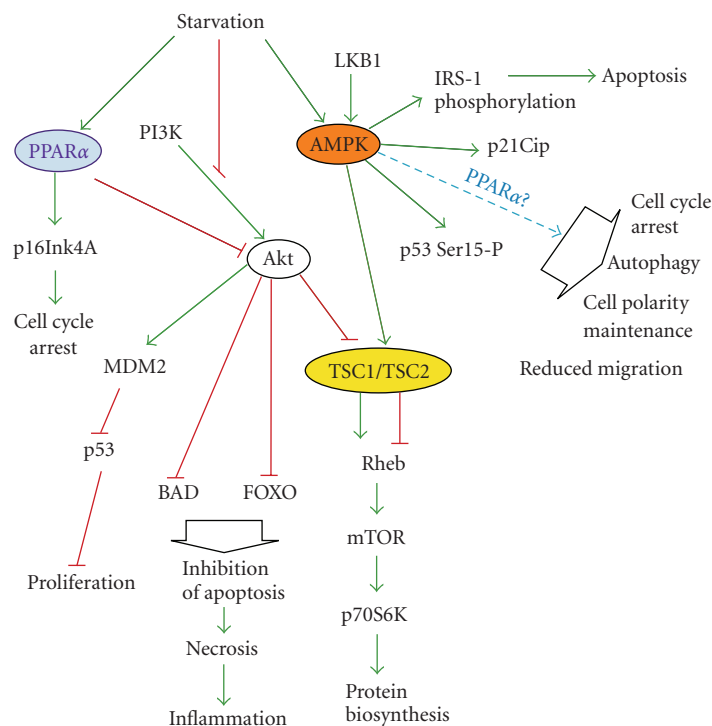
FIGURE 2: PPARα and AMPK activities in the cancer cells exposed to energetic stress. AMPK switches on p53-dependent cell cycle metabolic check point and autophagy and blocks Akt/mTOR protein de novo synthesis pathway. PPARα induces cell cycle arrest and downregulates Akt neutralizing its antiapoptotic actions. For more details, see the text. Arrowheads represent activation/upregulation, and blunted lines indicate inhibition/downregulation of the cellular proteins or processes. IRS-1—insulin receptor substrate-1; mTOR—mammalian target of rpamycin kinase; TSC1—tuberous sclerosis 1 (hamartin); TSC2—tuberous sclerosis 2 (tuberin).

was responsible for AMPK-induced fatty acid oxidation in cardiac and skeletal muscle [48, 49]. This might suggest that PPARα mediates other activities of AMPK. AMPK is a potent inhibitor of PI3K/Akt signaling, especially of Akt-induced glycolysis and protein synthesis [45, 50, 51]. Oncogenic Akt is responsible for increased activity of mammalian target of rapamycin (mTOR) kinase, which phosphorylates downstream regulators of translation such as 4EBP-1 and p70S6 kinase (Rsk) [51, 52]. AMPK antagonizes this Akt-induced mTOR activation by activating tumor suppressor tuberous sclerosis 2 (TSC2, tuberin), which in turn inactivates a small G-protein, Rheb, and in consequence disabled Rheb cannot activate mTOR [53–55]. Some of theses multiple signaling and metabolic connections between PPARα, AMPK, and mTOR are additionally explained in Figures 1 and 2.

We have demonstrated that PPARα activation inhibits Akt phosphorylation and reduces the metastatic potential of mouse melanoma cells [42]. This may provide an interesting synergy between AMPK and PPARα toward mTOR inhibition and the activation of autophagy. Although the mechanism by which fenofibrate attenuates Akt phosphorylation is still under investigation. It has recently been reported that fenofibrate increases plasma membrane rigidity in a manner similar to elevated cholesterol content [56]. In this report, fenofibrate did not change the membrane content of cholesterol but increased plasma membrane rigidity by itself, altering activities of different membrane-bound proteins.

Therefore, one could speculate that fenofibrate, besides its role as a PPARα agonist, may also act in a nonspecific manner by altering membrane-bound growth factor receptors such as IGF-IR or EGFR, which are known to have a strong signaling connection to Akt. Further experiments are required to determine whether similar fenofibrate-mediated changes in the fluidity of the plasma membrane are indeed responsible for the attenuation of the ligand-induced clustering of receptor molecules—a critical step in the initiation of growth and survival promoting signaling cascades.

It has also been demonstrated that omega 3 polyunsaturated fatty acids (n-3 PUFA), which are potent ligands of PPARα, induce fatty acid β-oxidation via AMPK [57]. AMPK is regulated by a tumor suppressor LKB1 and coordinates various cellular responses, which can exert antineoplastic effects [58]. One of them is autophagy, which has been intensively explored in the context of carcinogenesis. Autophagy, also called a type II programmed cell death, is a lysosomal-mediated digestion of different cellular components, including organelles to obtain energy, however, it may also lead to cell death [3, 59, 60]. There is a growing body of evidence that defective autophagy may result in cancer progression [59, 61]. Beclin 1, a protein required for autophagy, is frequently lost in ovarian, breast, and prostate cancers, and beclin 1 +/− mutant mice are prone to increase incidence of tumors derived from epithelial or lymphopoietic tissues [62, 63]. Autophagy is negatively controlled by Akt/PI3K

signaling and specifically by mTOR, which acts as a sensor of growth stimuli and nutrient availability and at the same time is the main target for the rapamycin-mediated antitumor activity [64]. Degenhardt et al. [3] demonstrated that cells transformed by Akt overexpression and by deficiency in proapoptotic genes, BAX, and BAK show a highly invasive phenotype, however, became necrotic when deprived of oxygen and glucose.

Although Akt activation provides a growth advantage, it simultaneously impairs autophagy in response to metabolic stress and condemns cells to necrotic death. Abundant necrosis stimulates inflammation and enhances macrophage infiltration within tumors, which is a poor prognostic factor, and actually accelerates tumor growth [3]. These findings support the notion that loss of autophagy in apoptosis-incompetent cells can have tumor promoting effects. This can happen in cells with constitutively activated Akt, as it triggers a strong antiapoptotic signal, mainly by the inactivation of proapoptotic proteins, BAD, and FOXO [52].

In the state of nutrient deprivation, AMPK induces autophagy in a p53-dependent manner and evokes apoptosis through the serine phosphorylation of insulin receptor substrate (IRS-1), which in turn inhibits PI3K/Akt signaling pathway [65]. It is not known if PPARα is involved in these actions downstream of AMPK, but possibly can support them by the inhibition of Akt [66]. In this respect, inhibition of Akt by PPARα ligand, fenofibrate, significantly suppressed anchorage-independent growth, cell motility and cell migration in vitro; and in the experimental animal model, fenofibrate treatment reduced metastatic spread of hamster melanoma cells to the lungs [42, 67]. This apparent inhibition of cell migration and compromised cell invasiveness was likely associated with alterations in the cytoskeletal structure. Interestingly, AMPK has been implicated in the maintenance of epithelial cell polarity, by affecting actin-fiber distribution during energy deprivation [68]. In particular, AMPK mutations disrupted the polarity of the epithelium and triggered tumor-like hyperplasia, again supporting the notion of a possible cooperation between PPARα and AMPK.

3. PPARα AND INFLAMMATION

The anticancer effects of activated PPARα can be attributed to its well-characterized anti-inflammatory properties. PPARα inhibits expression of variety of inflammatory genes, such as interleukin 6 (IL-6) and inducible cyclooxygenase-2 (COX-2), as well as reduces nitric oxide production in murine macrophages exposed to bacterial lipopolisaccharide (LPS) [69–71]. These events can be ascribed to the PPARα antagonistic action against the main transcription factors mediating inflammatory responses, nuclear factor-κB (NF-κB), and activating protein-1 (AP-1) (Figure 3). NF-κB activity is repressed by inhibition of p50 and p65 nuclear translocation or by I-κB upregulation, which induces p65 phosphorylation and subsequent proteasomal degradation [72–76]. AP-1 is affected by PPARα through inhibition of its binding to the consensus DNA sequence and by suppressing c-Jun activity [77–79]. Inhibition of inflammatory
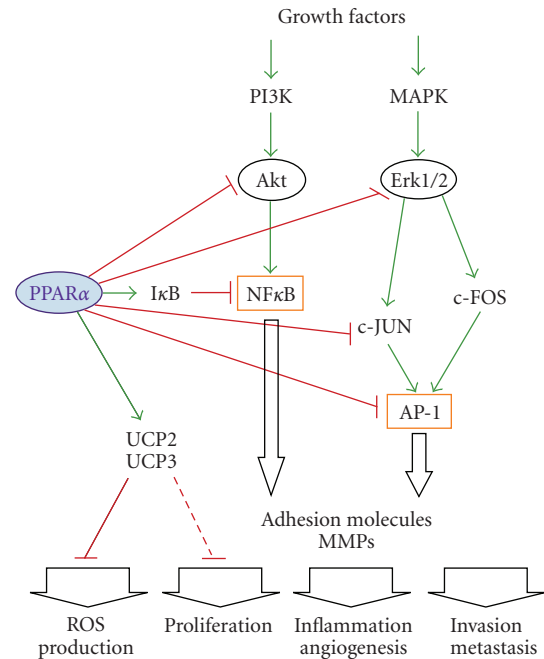

FIGURE 3: PPARα antagonizes main inflammatory signaling pathways through repression of the main inflammatory transcription factors: NFκB and AP-1. Additionally, PPARα reduces ROS-mediated inflammation by upregulation of uncoupling proteins UCP2 and UCP3. See the text for more detailed explanation. Arrowheads represent activation/upregulation, and blunted lines indicate inhibition/downregulation of the cellular proteins or processes. AP-1—activating protein-1; Erk1/2—extracellular signal response kinase 1/2; IκB—inhibitor of NFκB; MAPK—mitogen activated protein kinase; NFκB—nuclear factor κB; ROS—reactive oxygen species.

signaling is important for anticancer therapy in order to reduce mitogenic and angiogenic cytokines and growth factors released by activated immune and stromal cells [80]. Moreover, inhibition of NF-κB, which coordinates a number of antiapoptotic pathways, sensitizes neoplastic cells to nutrient deficiency stress and facilitates apoptosis [81]. NF-κB induces expression of matrix metalloproteinases, such as MMP-9 and urokinase-type plasminogen activator (uPA), and a number of adhesion molecules including ICAM-1, VCAM-1; thus promoting cancer cells' invasiveness and dissemination [82–84]. Therefore, one could speculate that PPARα-mediated inhibition of NF-κB could contribute to the observed reduction of metastatic spread in melanoma-bearing animals treated with fenofibrate [67].

Recently, a completely new image of PPARα in tumor development has been proposed. Kaipainen and coworkers were the first who initiated studies on the role of PPARα expression in host-tumor interaction. They demonstrated that PPARα depletion in the host significantly reduced tumor growth and metastasis [85]. This effect was not correlated with the tumor type and was independent from the presence or absence of PPARα in the tumor cells. The loss of PPARα in the host was associated instead with decreased microvessel density and enhanced granulocyte infiltration in the tumor

tissue and with the elevation of the angiogenesis inhibitor, thrombospondin (TSP-1) [85].

Since necrosis and chronic inflammation within the tumor are associated with intensified macrophage infiltration and poor prognosis [86], it is not entirely clear why granulocyte influx is much more effective in eliminating tumor cells and apparently does not increase the risk of increased tumor vascularization. The possible answer might be a distinct profile of cytokines/chemokines released by macrophages and by granulocytes. The other speculative explanation could be associated with acidic tumor microenvironment, which is known to impair cellular and humoral immune responses. However, it affects differentially macrophages, neutrophils, and lymphocytes, leaving the latter two less prone to this acidic inactivation [87].

4. CONCLUDING REMARKS

As presented above, PPARα contributes to the maintenance of physiological homeostasis by multiple mechanisms. Particularly interesting is the interplay between PPARα and AMPK, which represents evolutionary conserved sensor of the metabolic equilibrium, governing the balance between cell death and cell survival. The possible involvement of PPARα in the control of autophagy is an exciting direction to explore, which may reveal new aspects of PPARα role in carcinogenesis.

The metabolic, anti-inflammatory and antiproliferative properties of PPARα ligands provide premises for the potential use as supplementary agents in anticancer treatment, and especially antimetastatic therapies. In addition, low toxicity of synthetic PPARα agonists and the abundance of effective natural ligands provide additional encouragement for the anticancer treatment. However, it should be kept in mind that PPARα was first described to promote peroxisome proliferation and hepatocellular neoplasia in rodents which conversely to humans, and the majority of other species, turned out to be particularly sensitive to PPAR ligands.

Finally, role of PPARα in the tumor-host interactions should be thoroughly studied and explained in order to design effective anticancer therapies with minimized risk of unwanted side effects.

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