Peer-reviewed version available at Int. J. Mol. Sci. 2018, 19, 1907; doi:10.3390/ijms19071907

The involvement of PPARs in the peculiar energetic metabolism of tumor cells

Antonosante A[1], d'Angelo M[1], Castelli V[1], Catanesi M[1], Iannotta D[1], Giordano A[2,3], Ippoliti R[1], Benedetti E[1], Cimini A[1,2,4]

1Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy

2 Sbarro Institute for Cancer Research and Molecular Medicine, Departement of Biology, Temple University, Philadelphia, USA

3Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

4National Institute for Nuclear Physics (INFN), Gran Sasso National Laboratory (LNGS), Assergi, Italy

Energy homeostasis is crucial for cell fate since all cellular activities are strongly dependent on the balance between catabolic and anabolic pathways. In particular, metabolic and energetic modulation has been reported in cancer cells long time ago, but have been neglected for a long time. Instead, during the past 20 years a recovery of the study of cancer metabolism has led to better consider metabolic alterations in tumors. Cancer cells must adapt their metabolism to meet the energetic and biosynthetic demands that accompany rapid growth of the primary tumor and colonization of distinct metastatic sites. They are largely dependent on aerobic glycolysis for their energy production and also are associated with increased fatty acid synthesis and increased rates of glutamine utilization. Emerging evidence has shown that therapeutic resistance to cancer treatment may arise due to deregulation in glucose metabolism, fatty acid synthesis, and glutamine utilization. Cancer cells exhibit a series of metabolic alterations induced by mutations leading to gain-of-function of oncogenes and loss-of-function of tumor suppressor genes that include increased glucose consumption, reduced mitochondrial respiration, increased reactive oxygen species generation and cell death resistance, all of which responsible for cancer progression. Cholesterol metabolism is also altered in cancer cells and supports uncontrolled cell growth. In this context, we review the roles of PPARs transcription factors, master regulators of cellular energetic metabolism, in the control and deregulation of energetic homeostasis observed in cancer. We highlight the different contribution of the different PPAR isotypes in different cancers and the differential control of their transcription in the different cancer cells.

Introduction

Mammalian cellular activities require a significant energy source, which is produced by specific mechanisms involved in regulation of cellular energy homeostasis. The correct balance between catabolic and anabolic pathways strongly influence cellular fate, because they are involved in biochemical reactions that drive ATP production/consumption. ATP is the mainly energy source for cells and its production is linked to glucose and lipid metabolism. Oxidative glucose metabolism by OXPHOS (oxidative phosphorylation) produces up to 36 ATP per mole of glucose, whereas non-oxidative glucose metabolism by glycolysis results in 2 ATP per mole of glucose [1]. Hence, oxygen availability provides an optimal cellular condition to produce high levels of energy. Hypoxia determines a less efficient cellular condition in which the cell uses glycolysis to produce energy. Another way to cope with cellular energetic demands is lipid metabolism by fatty acids (FAs) peroxisomal and mitochondrial β-oxidation, that can provide energy in the form of redox potential [2-3]. FAs can be acquired through diet and *de novo* synthesis, beyond the energetic demands they are essential for membrane biosynthesis and intracellular signal transduction by specific molecules [4]. Moreover, many cells types present cytosolic lipid deposits, also called lipid droplets (LDs), dynamic organelles that contain triacylglycerlos (TAGs) and cholesteryl esters, that

present several functions such as: reducing lipotoxicity, lipid storage, lipid metabolism and are directly involved in cellular physiology [5-7]. Unlike normal cells, cancer cells exhibit uncontrolled proliferation that needs adjustments of energy metabolism in order to ensure cell growth and division. Although, in normoxia healthy cells use degradation of glucose to pyruvate and later TCA (tricarboxylic acid cycle) to produce ATP, neoplastic cells prefer to maintain active glycolytic pathway rather than oxidative phosphorylation. The first observation of this phenomenon date back to about eighty-eight years ago, Otto Warburg noticed that tumor cells switch toward a glycolytic metabolism even in aerobic conditions, associated with mitochondrial metabolism suppression, in this regard that metabolic adaptation is called "aerobic glycolysis" or "Warburg effect" [8]. To date, the researchers do not have clear answer to explain this metabolic switch that occurs in cancer cells, even though several hypothesis were provided. Usually the solid tumor masses are characterized by the presence of a hypoxic zone near the core of the masse, this hypoxic environment supports glycolytic metabolism and gives resistance from chemotherapy, mainly due to CSCs (cancer stem cells) [9-11]. It was also noticed that many different types of cancer cells (glioma, hepatoma and breast) are able to obtain ATP from OXPHOS and they can pass from a fermentative to an oxidative metabolism and vice versa according to environmental conditions, glucose is directly involved in this switch [12-15]. The glucose-dependent suppression of mitochondrial respiration is referred to as "Crabtree effect" [16], this effect is reversible and collaborates with "Warburg effect" to maintain cancer cells independently from the presence or absence of oxygen [17]. In a recent study, using a mathematical computational model, Epstein et al. [18] have explored the coexistence between glycolytic and oxidative pathways in cancer cells. Starting from the assumption that cancer cells in different activities (division, migration and invasion) quickly need ATP but also need to maintain baseline levels of ATP during moments of apparent stand by. Hence, in relation to fluctuating energy demands and assuming that tumor cells exist in a heterogeneous environment due to altered intra-tumoral blood vessels, they can use a glycolytic pathway to produce ATP very quickly in short-term energy requests, but at the same time they maintain baseline levels of energy with OXPHOS [18]. Noteworthy, is the fact that some tumor present different cell subpopulations, one in hypoxic layer and glucose-dependent that release lactate as waste, which is used by the second sub populations in normoxic layer as main energy source by TCA [19]. These evidences lead to think that there is cooperation between the different types of cells within the tumor, which could be a key mechanism for tumor progression. The adjustment of cancer cells to the metabolic switch is regulated by several genes involved in glycolytic pathway, some of them are also oncogenes. The constant activity of PI3K/Akt signalling up-regulates protein related to glucose transport (GLUTs) in association with high hexokinase II (HKII) activity. HKII is able to bind voltage-dependent anion channel (VDAC) on the outer mitochondrial membrane to protect cells from apoptosis [20-21]. Altered c-Myc regulation affect expression of genes related to glutamine metabolism and glycolysis (HKII, lactate dehydrogenase (LDH), pyruvate kinase isoenzyme M2 (PKM2), phosphofructokinase 1 (PFK1) and GLUT1) [21-22]. PKM2 presents low activity and is a typical isoform in tumor cells, more likely the reduced activity of PKM2 allows keeping stocks of glycolytic metabolites to ensure macromolecules biosynthesis [23]. The main genes involved in glycolysis result up-regulated in hypoxic environment and they are directly under hypoxic inducible factor-1α (HIF-1α) transcriptional control [24]. In addition to supporting the production of cellular energy, aerobic glycolysis is also essential for the macromolecule biosynthesis, in order to provide the structural components for cell proliferation. The increase in glucose uptake, by overexpression of glucose transporter such as GLUT1, is the first step in glycolysis, while the pyruvate is the last step that provides the carbon source for anabolic process, such as *de novo* synthesis of nucleotides, lipids and proteins. As well as for cellular building blocks, generation of macromolecules in cancer cells is useful to produce reducing equivalents, as NADH and NADPH, in turn essential to ensure glucose metabolism, macromolecule biosynthesis and degradation [25]. In this view, lipid synthesis and glutamine utilization are essential for tumor survival and related pathway are affected by different alterations, closely relate to tumor type. Fatty acids synthesis is typically reactivated in

cancer cells, by upregulation of lipogenic enzymes to provide monomeric components for: membrane building, lipid signalling and post-translational modification of the proteins [26]. Breast and prostate cancer show an increase in expression levels of fatty acids synthase enzyme (FAS) and elongation of very-long-chain fatty acid protein enzymes, such as ELOVL1-7 [27-28]. Stability and fluidity of cellular membranes are cholesterol-dependent and lipid rafts (involved in the regulation of intracellular transduction signals) are mainly composed of cholesterol [29]. Furthermore, cholesterol synthesis and related mevalonate pathway (MVA) also are linked to production of intermediates needed for post-translational modifications of Rho, Ras and other small GTPase (isoprenylation, farnesylation and genarylation) [30]. Interestingly, Statins are drugs used to decrease plasma cholesterol levels in hypercholesterolemia conditions, by inhibiting HMG-CoA reductase (HMGCR). This enzymes is involved in reduction of HMG-CoA to mevalonate, the rate-limiting step of cholesterol synthesis. It was demonstrated that statins are able to decrease proliferative index of breast cancer and acute myeloid leukemia cells and makes colorectal cancer cells more sensitive to chemotherapy [31-33]. Moreover, prostate cancer cells showed high levels of cholesterol [34]. The excess amount of LDs in cancer cells is further evidence that FAs and cholesterol accumulate in many type of cancer. By label-free Raman spectroscopy imaging high grade prostate cancer and metastasis it was revealed abnormal LDs accumulation associated with PTEN loss and PI3K/Akt activation [35]; similar evidences were observed in breast cancer cell line [36] and colon cancer stem cells [37], while in gliomas higher amount of LDs was directly proportional to tumor aggressiveness degree [38]. As previously mentioned, FAs derived from free triacylglycerides or intracellular deposit can be metabolised to produce energy in the form of redox fuel, this process starts in cytoplasm (triglyceride and monoacylglycerol lipases) and ends in mitochondria. The process inside the mitochondria is termed fatty acid β-oxidation (FAO), but it can occur also in the lumen of peroxisomes. The end products of lipid decomposition are NADH, $FADH_2$ and acetyl-CoA directed towards TCA cycle. Some tumor cells need of FAO to meet their energetic demands, mainly non-glycolytic cancer such as prostate cancer and large B-cell lymphoma [39-41], but also glucose's consuming cancer like pancreatic cancer [42], while in glioblastoma FAO contributes to protect the cells from oxidative stress by up-regulation of detoxification enzymes, such as glutathione (GSH) [43]. Unlike glycolysis, where hypoxic condition increases glucose utilization, lipid biosynthesis is underdog by oxygen lack, therefore lipid accumulation in LDs is supported [44-45]. In this scenario, the carbon source to synthesize lipid compounds is supplied by glutamine, isocitrate dehydrogenase-1 (IDH1) activity releases citrate in the cytosol after carboxylation of α-Ketoglutarate glutamine-derived, at the same time some hypoxic cancer cells show inhibition of mitochondrial β-oxidation [46-48]. Moreover, Ras oncogene together with hypoxia induces the pyruvate dehydrogenase kinase 1 (PDK1) that in turn inhibits pyruvate dehydrogenase (PDH) and forces cells to implement glutamine-dependent anaplerotic behaviour [44,47,49]. This phenomenon restores TCA cycle under specific conditions and highlighted the key role of glutamine metabolism in cell growth. Beyond the anaplerotic involvement, glutamine catabolism provides nitrogen to synthetizes nucleotide, glutathione and results the major energy source in transformed cells [50]. Cancer cells rely on glutamine uptake to ensure a further pathway to support their accelerated metabolism. Gao et al. [22] showed that c-Myc stimulates glutaminase (GLS) expression through the suppression of miR-23a/b, while inhibition of Rho-GTPase by small compound determines reduction of glutaminase activity NF-kB-dependent in breast cancer and B lymphoma cells [51]. In addition DeBerardinis at al. [52] observed that glioblastoma cells performed aerobic glycolysis associated with elevated glutamine catabolism to obtain redox energy and TCA cycle intermediates in order to support biosynthetic activity, mainly FAs. Interestingly, high-invasiveness ovarian cancer cells showed more remarkable glutamine dependence than low-invasiveness ovarian cancer cells, this feature being related to glutamine mediated STAT3 modulation [53].

In this context, we review the roles of PPARs transcription factors, master regulators of cellular energetic metabolism, in the control and deregulation of energetic homeostasis observed in cancer.

We highlight the different contribution of the different PPAR isotypes in different cancers and the differential control of their transcription in the different cancer cells. Our purpose in this review is to describe recent observations that demonstrate the key role of PPARs in promoting or preventing characteristic metabolic switch that provide energy for tumour survival.

PPARs

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. PPARα (NR1C1) was the first described as the receptor mediating peroxisome proliferation in rodent hepatocytes in 1990, later two related isotypes, PPARβ/δ (NR1C2) and PPARγ (NR1C3) were found and characterized. PPARα is mainly expressed in tissues presenting high fatty acid catabolism activity such as the liver, the heart, the brown adipose tissue, the kidney and the intestine; it is also involved in regulation of lipoprotein synthesis. Regarding PPARγ, there are two isoforms: γ1 and γ2 obtained by alternative splicing, Both isoforms act in the white and brown adipose tissues to promote adipocyte differentiation and lipid storage while only of PPARγ1 is expressed in other tissues such as the gut or immune cells. PPARγ transcriptional activities are also involved in the control of inflammation process, cell cycle regulation and glucose metabolism by ameliorating of insulin sensitivity; in fact it is a useful target for type 2 diabetes. PPARβ/δ is ubiquitously expressed, although it has important functions in the skeletal muscle, adipose tissue, skin, gut and the brain including: fatty acid oxidation regulation, keratinocyte differentiation and wound healing [54-57].

Ordinarily, PPARs are active at transcriptional levels only in presence of their specific ligands and each ligand is able to trigger a specific PPAR response, but some findings demonstrated the basal activity of PPARs also in the absence of ligands [58]. Unlike the steroid hormone receptors (nuclear receptors class 1) that function as homodimers, PPARs (nuclear receptors class 2) are active when they heterodimerize with Retinoid X Receptors (RXR) and when each monomer binds a specific DNA sequence, also called PPREs (peroxisomes proliferator response elements). PPREs are direct repetition located in promoter region of target gene as single or multiple copies [57, 59-60]. As mentioned above, specific PPARs transcriptional activities are strictly related to lipid ligand type and as a consequence, a wide range of natural or synthetic lipids can bind to ligand binding domain of PPARs. These ligands can be derived from diet or intracellular signalling pathways, among which FAs from prostaglandins and leukotrienes, but also synthetic ligands have been described. Peculiar fatty acid binding proteins (FABPs) allow the ligand transport toward the nucleus, where PPARs reside [61]. Long chain unsaturated FAs, eicosanoids and hypolipidemic drugs (fibrates) can activate the PPARα, while thiazolidinediones (TZDs) are able to active PPARγ and increase insulin sensitivity, in this regard PPARs are considered important therapeutic targets, mainly for metabolic diseases [62, 63]. Given their role as master regulator of cellular energy pathway and considering the metabolic alterations in tumour cells, PPARs modulation is definitely involved in the specific metabolic rewiring undertaken by neoplastic cells. The central debate is whether the transcriptional activity of PPARs promotes or hinders tumorigenesis and tumour progression. To date research activity has yielded conflicting evidence in this regard. There are different results about the tumour suppression related to PPARα and PPARγ transcriptional activation [64-70], but likewise proofs of their cancer promotion activity [71-73]; instead regarding PPARβ/δ activity the majority of study conducted shows its oncogenic role [74-76]. Although it must be emphasized that PPARs behaviour, both as pro- or anti-tumour, is strictly dependent on the tissue type and tumour microenvironment. Our purpose in this review is to describe recent observations that demonstrate the key role of PPARs in promoting or preventing characteristic metabolic switch that provide energy for tumour survival.

PPARα and cancer metabolism

The process of tumorigenesis can be described by a series of molecular features, among which alteration of cellular metabolism has recently emerged. This metabolic rewiring fulfills the energy and biosynthetic demands of fast proliferating cancer cells and amplifies their metabolic repertoire to survive and proliferate

in the poorly oxygenated and nutrient-deprived tumor microenvironment. This include deregulation of glucose and glutamine metabolism, alterations of lipid synthesis and oxidation, and a complex rewiring of mitochondrial function. However, mitochondria are not the only metabolically active organelles within the cell, for example peroxisomes, harbor components of the metabolic network. For instance, it was recently reported that in glioblastoma an increase of peroxisomes triggers the increase of mitochondria [77]. Many tumors experienced metabolic reprogramming in order to sustain uncontrolled proliferation, hypoxic conditions and angiogenesis. While it is generally accepted that cancer cells are fueled by glucose recent studies demonstrate the involvement of fatty acid oxidation and also of mevalonate pathway in cancer cell viability

PPARα mainly regulates the gene expression of specific proteins involved in mitochondrial and peroxisomal β-oxidation, glucose metabolism and fatty acid transport [55, 57]; deregulation of these catabolic processes it is important for tumour malignancy, therefore a relationship between PPARα gene regulation and tumour metabolism, that can be onco-suppressive or pro-oncogenic exists. PPARα activation and tumor suppression was reported in melanoma [78] and glioblastoma [79], on the other hand it was demonstrated a positive role of PPARα activation in stimulating proliferation of breast and renal carcinoma cell lines [80-81], while *PPARα*-null mice resulted insensitive to hepatic carcinogenesis induced by PPARα agonist [82]. Several evidences support the paradigm that tumors originate from cancer stem and/or progenitor cells, namely tumor initiating cells or cancer stem-like cells (CSCs). CSCs represent a small population of cancer cells that exhibit self-renewal and differentiation characteristics similar to normal stem cells but differ in that their self-renewal pathways are deregulated. Based on the CSC presence, CSCs are responsible for tumor formation, progression, metastasis, and recurrence; as well as, drug resistance. Although it is generally accepted that tumor cells, particularly CSC, modify their glucose and lipid metabolism inside tumor microenvironment, the specific metabolic pathways and their regulation are still poorly understood [11]. Owing to their crucial roles in energetic metabolism, many Authors have considered the role of the peroxisome proliferator-activated receptors (PPARs) in tumorigenesis, showing an up-regulation of the α isotype in several tumors and CSCs.

Recently, we demonstrated that antagonizing PPARα by synthetic ligand (GW6471) in glioblastoma stem cells (GSCs) we observed decreased tumor proliferation with alteration of glucose and lipid tumor metabolism [83]. GSCs are responsible for drug resistance and relapse, they reside in intratumoral perivascular and necrotic/hypoxic niche which provides them the optimal environment to keep stemness features. Hypoxia is associated with glioblastoma progression and plays a crucial role in stem cells biology, HIF proteins regulate the cellular response to hypoxia or variable oxygen concentrations by up-regulation of genes related to tumor progression, angiogenesis, drug resistance, GSCs phenotype maintenance. Between HIF proteins, HIF-1α triggers the expression of genes related to tumor metabolic switch that triggers glucose uptake, glycolytic enzyme activity, lactate production and anaerobic production of ATP, but it is also able to control synthetic pathways (fatty acids and glycogen synthesis) stimulating the expression of anabolic enzymes, such as those involved in glucose-glycogen conversion [11, 84-85]. We demonstrated that glioblastoma and GSCs in hypoxic condition showed higher levels of PPARα compared to the normoxic condition [86], while PPARγ levels were down-regulated under hypoxia [83]. In GSCs glycogen storage apperared more abundant in hypoxia than in normoxia, since hypoxic cells need glucose to quickly produce ATP by glycolysis and the glycogen storages are essential to feed this very fast energetic process. Moreover, HIF-1α stimulates the expression of gene involved in glycogen synthesis, as glycogen synthase kinase 3β (GSK3β), when GSK3β is phosphorylated at Ser 9 results inactive and it is unable to phosphorylate Glycogen synthase, thus allowing the launch of anabolic process [87]. The treatments with GW6471, a specific PPARα antagonist, decreased GSCs viability, neurospheres number and size and induced apoptosis, associated with low glycogen content, increase of glycogen degradation is due to Glycogen phosphorylase (GPBB) up-regulation and down-regulation of phosphorylated GSK3β at Ser 9. Furthermore, decreased amount of GLUT3 and glucose uptake in hypoxic treated GSCs were reported in the same study. Moreover, it was also demonstrated higher LDs contents in cancer cells,

mainly in hypoxic environment [21, 38, 86, 88]. FABP7 (fatty acid binding protein 7) transports the fatty acids toward the nucleus and replenish the LDs to promote tumor growth [89-90] and it appeared increased by hypoxia. GW6471 treatments induced the loss of LDs contents, cholesterol reserves and the transcriptional activity of genes encoding for mevalonate pathway enzymes, while FABP7 levels appeared decreased only in hypoxic GSCs treated with the antagonist, since the inhibition of PPARα transcriptional activity in hypoxic GSCs adversely affects fatty acid and cholesterol amount. Besides, MVA pathway plays a central role in glioblastoma survival and its inhibition by PPARα antagonist is linked to cell death and tumor suppression; this effect is similar to that triggered by statin because induced down-regulation of MVA pathway together with up-regulation of PPARγ. These results seems to emphasize the key role of PPARα in metabolic switch that occurs in cancer hypoxic cells, such as GSGs; in harsh environmental conditions PPARα was up-regulated and gives the metabolic directives to ensure energy for tumor cells, in this regard the antagonist GW6471 is able to reduce synthetic process, such as glycogen synthesis and LDs biogenesis, that ensure fast-acting energy for cancer cells.

In another study, Abu Aboud et al. [81] using the same PPARα antagonist (GW6471) on two cell line (Caki-1 and 786-O cell line) of renal cell carcinoma (RCC), observed that PPARα levels were higher in high grade RCC tissue compared to low grade tissue, linking PPARα protein levels to RCC aggressiveness. RCC high grade presents more energy demands than low grade, therefore requires active fatty acid oxidation (FAO), which is up-stream regulated by PPARα gene transcription [91]. Both the antagonist and siRNA direct to PPARα activity showed attenuation of c-Myc protein levels, likely by alteration of oncoprotein stabilisation PPARα-mediated, in association with down-regulation of cyclin D1/CDK4 and block the G1/S transition with cell cycle arrest in G0/G1 phase [92-93]. The Authors hypothesized that when the transcriptional activity of PPARα was inhibited, renal carcinoma cells were ineffective in using FAO converging on glycolysis to obtain energy. In fact, GW6471 effects were more pronounced in media with low glucose concentration than media with normal glucose concentration, furthermore 2-Deoxy-D-glucose (2-DG), an inhibitor of glycolysis, acted in synergy with GW6471 to induce tumor death. About that, blocking PPARα in RCC cell line, the researchers demonstrated the reduction of cell viability with attenuation of c-Myc, cyclin D1 and CDK4 protein levels in synergy with glycolysis inhibition.

It is ascertain that the most of oncogenes are involved in metabolic reprogramming that occurs in tumor cells [94-95], among them cyclin D1, contrary to what has just been mentioned, in some cases it was demonstrated to inactive PPARα-mediated gene expression of enzymes related to FAO, in hepatocytes, hepatocellular and breast cancer derived cell line [96]. Previous evidences have demonstrated cyclin D1 ability to regulate androgen and estrogen receptors, thyroid hormone receptor and PPARγ [97-98] in different cell types. Lines of evidences about cyclin D1 regulation of cell metabolism via inhibition of PPARα transcription factor were provided, while overexpression of cyclin D1 induced low expression of genes related to FAO, contrariwise knockdown of cyclin D1 gene promoted FAO enzymes expression but this effect was weakened by PPARα gene silencing. These results highlight the role of cyclin D1 in affecting FAO by PPARα-dependent manner, for instance cancer cell line mitogen stimulated showed low PPARα and FAO activity, indicating that probably transition from quiescent state to proliferation state requires less energy from fatty acid [99]. Data reported in [96] suggest that cyclin D1 somehow blocks the binding of PPARα on the PPRE of specific FAO enzymes, at the same time cyclin could disturb the association of specific co-activators with PPARα and then determine some changes in chromatin conformation, cyclin D1 controls the expression of CBP/p300 [100-101].

Fatty acid synthase (FAS) is up-regulated in tumor of the urinary tract, such as RCC, and the down-stream intermediates of fatty acid synthesis are endogenous ligands of PPARα, furthermore inhibition of FAS in liver of mice provides rodents with PPARα dysfunction [102-104]. As mentioned above [81], histological grade of RCC is directly linked to PPARα levels and its inhibition leads to cell cytotoxicity, cell cycle arrest tighter with glycolysis and FAO attenuation. Recently, in RCC cell line (Caki-1 and 786-O) and normal human kidney cells (NHK) it was

reported that inhibition of glycolysis triggered FAO and OXPHOS, these processes were undermined with PPARα inactivation. Besides in normal cells PPARα antagonist did not inhibit the glycolysis, conversely in RCC cell line glycolysis was attenuated, likely due to a difference of c-Myc protein levels between cancer cells and normal cells [105]. FAO can be considered an alternative to produce energy when the glycolysis is obstructed, in fact RCC cell line showed incremented levels of palmitate 24 hours following 2-DG treatment, but in association with GW6471, these levels were decreased. Usually fatty acid β-oxidation provides the acetyl-CoA groups to feed TCA cycle and OXPHOS that in turn was more active with glycolysis inhibition. When RCC cell lines were also treated with PPARα antagonist (GW6471) the OXPHOS activity levels showed no significant differences, while GW6471 alone was able to impair oxidative phosphorylation but not FAO. Noteworthy, PPARα antagonist adversely affected the levels of oncogene c-Myc in RCC cell line, which is involved in over-activation of protein related to glucose uptake and glycolysis. Most likely, PPARα controls glycolysis via c-Myc at least in RCC cell lines, with the inhibition of nuclear receptor the cancer cells loses the key actor that operates as a bridge between tumor environment and metabolic switch [81, 105].

Human hepatocellular carcinoma (HCC) tissue showed increased mRNA levels of gene involved in FAO and glucose metabolism, among which PPARα, carnitine palmitoyl transferase 1A (CPT1A is the rate limiting enzymes of FAO), glyceraldehyde 3-phosphate dehydrogenase (G3PDH) and up-regulation of cyclin D1 mRNA. Although, increased levels of PPARα were associated with deregulation of metabolic pathways that trigger carcinogenesis, there are not evidences of HCC incidence in human patients who were exposed to peroxisome proliferators [106].

About carnitine palmitoyl transferase enzyme, it was recently demonstrated the possible regulatory role of PPARα-CPT1C axis in tumor proliferation and senescence [107]. As mentioned earlier, as CPT1A, also CPT1C is a rate limiting enzymes in FAO, the enzymatic reaction allows the acylation of long fatty acid chain and its entry in the mitochondria, in cancer cells these enzymes are up-regulated [108-110]. Moreover it was identified PPRE in the first exon of CPT1B gene [111-112]. The analyses were performed on two different cancer cell lines, MDA-MB-231 (breast cancer cell line) and PANC-1 (pancreas cancer cell line) with knockdown or overexpression of PPARα gene. Dual-luciferase reporter gene assays proved *CPT1C* active transcription by PPARα and its overexpression was related to cell proliferation and reverse of senescence, of course with higher CPT1C mRNA levels in the cell lines tested. Effects were completely different when PPARα gene was depleted, an increase in senescence with low proliferation rate was observed; indicating that CPT1C gene is regulated by PPARα, this is a further evidence of the PPARα ability to modulate cancer cell metabolism [107].

During carbohydrate deprivation the cells can adopt ketogenesis pathway to ensure lipid-derived energy and this process is essential for tumor initiation and metastasis [113], mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2), belongs to the HMG-CoA family, catalyzes the first enzymatic reaction in ketogenesis. Several proteins related to ketogenesis pathway were over-expressed in prostate cancer cells [114], among which HMGCS2; on this basis, some researchers demonstrated the direct interaction between PPARα and HMGCS2 [115], that in this case acts as transcription factor resulting in Src activation and malignancy and invasion promotion. In this study it was demonstrated the correlation between the increased mRNA levels of HMGCS2 and poor clinical outcomes as well as grade malignancy, in colorectal cancer (CRC) and oral squamous cell carcinoma (OSCC) tumor biopsy from affected patients. The demonstration of HMGCS2 direct interaction at nuclear level with PPARα is very interesting, others analysis confirmed that this heterodimeric complex binds *Src* promoter region and induced genes linked to tumor invasion [115].

Chronic lymphocytic leukemia (CLL) patients present poor clinical outcome and the most effective therapy is based on high dose of glucocorticoids (GCs) with or without monoclonal antibodies, nevertheless this therapeutic protocol is not curative and is characterize by progressive tumor resistance to GCs [116]. Glucocorticoids have immunosuppressive functions, inhibit glucose

metabolism and increase FAO in tissue under starvation. Tung at al. [117] found in CLL primary culture from patient's blood that GCs increased the PPARα expression with pronounced tumor dependence on FAO, but lipid oxidation was a double edge sword, because it could guarantee tumor survival by providing an alternative mechanism to metabolic limitations dictate by GCs. PPARα antagonist impaired this resistance mechanism. Pyruvate kinase M2 (PKM2) activity was down-regulated at transcriptional and protein level by dexamethasone (DEX), in spite of this acetate levels were kept constant, suggesting an increase in FAO activity linked to DEX. PPARα and PPARβ/δ mRNA levels were increased after DEX treatment, the PKM2 down-regulation occurred before the PPARα up-regulation, likely the nuclear receptor did not affected pyruvate kinase gene transcription. Although, pyruvate dehydrogenase kinase 4 (PDK4) gene is under transcriptional control of PPARα and PPARβ, PDK4 phosphorylates and inhibits pyruvate dehydrogenase thus pyruvate is useful for FAO rather than for OXPHOS [118]. The Authors evaluated the PDK4 mRNA levels showing that DEX increased these levels. Moreover, in order to understand the role of DEX in triggering FAO and the chemoresistance, it was investigated the effects of DEX treatment in association with fatty acid oxidation substrates on tumor cells resistance. CLL cells were co-cultured with OP-9-derived adipocyte to evaluate if lipids from cells with adipocytic phenotype could improve tumor survival; this model was used to mimic *in vivo* tumor environment, where CLL cells are close to adipocyte [119-120]. CLL showed greater resistance to DEX when cultured with adipocytes compared to CLL cells in serum-free media and the effect were the same with conditioned media from OP-9-derived adipocytes, highlighting that resistance was conferred by lipids secreted from OP-9-derived adipocytes. These lipids can be PPARα ligands and FAO substrates. These experimental evidences demonstrated the direct involvement of PPARα in GCs tumor resistance, since it is up-regulated by DEX and is a well-known FAO regulator, and since PPARα antagonists revoked this effects and sensitized CLL cells to DEX activity [117].

Unlike what stated so far, PPARα activation could be useful to fight tumor progression in some tissue, as evidenced in melanoma [78]; in addition to positively affect transcription of FAO enzymes, PPARα is able to decrease transcription of fatty acid synthesis genes. Chandran et al. reported favourable results on the protective roles of the PPARα agonist, clofibrate, in discouraging breast cancer inflammation and invasion [121]. They used two triple negative breast cancer cell line, SUM149PT and SUM1315MO2, the first from invasive ductal carcinoma of a patient with inflammatory breast cancer, and the second from highly invasive breast cancer specimen of patient with skin metastasis. These two cell line showed increased expression of PPARα respect to primary human mammary epithelial cells (HMEC). Clofibrate was able to reduce inflammation by decreasing the levels of COX-2 and 5LO in association with growth tumor inhibition. Early events of cancer development require fatty acid synthesis up-regulation, which is dramatically accentuated during late tumor progression [122]. Activity of FAS was attenuated by clofibrate that in turn down-regulated expression of HMG-CoA synthase 2, acyl-CoA oxidase and SREBP-1c gene, the first two involved in mevalonate pathway and the third is a transcription factor that binds sterol regulatory element DNA sequences. SREBP-1c (sterol regulatory element binding protein 1c) plays an important role in regulation of *de novo* fatty acid synthesis, while its cognate SREBP-2 regulates genes of the cholesterol metabolism [123], SREBPs pathway has a key role in fatty acid *de novo* synthesis of prostate cancer cells [124]. In addition to impairment of lipid synthetic pathway, such as SREBPs, the activation of PPARα by clofibrate was able to up-regulate CPT-1a (first enzyme in FAO) and to reduced the onco-protein levels, such as NF-kB and Erk1/2, in breast cancer cells derived from high metastatic inflammatory tumor specimens [121].

Some evidences indicated PPARα activation as a possible trigger of ineffective tumor metabolism, it was reported that fenofibrate (PPARα agonist) treatment, on cell line and mouse model of oral cancer, supported hexokinase II and VDAC (voltage-dependent anion channel) dissociation, this event destabilized Warburg effect and provided a metabolic switch to OXPHOS, furthermore affected protein expression levels of hexokinase II, PDH and VDAC [125-127]. Recently, Huang and Chang [129] studied, by proteomic analysis, the differences between normal and cancer oral

tissue from mice, in relation to enzymes involved in Warburg effect, contextually they investigated about the PPARα role in fibrate-dependent metabolic changes of oral cancer cell line. Proteomic analyses were performed in basic pI range, because the enzymes of glycolysis, TCA cycle and OXPHOS show mainly alkaline pI [128-129]. They found seven proteins with decreased levels in tumor tissue compared to normal tissue, triosophosphate isomerase and pyruvate dehydrogenase E1 component subunit beta for glycolysis, IDH3 and aconitate hydratase for TCA cycle, NADH dehydrogenase [ubiquinone] 1 alpha sub-complex subunit 10 and cytochrome c1 for respiratory chain. Assuming that these results demonstrated the oral cancer cell dependence on Warburg effect, the researchers evaluated the effect induced by fibrate; PPARα activation induced reduction of hexokinase II protein levels, ATP levels and enhancement of PDH activity, besides reduced cell viability. Interestingly, they observed a significant increase in TCA metabolites after fenofibrate treatments in primary cell culture from mouse tongue tumor tissue. Probably, when PPARα agonist increased PDH activity, accordingly pyruvate was decarboxylated to acetyl-CoA and TCA cycle was encouraged. Otherwise, fenofibrate could increased FAO resulting in high acyl group levels useful for TCA reaction [126, 129].
Regarding to Warburg effect and related glycolysis, it was reported the repression activity of PPARα on GLUT1 gene with reduced glucose uptake, these evidences were obtained in different cancer cell line (HCT-116, SW480, MCF-7 and HeLa) [70].

PPARγ and cancer metabolism

Different cell types express PPARγ and it is involved in different mechanisms essential to sustain normal cell life. Adipose tissue and liver tissue, muscle, brain and immune cells, mainly macrophages, require PPARγ activation to meet energy request and to regulate glucose and lipid metabolism, insulin sensitivity and cell fate. PPARγ plays a key role in adipocytes and macrophages differentiation [130-132]. As for PPARα, also for PPARγ there are several demonstrations about its role in tumorigenesis, some related to anti proliferative effects of PPARγ activation, such as in breast [133], hepatic [134], lung [135] and colorectal cancer [136], furthermore its activation negatively affects the epithelial mesenchymal transition (EMT) [137]. However, there are other works that prove the tumorigenic potential of PPARγ activation, such as in colorectal cancer [138-140], breast cancer [141-142] and urological cancer [143], both roles of PPARγ are strictly tumor tissue-dependent and tumor microenvironment-dependent.
Several types of epithelial cancers show a common feature, deregulation of Wnt/β-catenin pathway resulting in the up-regulation of enzymes related to aerobic glycolysis. When Wnt ligands are available, β-catenin translocates into the nucleus where it is able to bind specific target genes, among which pyruvate dehydrogenase kinase (PDK), monocarboxylate lactate transporter-1 (MCT-1), c-Myc, cyclin D1 and COX-2. When Wnt ligands are absent, β-catenin is phosphorylated and then demolished by proteasome. In this view PPARγ down-regulation was observed, whenWnt/β-catenin is up-regulated, but it was also observed the inhibition of Wnt/β-catenin when PPARγ is activated. Accordingly, it is not unconceivable to think about a mechanism of interconnection between Wnt/β-catenin and PPARγ, in which each one is able to prevent the pathway of the other as already demonstrated [144]. PDK1 acts phosphorylating pyruvate dehydrogenase, and then pyruvate is transformed in lactate by activation of lactate dehydrogenase, while MCT-1 is involved in lactate secretion outside the cytoplasm, these two events allow to improve angiogenesis and biosynthesis of macromolecules thus providing a unique and favourable tumor microenvironment [21]. In this context PPARγ suppresses *PDK1* gene transcription and it could somehow make ineffective the Wnt/β-catenin pathway [145].
Studies conducted on PPARγ agonist or with PPARγ overexpressing cells support the idea that PPARγ activation is useful to fight tumor progression, in fact, thiazolidinediones (TZDs) showed to be able in slow down tumor growth *in vitro* and *in vivo* models of lung cancer. In addition it was reported the over-expression of PPARγ in a group of non-small lung cancer cells and its activation

affect some genetic pattern underlying to tumor metabolic demand [146]. Srivastava et al. [135] reported in two lung adenocarcinoma cell lines (NCI-H2347 and NCI-H1993) that PPARγ activation compromised glucose, fatty acid and glutamine metabolism associated with increased of ROS and hypophosphorylated RB (retinoblastoma protein), dephosphorylated RB is opposed to the cell cycle progression. Unlike what it was previously mentioned, in this work they found an up-regulation of PDK4 expression by pioglitazone, and it was suggested that PDK4 induced a metabolic switch from glucose oxidation to fatty acid oxidation. PDK4 knockdown reversed the effect induced by pioglitazone related to RB hypophosphorylation and ROS levels, contextually the same results were achieved in cell lines and xenograft mice models by inhibiting FAO with chemical compounds. These results suggested that PDK4 up-regulation by pioglitazone compromised glucose utilization and triggered FAO with subsequent increase of ROS levels, which in turn induced RB hypophosphorylation. Moreover, the researchers reported alterations in glutamine metabolism, impairment of glutaminolysis and down-regulation of reduced glutathione (GSH) levels, therefore tumor cells was unable to carry out ROS detoxification processes[135].

Common feature of several tumors such as non-small cell lung cancer (NSCLC) is the resistance to radiation and chemotherapy, the specific mechanisms are not entirely understood but it is well known that hypoxia supports the malignancy and the expression of ATP-binding cassette (ABC) transporters, which drive chemotherapeutic agents outside the cells [147-148]. Hypoxic conditions are also combined with down-regulation of mitochondrial uncoupling protein 2 (UCP2) in NSCLC, as highlighted in a recent work [149]. UCP2 is a mitochondrial proteins involved in the detoxification process for reducing ROS levels, because the cells are more sensible to superoxide anion released after proton force development by electron transport chain. Moreover, a double role was suggested for UCP2, reduction of ROS levels in concert with metabolic regulation of glycolysis, fatty acid and glutamine oxidation [150]. Down-regulation of UCP2 by hypoxia was associated with PPARγ repression and up-regulation of ABC transporter ABCG2, increasing aerobic glycolysis and chemoresistance. HIF-1 was directly involved in PPARγ and FAO down-regulation; this condition negatively affected the *UCP2* transcription, conversely glucose consumption was stimulated and a progressive increase of ROS was established in concert with ABCG2 up-regulation [149, 151].

Several studies displayed the ability of ATRA (all trans retinoic acid) to induce differentiation of some myelocytic cell lines (HL-60, U937 and NB4) into mature phagocytic cells. ATRA treatment is useful for therapy of acute promyelocytic leukemia (APL), but the permanent administration of ATRA causes high resistance at differentiation, because there is over-expression of cytosolic retinoic acid binding proteins [152-153]. In this regard the association between ATRA and PPARγ ligands was demonstrated to be synergistic in the differentiation effect on myelocytic leukemia cell lines [130]. The synergistic effect also concerned the enhancement of lipogenesis, as evidenced in NB4 cell line by accumulation of lipid droplets, therefore induction of differentiation by ATRA and pioglitazone or PGJ2 results in high activity of triacylglycerol synthesis in human myelocytic leukemia cell lines [154].

Induction of PPARγ activity and concomitant autophagic cell death in human chronic myeloid leukemia (CML) cell lines (K562 and KCL-22) was reported by Shinohara et al. [155]. By docking analysis they observed that anti-cancer fatty-acid derivative, called AIC-47, was able to bind PPARγ making it transcriptionally active, and indirectly reducing c-Myc protein levels since PPARγ activation is related to proteasome degradation of β-catenin, as already mentioned [144]. Other interesting results also demonstrated the AIC-47/PPARγ involvement in deregulation of glycolytic pathway. Up-regulation of c-Myc is a cause and consequence of aerobic glycolysis in tumor cells, as previously demonstrated, c-Myc can induce overexpression of three heterogeneous nuclear ribonucleoproteins (hnRNPs) that in turn can suppress the alternative splicing of PKM1, the isoform less present in cancer cells. Unlike other isoform of PK that need of allosteric regulation to be active, PKM1 is a tetrameric stable and active enzyme, for this reason cancer cells prefer to use PKM2 for their metabolic purposes. PKM2 shows low activity in cancer cells, because it also

allows the biosynthetic pathways, for this reason in cancer cells PKM1/PKM2 ratio is low and c-Myc-dependent [155-156]. PPARγ activation AIC-47-dependent induced c-Myc down-regulation resulting in β-catenin inactivation with the increase of the PKM1/PKM2 ratio and the metabolic switch from glycolysis to TCA cycle concomitant with increased ROS levels, which results in autophagy induction [155].

Survival in hepatocellular carcinoma (HCC) patients is related to expression pattern of some genes, among which ODC1 (ornithine decarboxylase 1), its overexpression is associated with reduced patients survival [157]. OCD1 enzyme catalyses the first reaction in biosynthesis pathway of polyamine, its mRNA and protein levels are increased together with c-Myc activity in HCC compared to normal tissue [158]. Impairment of OCD1 expression by gene silencing was related to cell cycle interruption and apoptotic cell death, furthermore phenotypic alterations occurred with characteristic deregulation of 119 genes. Among them, it was interesting the down-regulation of PPARγ gene and lipogenesis, both linked to up-regulation of KLF2 (krüppel-like factor 2) oncogene. It was reported that siRNA of ODC1 gene induced up-regulation of KLF2 gene in concert negatively affecting PPARγ expression thus causing down-regulation of lipogenic enzymes, such as FAS and ACC2 (acetyl-CoA carboxylase 2), as already evidenced [159-160].

Regarding *de novo* fatty acid synthesis, in ERBB2-positive breast cancer cells a remarkable amount of lipid droplets was observed. ERBB2 cells assumed this metabolic behaviour under the transcriptional control of PPARγ, inhibition of PPARγ decreased tumor cell viability. By RNA interference screening some genes related to fatty acid metabolism required for tumor cell survival were identified [161]. Within this group of genes, two were associated with PPARγ activity, PBP (PPARγ-binding protein) and NR1D1 (nuclear receptor subfamily 1, group D, number 1), both were identified as activators of PPARγ expression, likely PBP as co-activator and NR1D1 as target gene [162]. The gene sequence of *PBP* and *NR1D1* was localized in the ERBB2 amplicon, and in breast cancer, mutations in this gene locus was linked to high lipid synthesis and PBD, NR1D1 overexpression, their activity was aimed at regulation of FAS (fatty acid synthase), ACLY (ATP citrate lyase) and ACACA (acetyl-coenzyme A carboxylase α) expression [162-163]. In this regard, the last metabolic product of fatty acid synthesis pathway, palmitate, was described as lipotoxic agent, likely by ROS induction [164]. Some researchers identified a protective role of PPARγ against palmitate-induced lipotoxicity in ERBB2-positive breast cancer cell lines (BT474 and MDA-MB-361) but not in other type of breast cancer (MCF-7) and normal cells. The PPARγ activity allowed induction of triacylglycerol synthesis, in order to remove the excess of fatty acid and enclose them in specific stores (LDs) to relieve lipotoxicity. Moreover, PPARγ played a central role in keeping active the FAS by confinement of palmitate in specific stores. The inhibition of PPARγ by antagonist reversed the protective mechanism and ERBB2 cells were more sensible to palmitate-dependent toxicity [165]. A pertinent work showed the suppressive effects of PPARγ antagonism in cancer stem cells (CSCs) populations derived from ERBB2-positive breast cancer cell lines (BT474 and SKRB3) that expressed high levels of ALDH activity and protein with lipid storage bigger than ERBB2-negative cells. Also in this case the tumor suppressive effects was related to increased ROS levels and damage by lipogenesis pathway, the researchers assumption was that ACLY (ATP citrate lyase) epigenetic pattern could be altered by PPARγ inactivation, considering ACLY gene a PPARγ target gene. In fact, acetylation levels of H3 and H4 histone were found different between ERBB2-positive cells and control cells [166].

Recently an interesting approach, called *sleeping beauty (SB)*, was used to find mainly genes that lead to cancer prostate metastatic events. Briefly, this approach is based on transposons that induce somatic mutations, the expression of transposase could be tissue specific or ubiquitously [167]. Most of the analyses were conducted on PTEN-null mice, because patients with poor prognosis presented low PTEN levels and conversely high PPARγ and FAS levels. Noteworthy, insertion within PPARγ gene in PTEN deleted mice established greater tumor aggressiveness than mice without insertion. Also in this study the overexpression PPARγ determined up-regulation of

enzymes involved in *de novo* fatty acid synthesis that was reverted by PPARγ knockout and down-regulation [168].
Tumor-associated macrophages (TAMs) are in close relationship with tumor microenvironment and incentive tumor progression. Several evidences support the idea that stromal cells play a key role in tumor maintenance, since tumor cells exploit them by using energy resource, in form of metabolic intermediates or end products (lactate, ketones, glutamine and fatty acids), secreted by stromal cells. It was reported that caspase-1 was able to cut PPARγ in a 41 kDa fragment and that the fragment translocates into mitochondria to dampen MCDA activity. Medium-chain acyl-CoA dehydrogenase (MCDA) contributes to fatty acid β-oxidation [169], its inactivation was linked to lipid synthesis and LDs increase with concomitant TAMs differentiation. Considering caspase-1/ PPARγ/MCDA axis as an important mechanism to improve TAMs differentiation, thus tumor aggressiveness, when this axis was damaged with caspase-1 inhibitor, TAMs cells suffered a specific commitment that negatively affected tumor progression [170].

PPARβ/δ and cancer metabolism

PPARβ/δ, like other PPAR isotypes, regulates the transcription of genes required for the main metabolic processes, such as glucose and fatty acid catabolism, although its regulatory role is also implicated in cell proliferation, cell differentiation, wound healing and inflammation [54, 171-172]. Several scientific evidences reported the pro-tumorigenic role of PPARβ/δ, but to date there are conflicting information on its exact role in carcinogenesis [74, 173]. This aspect was especially investigated in breast cancer with opposed results, showing that the estrogen receptor was involved in the effects induced by PPARβ/δ modulation. In fact, proliferation in MCF-7 cell line (estrogen receptor positive, ER^+) was increased by PPARβ/δ overexpression, conversely MDA-MB-231 cell line (estrogen receptor negative, ER^-) showed no effect on cell proliferation rate. Unfortunately, these results are not consistent with other evidences, showing that in MCF-7 PPARβ/δ overexpression induced differentiation and cell cycle interruption [174-176]. Conversely, it was reported the negative effect of PPARβ/δ activation on tumor survival in MCF-7 and MDA-MB-231 cell lines [177].
Tumor progression in non-small cell lung cancer (NSCLC) was associated with PPARβ/δ up-regulation and increased VEGF levels, and by activation of PI3K/Akt pathway [178]. PPARβ/δ could be considered an upstream PI3K/Akt regulator, considering its capability to reduce PTEN levels and increase PDPK1 (3-phosphoinositide-dependent protein kinase-1) expression [179]. Since PDPK1 gene presents PPRE specific for PPARβ/δ, as already demonstrated [180], an interesting analysis was conducted on mammary tumorigenesis *in vivo* model, with transgenic mice carrying PDPK1 gene under the transcriptional control of mouse mammary tumor virus (MMTV-mice), with the expression limited to the mammary gland [181]. Transgenic mice showed higher PPARβ/δ expression levels than control mice, the expression was further increased in MMTV-mice feeded with PPARβ/δ agonist, mammary carcinogenesis was promoted in both wild type and transgenic mice under feeding treatment, especially in transgenic mice. The researchers emphasized the differences between wild type and MMTV mice about the treatment response, because mice bearing PDPK1 transgene and treated with PPARβ/δ agonist were more prone to tumor initiation, maybe due to differences in the metabolic pathway engaged. In this regard, PI3K/Akt pathway is able to phosphorylates and activates ATP citrate lyase, while PDPK1 slow down the pyruvate flow into oxidative phosphorylation and Acss2 (Acyl-coenzyme A synthetase short-chain family member 2) support the conversion of lactate to pyruvate. These three proteins work in concert to raise the acetyl-CoA amount in order to promote glycolysis and fatty acid synthesis, and PPARβ/δ agonist treatment increased their efficiency. Despite the fact that PDPK1 expression alone was not able to induce carcinogenesis, its association with PPARβ/δ activation triggered a malignancy molecular pathway more aggressive than that observed in wild type mice treated with PPARβ/δ agonist. Therefore, two different metabolic mechanisms were activated, whereby PDPK1 induces the

PPARβ/δ expression and vice versa, this loop in turn supports the transcription and the activity of genes related to glycolysis and lipid synthesis. Fatty acid synthesis could be useful for supplying PPARβ/δ endogenous ligands and continue to feed PDK1-PPARβ/δ loop activity [181].

Hematopoietic stem cells (HSCs) maintenance and muscle cells endurance are safeguarded trough PPARβ/δ activity, despite the unfavourable metabolic condition occurring during these cell retention processes. Likely PPARβ/δ unleashes specific molecular mechanisms related to metabolic switch that allow cell life cycle [182-183]. As already demonstrated by Tung et al. [117], PPARβ/δ transcription was incentivised when leukemic cells was stressed by glycolysis inhibitors, the same results were obtained in a recent paper but in breast cancer cell lines. When the cells grow in standard culture conditions for ten days without replacement, the overexpressing-PPARβ/δ cells continued to proliferate much better than control cells, but those with the PPARβ/δ KO by CRISP/Cas9 showed a proliferation rate comparable to the control levels. However, low glucose culture conditions induced in transfected cells a more pronounced PPARβ/δ up-regulation compared to standard culture conditions, confirming the central role of PPARβ/δ in tumor metabolic modulation. Furthermore, these events were associated with increased levels of catalase and Akt protein as well as up-regulation of the antioxidant defences [184].

As mentioned above [183], PPARβ/δ in concert with FAO plays a key role in HSCs preservation also in presence of harsh environmental conditions. Nevertheless, PPARβ/δ-FAO pathway undergoes an upstream regulation by PML (promyelocytic leukemia) protein codified by a tumor-suppressor gene. For example, Ito et al. [183] demonstrated that HSCs with *Pml* gene deletion were less inclined to asymmetric division with significant variation of asymmetric/symmetric division ratio, and there are other results also in breast cancer cells supporting this observation [185]. These evidences provide further support regarding PPARβ/δ-FAO pathway regulation by PML upstream control, therefore blocking oxidative metabolism of fatty acid is harmful for cancer stem cells and for more differentiated scaffold cells [183]. In this regard the same effect was observed in chronic lymphocytic leukemia (CLL) cells (Daudi cell line and primary culture), where the stressful environmental conditions stimulated PPARβ/δ expression triggering a protective mechanism in cancer cells. Different kind of harsh condition were tested: low glucose, hypoxia, exposure to glucocorticoids and cytotoxic agents, in any case the tumor cells response was to improve antioxidant activity and make a better use of energy supplies through proper metabolic pathway [186]. More recently the involvement of PPARβ/δ signalling in CLL cell lines survival was reported and this event was associated at increased cholesterol and plasma membrane biosynthesis. Exposure to PPARβ/δ agonists was found to induce high cholesterol levels and STAT phosphorylation interferon-dependent. Cytokines stimulated the specific pathway related to cholesterol synthesis but it was demonstrated their inability to up-regulate PPARβ/δ, while PPARβ/δ could stimulate the cytokines expression in order to maintain tumor microenvironment [187].

Consistent with these results, also in colon cancer cells the direct role of PPARβ/δ in IL-8 gene transcription under hypoxia was observed [188]. Unlike PPARα and γ that present both pro- and anti-tumor effect in colorectal cancer, different experimental evidences show the pro-tumorigenic role of PPARβ/δ, mainly through its involvement in APC/β-catenin/K-Ras oncogenic pathway [189-190]. In human HCT116 colon cancer cells in hypoxic environment it was demonstrated the PPARβ/δ up-regulation as well as the p300/PPARβ/δ interaction triggered by HIF-1; p300 is an all-purpose co-activator for nuclear receptor that contributes to the formation of transcriptional complex. The authors reported that this complex was particularly active in IL-8 and VEGF overexpression under hypoxic conditions, and then stimulated tumor angiogenesis. At the same time PPARβ/δ was upstream regulated by PI3K/Akt but PPARβ/δ himself was able to regulate PI3K and Akt transcription, thus a permanently active closed loop was generated [188].

As mentioned above, PPARγ is directly involved in TAMs differentiation [170], it is worth mentioning that macrophages can assume two specific phenotype, M1 (inflammatory) and M2 (anti-inflammatory), however TAMs present a mix of both phenotypes [191]. As PPARγ also

PPARβ/δ is a regulator of macrophage final fate in tumor environment. Using $CD14^+$ monocytes cells from ovarian carcinoma ascites, as TAMs *in vitro* model, the PPARβ/δ transcriptional control on genes related to TAMs in ovarian cancer was reported [192]. In this study was evaluated which genes linked to TAMs were under PPARβ/δ transcriptional control, the overall results confirmed the regulation of metabolic pathway genes, but also of genes linked to inflammatory and migration processes. It was observed an up-regulation of these genes in presence of PUFA (poly unsaturated fatty acid) ligands, so PPARβ/δ transcriptional regulation could be associated not only with TAMs maintenance but also with tumor progression by up-regulation of genes encoding for soluble mediators of cancer progression, such as ANGPTL4 (angiopoietin-like 4). ANGPTL4 is a lipoprotein lipase regulator essential for tumor-metastatic progression, in fact angiopoietin-like 4 prevents the anoikis cell death [193-194]. However, the preservation of TAMs was dependent of PPARβ/δ activation that in turn induced the transcription of downstream elements, such as ANGPTL4 and PDK4, in order to allow metabolic switch to aerobic glycolysis. In fact, high lactate levels were detected, and cells from ascites resulted to have high fatty acid ligands for PPARβ/δ, thus the activity of nuclear receptor about TAMs maintenance was greatly facilitated by tumor microenvironment [192].

Since the metabolic fate undertaken by cancer cells is a response depending on the cell phenotypic/genotypic characteristics and on the specific microenvironment around the neoplastic bulk, also PPARβ/δ response undergoes this specific tumor conditioning. However, the microenvironment influencing towards cancer cells depends on cell capacity to acquire nutrients from extracellular compartment to cytoplasm, by trans membrane transporter proteins. In this regard, Zhang et al. [76] reported the direct PPARβ/δ binding on PPRE in genic sequences of *Glut1* and *Slc1-a5*, and highlighted their up-regulation by PPARβ/δ activation in order to ensure glucose and amino acids for tumor growth. Transfected SW480 cells (cell line from colon adenocarcinoma) with PPARβ/δ transgene showed high mRNA and protein levels of GLUT1 and SLC1-A5 (solute carrier family 1 member 5), and also as a consequence lactate increases and glucose, glutamine consumption. All these results were abolished by PPARβ/δ deletion by knockdown or by the use of antagonist. Moreover, overexpression of GLUT1 and SLC1-A5 with contemporary PPARβ/δ silencing caused an increase in proliferation rate, which was reverted in cells with specific deletion of transporter protein genes and overexpression of PPARβ/δ. Considering these results, it is conceivable to hypothesise that there is a PPARβ/δ-dependent molecular pathway that leads to GLUT1 and SLC1-A5 up-regulation, resulting in modulation of metabolic patterns suitable for tumor growth [76].

Unlike the evidence reported so far, recently it was demonstrated the suppressive activity of PPARβ/δ in prostate cancer [195]. From tumor tissue biopsy of prostate cancer it was observed low mRNA levels of PPARβ/δ compared to benigne tissue and the same results were obtained in prostate cancer cell lines (DU145, PC3, LNCAP, VCAP, C4-2, and 22RV), thus downregulation of PPARβ/δ was associated with high aggressiveness. In absence of ligands PPARβ/δ could exist as transcriptional repressor [173], in fact in this work it was demonstrated the inhibition of FAO when PPARβ/δ was overexpressed, but only in PC3 and LNCaP cell lines. Noteworthy, in presence of a PPARβ/δ agonist the repressive effect on FAO was abolished, without affecting PPARβ/δ transcription levels, the results obtained confirm the suppressive role of PPARβ/δ in its unliganded form [195].

Conclusions

Despite there is no clear view on the exact role of PPARs in carcinogenesis and considering that most of the experimental proofs are mutually conflicting, it is accepted the key role of PPARs in metabolic modulation faced by cancer cells to ensure own survival. Each cancer cell exhibits a specific metabolic signature related to specific genotypic and phenotypic features of the origin tissue. Nevertheless, the specific cell phenotype is in close relationship with microenvironment

around the tumor bulk, thus tumor phenotypic manifestations are the result of the effects induced by tumor microenvironment on cellular transcription events, different from tissue to tissue. About that, the PPARs transcriptional activity on specific target genes is deeply correlated to tumor-derived tissue type and tumor microenvironment and for this reason each PPAR isotype establishes different effects on various tumor cell types. Overall these factors determine whether PPARs promote tumorigenesis and tumor progression or disadvantage cancer survival. Moreover, tumor microenvironment provides PPARs ligands, consequently extracellular environment can directly modulate PPARs activities.

The most recent evidences reported in this review demonstrate the involvement of PPARs in metabolic switch that occurs in different cancer types. The oncogenic metabolic pathway of PPARα is characterized by high glycolysis in concert with c-Myc and cyclin D1 up-regulation, high levels of lipid and glycogen synthesis. In addition great amount of LDs are associated with up-regulation of MVA pathway, while less frequently PPARα oncogenic activity can be connected to induction of OXPHOS and FAO. Moreover, increase in fatty acid oxidation was reported to confer chemoresistance, i.e. against glucocorticoids [116]. Hypoxia exerts its oncogenic role through stimulation of PPARα transcriptional activity (Figure 1A). Oncogenic metabolic behaviour related to PPARγ activity is mainly inclined to trigger increase in lipid synthesis and to reduce FAO, while lipotoxicity related to high amount of palmitate is arrested by PPARγ that drives palmitate confinement into LDs. Intriguing is the positive role of PPARγ in TAMs differentiation, the tumor stromal cells behaviour is affected by PPARγ inhibition of FAO and high lipid synthesis (Figure 1B). Unlike other two PPARs isotypes, most of the evidences regarding PPARβ/δ activity highlight its oncogenic role. Environmental stress, such as hypoxia and low glucose, triggers tumor metabolic pathway under PPARβ/δ transcriptional control, thus aerobic glycolysis, lipid synthesis, anaplerosis and FAO are stimulated. Noteworthy, in leukemia, the upstream regulation of cytokines by PPARβ/δ is related to high cholesterol levels and malignancy (Figure 1C).

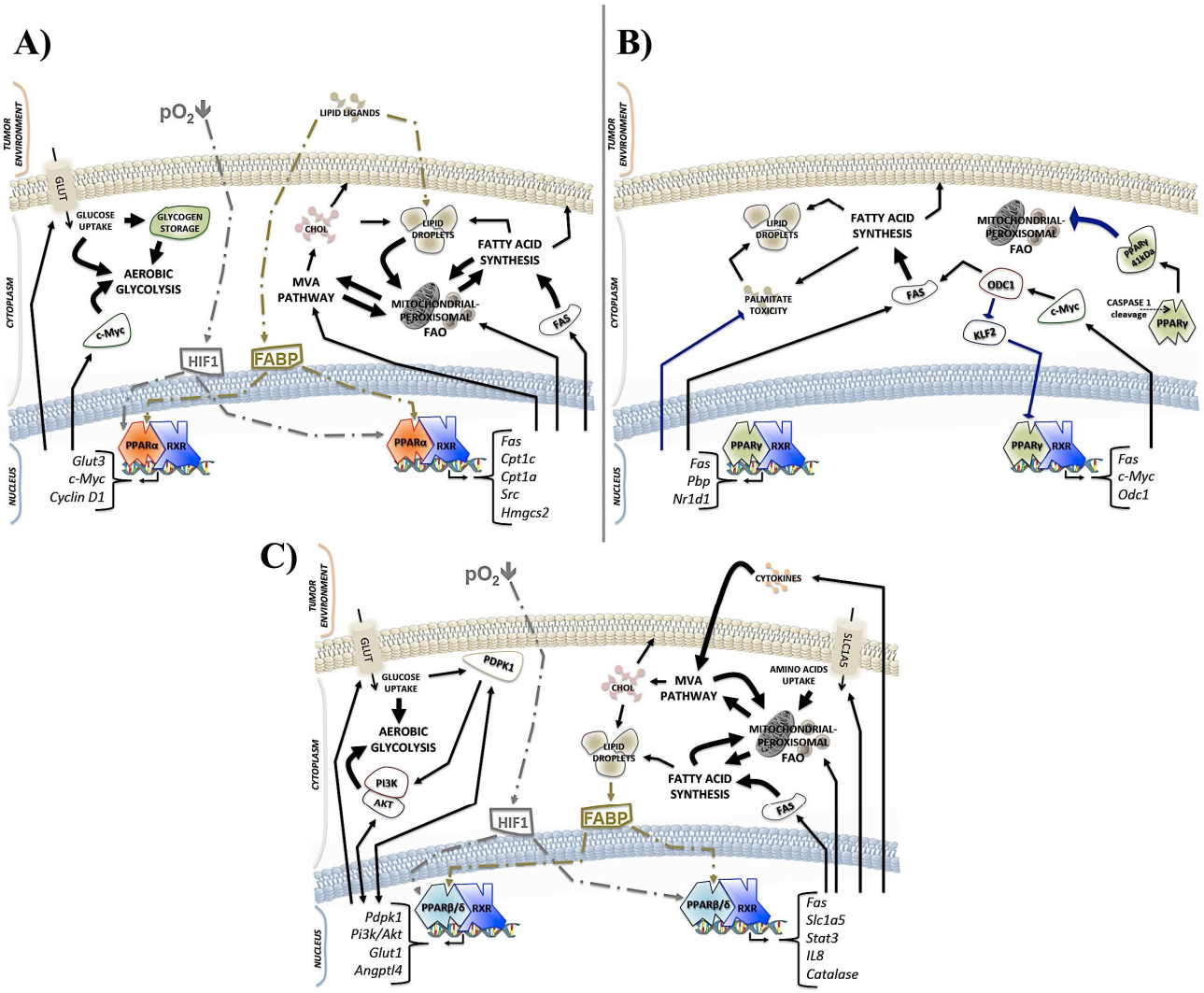

Figure 1. *Schematic representation of PPARs-dependent oncogenic metabolic pathways highlighted in this review. The representation concerns the metabolic mechanisms that are activated/inhibited in tumor cells under PPARs transcriptional control, these hypothesis of molecular mechanisms are based on evidences obtained by different cancer types. For each PPARs isotypes the specific activated/inhibited metabolic pathways are reported together with some PPARs target genes.* ***(A)*** *Hypoxia inducible factor 1 (HIF1) can active PPARα that in turn activates the transcription of specific genes resulting in high glycolysis, high glycogen storage and proliferation rate (glucose transporter 3 (GLUT3), c-Myc and cyclin D1). However, PPARα activation is also related to induction of fatty acid oxidation (FAO) by up-regulation of carnitine palmitoyl transferase 1 (CPT1) and fatty acid synthesis by up-regulation of fatty acid synthase (FAS). Noteworthy, mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2) is up-regulated by PPARα, but HMGCS2 can take part in heterodimeric complex with PPARα to induce Src. Phosphorylation of Src triggers mevalonate (MVA) pathway resulting in cholesterol (CHOL) high levels. Lipid components and cholesterol are useful for membrane synthesis and their large amounts are confined in lipid droplets. Extracellular lipids and some intracellular lipids (from lipid droplets) can be PPARα ligands, they are delivered to the nucleus by fatty acid binding protein (FABP).* ***(B)*** *PPARγ transcriptional activity activates some proteins related to fatty acid synthesis, such as FAS, c-Myc, PBP (PPARγ-binding protein), NR1D1 (nuclear receptor subfamily 1, group D, number 1) and ODC1 (ornithine decarboxylase 1). ODC1 is able to inhibit krüppel-like factor 2 (KLF2) thus its inhibitory activity on PPARγ. Others PPARγ-dependent mechanisms are able to reduce palmitate toxicity by confining its into lipid droplets. Moreover, PPARγ 41kDa fragment, derived from caspase 1 cleavage, is able to inhibit FAO.* ***(C)*** *PPARβ/δ stimulates glycolysis by overexpression of GLUT1, angiopoietin-like 4 (ANGPTL4), phosphoinositide-dependent protein kinase 1 (PDPK1) and PI3K/Akt, likewise PDPK1 and PI3K/Akt can activate PPARβ/δ expression. Fatty acid synthesis and FAO are activated by PPARβ/δ transcriptional activity on FAS and SLC1A5 (solute carrier 1 A5) genes, the second is linked to amino acids uptake thus also the anaplerosis is positively affected, which can be useful for FAO. Interesting, PPARβ/δ up-regulates cytokines expression, for example interleukin 8 (IL8), and cytokines in concert with PPARβ/δ induce STAT3 overexpression. MVA pathway is a downstream process triggered by STAT3. The thin black continuous lines with arrows indicate up-regulation events, the thick black continuous lines with arrows indicate stimulation of metabolic pathway. The thin blue continuous lines with bar indicate inhibition events, the thick blue continuous lines with bar indicate inhibition of metabolic pathway. HIF1 mediated up-regulation of PPARs is represented by grey dash dot and arrow at the end, while FABP mediated ligands-dependent PPARs activation is represented by gold dash dot and arrow at the end.*

Under certain circumstance PPARs transcriptional activity is aimed at suppressing specific tumor metabolic pathway. PPARα can inhibit lipid and cholesterol synthesis in concert with FAO induction. Glycolysis is obstructed by PPARα-dependent destruction of hexokinase II/VDAC complex leading to metabolic switch and high OXPHOS levels, as demonstrated in oral cancer cells (Figure 2A) [127]. Unlike PPARα, in some tissue hypoxia inducible factor down-regulates PPARγ leading to loss of its tumor suppression activity. In normoxic conditions PPARγ represses the expression of gene related to glycolysis (Wnt/β-catenin, c-Myc), glutamine anaplerosis, chemoresistance and antioxidant defence. Conversely, its transcriptional activity encourages the expression of genes involved in tumor differentiation, TCA cycle and FAO in agreement with the PKM1/PKM2 ratio increase (Figure 2B). Among the few evidences in favour of the oncosuppressive PPARβ/δ role, it is accepted, in prostate cancer cells, the PPARβ/δ ability to decrease FAO and to disrupt tumor proliferation, but only in absence of its ligands (Figure 2C).

An overall view of this review highlights the central role of PPARs in tumor metabolic decisions, in turn affected by genetic specificity of tumor cells and by tumor specific micrenvironment. In this regard, epigenetic events could play a key role in regulation of PPARs activities in tumor metabolic response, while the possible relationship between the three PPARs isotypes in tumor metabolism should be taken in consideration, as already described in the pathogenesis of neurodegenerative diseases [196]. However, to fully understand the exact role of PPARs in cancer metabolism could be interesting to study epigenetic effects related to PPARs and the relationship between the three isotypes, in order to efficiently target the complex machinery that achieves the energy demands of cancer cells.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 May 2018 doi:10.20944/preprints201805.0034.v1

Peer-reviewed version available at Int. J. Mol. Sci. 2018, 19, 1907; doi:10.3390/ijms19071907

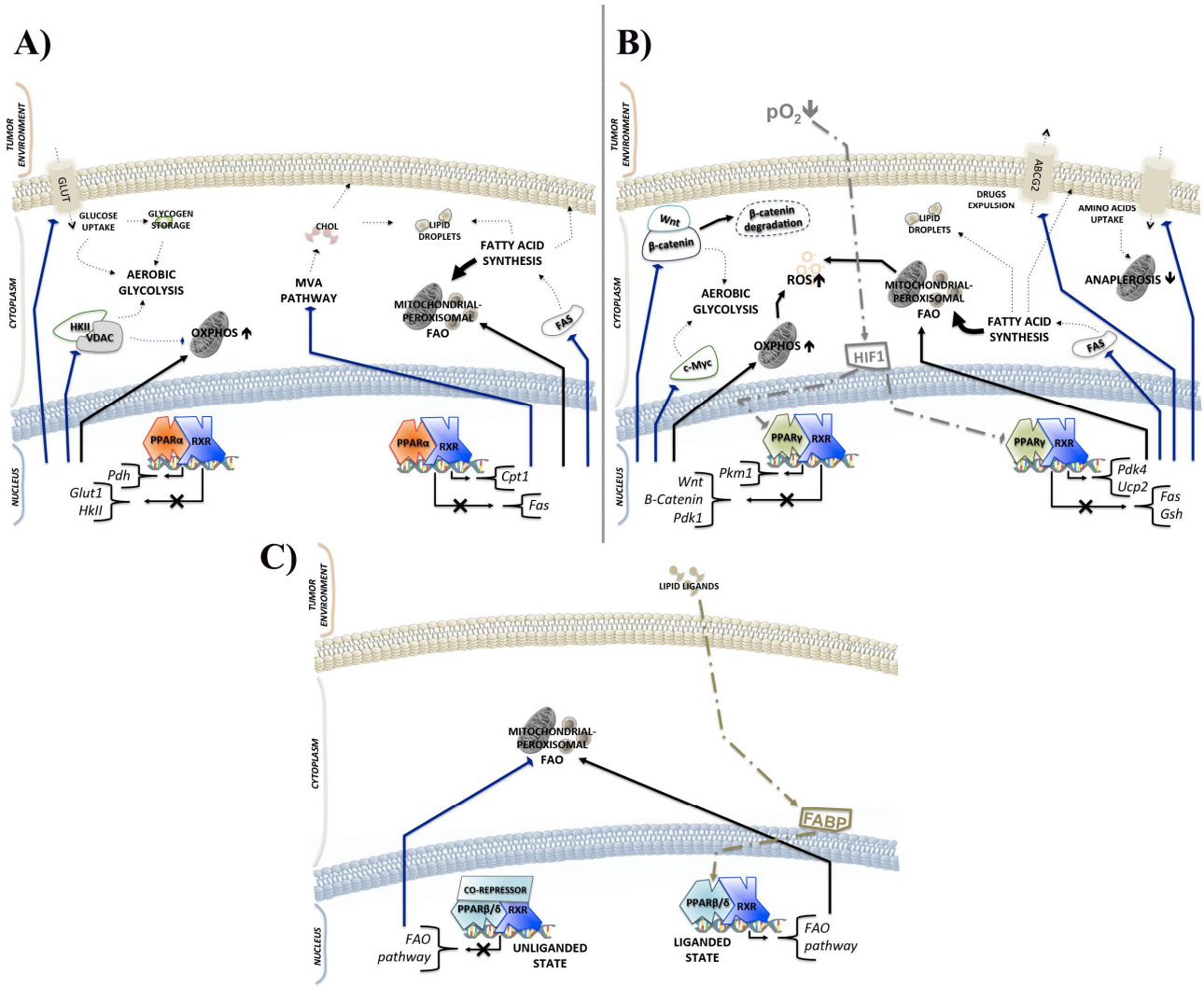

Figure 2. *Schematic representation of PPARs-dependent oncosuppressive metabolic pathways highlighted in this review. The representation concerns the metabolic mechanisms that are activated/inhibited in tumor cells under PPARs transcriptional control, these hypothesis of molecular mechanisms are based on evidences obtained by different cancer types. For each PPARs isotypes the specific activated/inhibited metabolic pathways are reported together with some PPARs target genes.* ***(A)*** *Aerobic glycolysis is inhibited by PPARα transcriptional repression of glucose transporter 1 (GLUT1) and hexokinase II (HKII) genes, while complex between voltage-dependent anion channel (VDAC) complex and HKII is destroyed by PPARα activity, thus adversely affecting glycolysis and increasing oxidative phosphorylation (OXPHOS). In addition pyruvate dehydrogenase (PDH) is up-regulated by PPARα to promote OXPHOS. Impairment in fatty acid synthesis by fatty acid synthase (FAS) down-regulation and impairment of mevalonate (MVA) pathway are due to adversely effect exerted by PPARα. Conversely carnitine palmitoyl transferase 1 (CPT1) is up-regulated by PPARα, this condition promotes fatty acid oxidation (FAO). Despite the reduced activity of fatty acid synthesis, FAO exhaust the reduced lipid reserve and impairs cancer cells life.* ***(B)*** *PPARγ down-regulates the c-Myc/Wnt/β-catenin axis and stimulates β-catenin proteasome degradation. Further down-regulation of pyruvate dehydrogenase kinase 1 (PDK1) and up-regulation of pyruvate kinase isoenzyme M1 by PPARγ promotes OXPHOS and impairs aerobic glycolysis. Fatty acid synthesis, amino acid uptake and anaplerosis are adversely affected by PPARγ activity in concert with increased levels of FAO related to up-regulation of PDK4 and mitochondrial uncoupling protein 2 (UCP2). Moreover PPARγ activity negatively affects ATP binding cassette G2 (ABCG2) and prevents chemoresistance associated with high sensitivity of tumor cells to ROS, which levels are increased through FAO and OXPHOS metabolic pathways. In addition there is glutathione (GSH) down-regulation and hypoxia inducible factor 1 (HIF1) is able to inhibit PPARγ activity.* ***(C)*** *In absence of ligands PPARβ/δ acts as a repressor, probably due to strong interaction between PPARβ/δ/RXR heterodimer and a co-repressor. However the repressor complex is able to down-regulate genes involved in FAO, this condition is reversed in presence of exogenous or endogenous PPARβ/δ ligands. The thin black continuous lines with arrows indicate up-regulation events, the thick black continuous lines with arrows indicate stimulation of metabolic pathway. The thin black dashed lines with arrows indicate reduction activity of metabolic pathways. The thin blue continuous lines with bar indicate inhibition events, the thin blue dashed lines with bar indicate reduction of metabolic pathway inhibition. HIF1 mediated down-regulation of PPARs is represented by grey dash dot and bar at the end, while FABP mediated ligands-dependent PPARs activation is represented by gold dash dot and arrow at the end.*

References:

[1] Nelson, D.; Lehninger, A.; Cox, M. Lehninger principles of biochemistry. **2008.**
[2] Poirier, Y.; Antonenkov, V.D.; Glumoff, T.; Hiltunen, J.K. Peroxisomal beta-oxidation--a metabolic pathway with multiple functions. *Biochim Biophys Acta*. **2006** Dec;1763(12):1413-26. Epub 2006 Aug 30. Review. PubMed PMID: 17028011.
[3] Santos, C.R;, Schulze, A. Lipid metabolism in cancer. *FEBS J.* 2012 Aug;279(15):2610-23. doi: 10.1111/j.1742-4658.2012.08644.x. Epub 2012 Jul 3. Review. PubMed PMID: 22621751.
[4] Young, S.G;, Zechner, R. Biochemistry and pathophysiology of intravascular and intracellular lipolysis. *Genes Dev.* 2013 Mar 1;27(5):459-84. doi: 10.1101/gad.209296.112. Review. PubMed PMID: 23475957; PubMed Central PMCID: PMC3605461.
[5] Cermelli, S;, Guo, Y.; Gross, S.P.; Welte, M.A. The lipid-droplet proteome reveals that droplets are a protein-storage depot. *Curr Biol.* 2006 Sep 19;16(18):1783-95. PubMed PMID: 16979555.
[6] Walther, T.C.; Farese, R.V. Jr. Lipid droplets and cellular lipid metabolism. *Annu Rev Biochem.* 2012;81:687-714. doi: 10.1146/annurev-biochem-061009-102430. Epub 2012 Apr 13. Review. PubMed PMID: 22524315; PubMed Central PMCID: PMC3767414.
[7] Khor, V.K.; Shen, W.J.; Kraemer, F.B. Lipid droplet metabolism. *Curr Opin Clin Nutr Metab Care.* 2013 Nov;16(6):632-7. doi: 10.1097/MCO.0b013e3283651106. Review. PubMed PMID: 24100667; PubMed Central PMCID: PMC4006541.
[8] WARBURG, O. On the origin of cancer cells. *Science.* 1956 Feb 24;123(3191):309-14. PubMed PMID: 13298683.
[9] Trédan, O.; Galmarini, C.M.; Patel, K.; Tannock, I.F. Drug resistance and the solid tumor microenvironment. *J Natl Cancer Inst.* 2007 Oct 3;99(19):1441-54. Epub 2007 Sep 25. Review. PubMed PMID: 17895480.
[10] Persano, L.; Rampazzo, E.; Della Puppa, A.; Pistollato, F.; Basso, G. The three-layer concentric model of glioblastoma: cancer stem cells, microenvironmental regulation, and therapeutic implications. *ScientificWorldJournal.* 2011;11:1829-41. doi: 10.1100/2011/736480. Epub 2011 Oct 23. Review. PubMed PMID: 22125441; PubMed Central PMCID: PMC3217608.
[11] Fidoamore, A.; Cristiano, L.; Antonosante, A.; d'Angelo, M.; Di Giacomo, E.; Astarita, C.; Giordano, A.; Ippoliti, R.; Benedetti, E.; Cimini, A. Glioblastoma Stem Cells Microenvironment: The Paracrine Roles of the Niche in Drug and Radioresistance. *Stem Cells Int.* **2016**;2016:6809105. doi: 10.1155/2016/6809105. Epub 2016 Jan 6. Review. PubMed PMID: 26880981; PubMed Central PMCID: PMC4736577.
[12] Martin, M.; Beauvoit, B.; Voisin, P.J.; Canioni, P.; Guérin, B.; Rigoulet, M. Energetic and morphological plasticity of C6 glioma cells grown on 3-D support; effect of transient glutamine deprivation. *J Bioenerg Biomembr.* **1998** Dec;30(6):565-78. PubMed PMID: 10206476.
[13] Guppy, M.; Leedman, P.; Zu, X.; Russell, V. Contribution by different fuels and metabolic pathways to the total ATP turnover of proliferating MCF-7 breast cancer cells. *Biochem J.* **2002** May 15;364(Pt 1):309-15. PubMed PMID: 11988105; PubMed Central PMCID: PMC1222574.
[14] Pasdois, P.; Deveaud, C.; Voisin, P.; Bouchaud, V.; Rigoulet, M.; Beauvoit, B. Contribution of the phosphorylable complex I in the growth phase-dependent respiration of C6 glioma cells in vitro. *J Bioenerg Biomembr.* **2003** Oct;35(5):439-50. PubMed PMID: 14740892.
[15] Rossignol, R.; Gilkerson, R.; Aggeler, R.; Yamagata, K.; Remington, S.J.; Capaldi, R.A. Energy substrate modulates mitochondrial structure and oxidative capacity in cancer cells. *Cancer Res.* **2004** Feb 1;64(3):985-93. PubMed PMID: 14871829.
[16] Crabtree, H.G. Observations on the carbohydrate metabolism of tumours. *Biochem J.* **1929**;23(3):536-45. PubMed PMID: 16744238; PubMed Central PMCID: PMC1254097.
[17] Smolková, K.; Plecitá-Hlavatá, L.; Bellance, N.; Benard, G.; Rossignol, R.; Ježek, P. Waves of gene regulation suppress and then restore oxidative phosphorylation in cancer cells. *Int J Biochem Cell Biol.* **2011** Jul;43(7):950-68. doi: 10.1016/j.biocel.2010.05.003. Epub 2010 May 10. Review. PubMed PMID: 20460169.
[18] Epstein, T.; Gatenby, R.A.; Brown, J.S. The Warburg effect as an adaptation of cancer cells to rapid fluctuations in energy demand. *PLoS One.* **2017** Sep 18;12(9):e0185085. doi: 10.1371/journal.pone.0185085. eCollection 2017. PubMed PMID: 28922380; PubMed Central PMCID: PMC5602667.
[19] Feron, O. Pyruvate into lactate and back: from the Warburg effect to symbiotic energy fuel exchange in cancer cells. *Radiother Oncol.* **2009** Sep;92(3):329-33. doi: 10.1016/j.radonc.2009.06.025. Epub 2009 Jul 13. Review. PubMed PMID: 19604589.
[20] Majewski, N.; Nogueira, V.; Bhaskar, P.; Coy, P.E.; Skeen, J.E.; Gottlob, K.; Chandel, N.S.; Thompson, C.B.; Robey, R.B.; Hay, N. Hexokinase-mitochondria interaction mediated by Akt is required to inhibit apoptosis in the presence or absence of Bax and Bak. *Mol Cell.* **2004** Dec 3;16(5):819-30. PubMed PMID: 15574336.
[21] DeBerardinis, R.J.; Lum, J.J.; Hatzivassiliou, G.; Thompson, C.B. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab.* **2008** Jan;7(1):11-20. doi: 10.1016/j.cmet.2007.10.002. Review. PubMed PMID: 18177721.
[22] Gao, P.; Tchernyshyov, I.; Chang, T.C.; Lee, Y.S.; Kita, K.; Ochi, T.; Zeller, K.I.; De Marzo, A.M.; Van Eyk, J.E.; Mendell, J.T.; Dang, C.V. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. *Nature.* **2009** Apr 9;458(7239):762-5. doi: 10.1038/nature07823. Epub 2009 Feb 15. PubMed PMID: 19219026; PubMed Central PMCID: PMC2729443.
[23] Atsumi, T.; Chesney, J.; Metz, C.; Leng, L.; Donnelly, S.; Makita, Z.; Mitchell, R.; Bucala, R. High expression of inducible 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (iPFK-2; PFKFB3) in human cancers. *Cancer Res.* **2002** Oct 15;62(20):5881-7. PubMed PMID: 12384552.
[24] Semenza, G.L. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. *Oncogene.* **2010** Feb 4;29(5):625-34. doi: 10.1038/onc.2009.441. Epub 2009 Nov 30. Review. PubMed PMID: 19946328; PubMed Central PMCID: PMC2969168.
[25] Liberti, M.V.; Locasale, J.W. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem Sci.* **2016** Mar;41(3):211-218. doi: 10.1016/j.tibs.2015.12.001. Epub 2016 Jan 5. Review. Erratum in: Trends Biochem Sci. 2016 Mar;41(3):287. Trends Biochem Sci. 2016 Mar;41(3):287. PubMed PMID: 26778478; PubMed Central PMCID: PMC4783224.
[26] Beloribi-Djefaflia, S.; Vasseur, S.; Guillaumond, F. Lipid metabolic reprogramming in cancer cells. *Oncogenesis.* **2016** Jan 25;5:e189. doi: 10.1038/oncsis.2015.49. Review. PubMed PMID: 26807644; PubMed Central PMCID: PMC4728678.
[27] Menendez, J.A.; Lupu, R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat Rev Cancer.* **2007** Oct;7(10):763-77. Review. PubMed PMID: 17882277.
[28] Tamura, K.; Makino, A.; Hullin-Matsuda, F.; Kobayashi, T.; Furihata, M.; Chung, S.; Ashida, S.; Miki, T.; Fujioka, T.; Shuin, T.; Nakamura, Y.; Nakagawa, H. Novel lipogenic enzyme ELOVL7 is involved in prostate cancer growth through saturated long-chain fatty acid metabolism. *Cancer Res.* **2009** Oct 15;69(20):8133-40. doi: 10.1158/0008-5472.CAN-09-0775. Epub 2009 Oct 13. PubMed PMID: 19826053.
[29] Lingwood, D.; Simons, K. Lipid rafts as a membrane-organizing principle. *Science.* **2010** Jan 1;327(5961):46-50. doi: 10.1126/science.1174621. Review. PubMed PMID: 20044567.
[30] Konstantinopoulos, P.A.; Karamouzis, M.V.; Papavassiliou, A.G. Post-translational modifications and regulation of the RAS superfamily of GTPases as anticancer targets. *Nat Rev Drug Discov.* **2007** Jul;6(7):541-55. Review. PubMed PMID: 17585331.
[31] Gray-Bablin, J.; Rao, S.; Keyomarsi, K. Lovastatin induction of cyclin-dependent kinase inhibitors in human breast cells occurs in a cell cycle-independent fashion. *Cancer Res.* **1997** Feb 15;57(4):604-9. PubMed PMID: 9044834.
[32] Newman, A.; Clutterbuck, R.D.; Powles, R.L.; Catovsky, D.; Millar, J.L. A comparison of the effect of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors simvastatin, lovastatin and pravastatin on leukaemic and normal bone marrow progenitors. *Leuk Lymphoma.* **1997** Feb;24(5-6):533-7. PubMed PMID: 9086443.

[33] Kodach, L.L.; Jacobs, R.J.; Voorneveld, P.W.; Wildenberg, M.E.; Verspaget, H.W.; van Wezel, T.; Morreau, H.; Hommes, D.W.; Peppelenbosch, M.P.; van den Brink, G.R.; Hardwick, J.C. Statins augment the chemosensitivity of colorectal cancer cells inducing epigenetic reprogramming and reducing colorectal cancer cell 'stemness' via the bone morphogenetic protein pathway. *Gut.* **2011** Nov;60(11):1544-53. doi: 10.1136/gut.2011.237495. Epub 2011 May 6. PubMed PMID: 21551187.

[34] Hager, M.H.; Solomon, K.R.; Freeman, M.R. The role of cholesterol in prostate cancer. *Curr Opin Clin Nutr Metab Care.* **2006** Jul;9(4):379-85. Review. PubMed PMID: 16778565.

[35] Yue, S.; Li, J.; Lee, S.Y.; Lee, H.J.; Shao, T.; Song, B.; Cheng, L.; Masterson, T.A.; Liu, X.; Ratliff, T.L.; Cheng, J.X. Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness. *Cell Metab.* **2014** Mar 4;19(3):393-406. doi: 10.1016/j.cmet.2014.01.019. PubMed PMID: 24606897; PubMed Central PMCID: PMC3969850.

[36] Abramczyk, H.; Surmacki, J.; Kopeć, M.; Olejnik, A.K.; Lubecka-Pietruszewska, K.; Fabianowska-Majewska, K. The role of lipid droplets and adipocytes in cancer. Raman imaging of cell cultures: MCF10A, MCF7, and MDA-MB-231 compared to adipocytes in cancerous human breast tissue. *Analyst.* **2015** Apr 7;140(7):2224-35. doi: 10.1039/c4an01875c. PubMed PMID: 25730442.

[37] Tirinato, L.; Liberale, C.; Di Franco, S.; Candeloro, P.; Benfante, A.; La Rocca, R.; Potze, L.; Marotta, R.; Ruffilli, R.; Rajamanickam, V.P.; Malerba, M.; De Angelis, F.; Falqui, A.; Carbone, E.; Todaro, M.; Medema, J.P.; Stassi, G.; Di Fabrizio, E. Lipid droplets: a new player in colorectal cancer stem cells unveiled by spectroscopic imaging. *Stem Cells.* **2015** Jan;33(1):35-44. doi: 10.1002/stem.1837. PubMed PMID: 25186497; PubMed Central PMCID: PMC4311668.

[38] Benedetti, E.; Galzio, R.; Laurenti, G.; D'Angelo, B.; Melchiorre, E.; Cifone, M.G.; Fanelli, F.; Muzi, P.; Coletti, G.; Alecci, M.; Sotgiu, A.; Cerù, M.P.; Cimini, A. Lipid metabolism impairment in human gliomas: expression of peroxisomal proteins in human gliomas at different grades of malignancy. *Int J Immunopathol Pharmacol.* **2010** Jan-Mar;23(1):235-46. PubMed PMID: 20378009.

[39] Liu, Y. Fatty acid oxidation is a dominant bioenergetic pathway in prostate cancer. *Prostate Cancer Prostatic Dis.* **2006**;9(3):230-4. Epub 2006 May 9. Review. PubMed PMID: 16683009.

[40] Liu, Y.; Zuckier, L.S.; Ghesani, N.V. Dominant uptake of fatty acid over glucose by prostate cells: a potential new diagnostic and therapeutic approach. *Anticancer Res.* **2010** Feb;30(2):369-74. PubMed PMID: 20332441.

[41] Caro, P.; Kishan, A.U.; Norberg, E.; Stanley, I.A.; Chapuy, B.; Ficarro, S.B.; Polak, K.; Tondera, D.; Gounarides, J.; Yin, H.; Zhou, F.; Green, M.R.; Chen, L.; Monti, S.; Marto, J.A.; Shipp, M.A.; Danial, N.N. Metabolic signatures uncover distinct targets in molecular subsets of diffuse large B cell lymphoma. *Cancer Cell.* **2012** Oct 16;22(4):547-60. doi: 10.1016/j.ccr.2012.08.014. PubMed PMID: 23079663; PubMed Central PMCID: PMC3479446.

[42] Khasawneh, J.; Schulz, M.D.; Walch, A.; Rozman, J.; Hrabe de Angelis, M.; Klingenspor, M.; Buck, A.; Schwaiger, M.; Saur, D.; Schmid, R.M.; Klöppel, G.; Sipos, B.; Greten, F.R.; Arkan, M.C. Inflammation and mitochondrial fatty acid beta-oxidation link obesity to early tumor promotion. *Proc Natl Acad Sci U S A.* **2009** Mar 3;106(9):3354-9. doi: 10.1073/pnas.0802864106. Epub 2009 Feb 10. PubMed PMID: 19208810; PubMed Central PMCID: PMC2651311.

[43] Pike, L.S.; Smift, A.L.; Croteau, N.J.; Ferrick, D.A.; Wu, M. Inhibition of fatty acid oxidation by etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death in human glioblastoma cells. *Biochim Biophys Acta.* **2011** Jun;1807(6):726-34. PubMed PMID: 21692241.

[44] Kim, J.W.; Tchernyshyov, I.; Semenza, G.L.; Dang, C.V. HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metab.* **2006** Mar;3(3):177-85. PubMed PMID: 16517405.

[45] Gimm, T.; Wiese, M.; Teschemacher, B.; Deggerich, A.; Schödel, J.; Knaup, K.X.; Hackenbeck, T.; Hellerbrand, C.; Amann, K.; Wiesener, M.S.; Höning, S.; Eckardt, K.U.; Warnecke, C. Hypoxia-inducible protein 2 is a novel lipid droplet protein and a specific target gene of hypoxia-inducible factor-1. *FASEB J.* **2010** Nov;24(11):4443-58. doi: 10.1096/fj.10-159806. Epub 2010 Jul 12. PubMed PMID: 20624928.

[46] Mullen, A.R.; Wheaton, W.W.; Jin, E.S.; Chen, P.H.; Sullivan, L.B.; Cheng, T.; Yang, Y.; Linehan, W.M.; Chandel, N.S.; DeBerardinis, R.J. Reductive carboxylation supports growth in tumour cells with defective mitochondria. *Nature.* **2011** Nov 20;481(7381):385-8. doi: 10.1038/nature10642. PubMed PMID: 22101431; PubMed Central PMCID: PMC3262117.

[47] Metallo, C.M.; Gameiro, P.A.; Bell, E.L.; Mattaini, K.R.; Yang, J.; Hiller, K.; Jewell, C.M.; Johnson, Z.R.; Irvine, D.J.; Guarente, L.; Kelleher, J.K.; Vander Heiden, M.G.; Iliopoulos, O.; Stephanopoulos, G. Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. *Nature.* **2011** Nov 20;481(7381):380-4. doi: 10.1038/nature10602. PubMed PMID: 22101433; PubMed Central PMCID: PMC3710581.

[48] Wise, D.R.; Ward, P.S.; Shay, J.E.; Cross, J.R.; Gruber, J.J.; Sachdeva, U.M.; Platt, J.M.; DeMatteo, R.G.; Simon, M.C.; Thompson, C.B. Hypoxia promotes isocitrate dehydrogenase-dependent carboxylation of α-ketoglutarate to citrate to support cell growth and viability. *Proc Natl Acad Sci U S A.* **2011** Dec 6;108(49):19611-6. doi: 10.1073/pnas.1117773108. Epub 2011 Nov 21. PubMed PMID: 22106302; PubMed Central PMCID: PMC3241793.

[49] Le, A.; Lane, A.N.; Hamaker, M.; Bose, S.; Gouw, A.; Barbi, J.; Tsukamoto, T.; Rojas, C.J.; Slusher, B.S.; Zhang, H.; Zimmerman, L.J.; Liebler, D.C.; Slebos, R.J.; Lorkiewicz, P.K.; Higashi, R.M.; Fan, T.W.; Dang, C.V. Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells. *Cell Metab.* **2012** Jan 4;15(1):110-21. doi: 10.1016/j.cmet.2011.12.009. PubMed PMID: 22225880; PubMed Central PMCID: PMC3345194.

[50] Fan, J.; Kamphorst, J.J.; Mathew, R.; Chung, M.K.; White, E.; Shlomi, T.; Rabinowitz, J.D. Glutamine-driven oxidative phosphorylation is a major ATP source in transformed mammalian cells in both normoxia and hypoxia. *Mol Syst Biol.* **2013** Dec 3;9:712. doi: 10.1038/msb.2013.65. PubMed PMID: 24301801; PubMed Central PMCID: PMC3882799.

[51] Wang, J.B.; Erickson, J.W.; Fuji, R.; Ramachandran, S.; Gao, P.; Dinavahi, R.; Wilson, K.F.; Ambrosio, A.L.; Dias, S.M.; Dang, C.V.; Cerione, R.A. Targeting mitochondrial glutaminase activity inhibits oncogenic transformation. *Cancer Cell.* **2010** Sep 14;18(3):207-19. doi: 10.1016/j.ccr.2010.08.009. Erratum in: Cancer Cell. 2010 Oct 19;18(4):397. PubMed PMID: 20832749; PubMed Central PMCID: PMC3078749.

[52] DeBerardinis, R.J.; Mancuso, A.; Daikhin, E.; Nissim, I.; Yudkoff, M.; Wehrli, S.; Thompson, C.B. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc Natl Acad Sci U S A.* **2007** Dec 4;104(49):19345-50. Epub 2007 Nov 21. PubMed PMID: 18032601; PubMed Central PMCID: PMC2148292.

[53] Yang, L.; Moss, T.; Mangala, L.S.; Marini, J.; Zhao, H.; Wahlig, S.; Armaiz-Pena, G.; Jiang, D.; Achreja, A.; Win, J.; Roopaimoole, R.; Rodriguez-Aguayo, C.; Mercado-Uribe, I.; Lopez-Berestein, G.; Liu, J.; Tsukamoto, T.; Sood, A.K.; Ram, P.T.; Nagrath, D. Metabolic shifts toward glutamine regulate tumor growth, invasion and bioenergetics in ovarian cancer. *Mol Syst Biol.* **2014** May 5;10:728. doi: 10.1002/msb.20134892. PubMed PMID: 24799285; PubMed Central PMCID: PMC4188042.

[54] Tan, N.S.; Michalik, L.; Noy, N.; Yasmin, R.; Pacot, C.; Heim, M.; Flühmann, B.; Desvergne, B.; Wahli, W. Critical roles of PPAR beta/delta in keratinocyte response to inflammation. *Genes Dev.* **2001** Dec 15;15(24):3263-77. PubMed PMID: 11751632; PubMed Central PMCID: PMC312855.

[55] Mandard, S.; Müller, M.; Kersten, S. Peroxisome proliferator-activated receptor alpha target genes. *Cell Mol Life Sci.* **2004** Feb;61(4):393-416. Review. PubMed PMID: 14999402.

[56] Lehrke, M.; Lazar, M.A. The many faces of PPARgamma. *Cell.* **2005** Dec 16;123(6):993-9. Review. PubMed PMID: 16360030.

[57] Feige, J.N.; Gelman, L.; Michalik, L.; Desvergne, B.; Wahli, W. From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. *Prog Lipid Res.* **2006** Mar;45(2):120-59. Epub 2006 Jan 25. Review. PubMed PMID: 16476485.

[58] Feige, J.N.; Gelman, L.; Tudor, C.; Engelborghs, Y.; Wahli, W.; Desvergne, B. Fluorescence imaging reveals the nuclear behavior of peroxisome proliferator-activated receptor/retinoid X receptor heterodimers in the absence and presence of ligand. *J Biol Chem.* **2005** May 6;280(18):17880-90. Epub 2005 Feb 24. PubMed PMID: 15731109.

[59] Juge-Aubry, C.; Pernin, A.; Favez, T.; Burger, A.G.; Wahli, W.; Meier, C.A.; Desvergne, B. DNA binding properties of peroxisome proliferator-activated receptor subtypes on various natural peroxisome proliferator response elements. Importance of the 5'-flanking region. *J Biol Chem.* **1997** Oct 3;272(40):25252-9. PubMed PMID: 9312141.

[60] Olefsky, J.M. Nuclear receptor minireview series. *J Biol Chem.* **2001** Oct 5;276(40):36863-4. Epub 2001 Jul 17. Review. PubMed PMID: 11459855.

[61] Tan, N.S.; Shaw, N.S.; Vinckenbosch, N.; Liu, P.; Yasmin, R.; Desvergne, B.; Wahli, W.; Noy, N. Selective cooperation between fatty acid binding proteins and peroxisome proliferator-activated receptors in regulating transcription. *Mol Cell Biol.* **2002** Jul;22(14):5114-27. Erratum in: Mol Cell Biol 2002 Sep;22(17):6318. PubMed PMID: 12077340; PubMed Central PMCID: PMC139777.

[62] Lehmann, J.M.; Moore, L.B.; Smith-Oliver, T.A.; Wilkison, W.O.; Willson, T.M.; Kliewer, S.A. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem.* **1995** Jun 2;270(22):12953-6. PubMed PMID: 7768881.

[63] Krey, G.; Braissant, O.; L'Horset, F.; Kalkhoven, E.; Perroud, M.; Parker, M.G.; Wahli, W. Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. *Mol Endocrinol.* **1997** Jun;11(6):779-91. PubMed PMID: 9171241.

[64] Pozzi, A.; Ibanez, M.R.; Gatica, A.E.; Yang, S.; Wei, S.; Mei, S.; Falck, J.R.; Capdevila, J.H. Peroxisomal proliferator-activated receptor-alpha-dependent inhibition of endothelial cell proliferation and tumorigenesis. *J Biol Chem.* **2007** Jun 15;282(24):17685-95. Epub 2007 Apr 3. PubMed PMID: 17405874.

[65] Hou, Y.; Moreau, F.; Chadee, K. PPARγ is an E3 ligase that induces the degradation of NFκB/p65. *Nat Commun.* **2012**;3:1300. doi: 10.1038/ncomms2270. PubMed PMID: 23250430.

[66] Hou, Y.; Gao, J.; Xu, H.; Xu, Y.; Zhang, Z.; Xu, Q.; Zhang, C. PPARγ E3 ubiquitin ligase regulates MUC1-C oncoprotein stability. *Oncogene.* **2014** Dec 4;33(49):5619-25. doi: 10.1038/onc.2013.504. Epub 2013 Dec 2. PubMed PMID: 24292674.

[67] Skrypnyk, N.; Chen, X.; Hu, W.; Su, Y.; Mont, S.; Yang, S.; Gangadhariah, M.; Wei, S.; Falck, J.R.; Jat, J.L.; Zent, R.; Capdevila, J.H.; Pozzi, A. PPARα activation can help prevent and treat non-small cell lung cancer. *Cancer Res.* **2014** Jan 15;74(2):621-31. doi: 10.1158/0008-5472.CAN-13-1928. Epub 2013 Dec 3. PubMed PMID: 24302581; PubMed Central PMCID: PMC3902646.

[68] Gao, J.; Liu, Q.; Xu, Y.; Gong, X.; Zhang, R.; Zhou, C.; Su, Z.; Jin, J.; Shi, H.; Shi, J.; Hou, Y. PPARα induces cell apoptosis by destructing Bcl2. *Oncotarget.* **2015** Dec 29;6(42):44635-42. doi: 10.18632/oncotarget.5988. PubMed PMID: 26556865; PubMed Central PMCID: PMC4792581.

[69] Xu, Y.; Jin, J.; Zhang, W.; Zhang, Z.; Gao, J.; Liu, Q.; Zhou, C.; Xu, Q.; Shi, H.; Hou, Y.; Shi, J. EGFR/MDM2 signaling promotes NF-κB activation via PPARγ degradation. *Carcinogenesis.* **2016** Feb;37(2):215-222. doi: 10.1093/carcin/bgv252. Epub 2015 Dec 30. PubMed PMID: 26718225.

[70] You, M.; Jin, J.; Liu, Q.; Xu, Q.; Shi, J.; Hou, Y. PPARα Promotes Cancer Cell Glut1 Transcription Repression. *J Cell Biochem.* **2017** Jun;118(6):1556-1562. doi: 10.1002/jcb.25817. Epub 2017 Jan 5. PubMed PMID: 27918085.

[71] Kaipainen, A.; Kieran, M.W.; Huang, S.; Butterfield, C.; Bielenberg, D.; Mostoslavsky, G.; Mulligan, R.; Folkman, J.; Panigrahy, D. PPARalpha deficiency in inflammatory cells suppresses tumor growth. *PLoS One.* **2007** Feb 28;2(2):e260. PubMed PMID: 17327920; PubMed Central PMCID: PMC1800345.

[72] Spaner, D.E.; Lee, E.; Shi, Y.; Wen, F.; Li, Y.; Tung, S.; McCaw, L.; Wong, K.; Gary-Gouy, H.; Dalloul, A.; Ceddia, R.; Gorzcynski, R. PPAR-alpha is a therapeutic target for chronic lymphocytic leukemia. *Leukemia.* **2013** Apr;27(5):1090-9. doi: 10.1038/leu.2012.329. Epub 2012 Nov 19. PubMed PMID: 23160450.

[73] Messmer, D.; Lorrain, K.; Stebbins, K.; Bravo, Y.; Stock, N.; Cabrera, G.; Correa, L.; Chen, A.; Jacintho, J.; Chiorazzi, N.; Yan, X.J.; Spaner, D.; Prasit, P.; Lorrain, D. A Selective Novel Peroxisome Proliferator-Activated Receptor (PPAR)-α Antagonist Induces Apoptosis and Inhibits Proliferation of CLL Cells In Vitro and In Vivo. *Mol Med.* **2015** Jun 9;21:410-9. doi: 10.2119/molmed.2015.00139. PubMed PMID: 26070013; PubMed Central PMCID: PMC4559529.

[74] Michalik, L.; Desvergne, B.; Wahli, W. Peroxisome-proliferator-activated receptors and cancers: complex stories. *Nat Rev Cancer.* **2004** Jan;4(1):61-70. Review. PubMed PMID: 14708026.

[75] You, M.; Yuan, S.; Shi, J.; Hou, Y. PPARδ signaling regulates colorectal cancer. *Curr Pharm Des.* **2015**;21(21):2956-9. Review. PubMed PMID: 26004416.

[76] Zhang, W.; Xu, Y.; Xu, Q.; Shi, H.; Shi, J.; Hou, Y. PPARδ promotes tumor progression via activation of Glut1 and SLC1-A5 transcription. *Carcinogenesis.* **2017** Jul 1;38(7):748-755. doi: 10.1093/carcin/bgx035. PubMed PMID: 28419191.

[77] Frattini, V.; Pagnotta, S.M.; Tala, Fan J.J.; Russo, M.V.; Lee, S.B.; Garofano, L.; Zhang, J.; Shi, P.; Lewis, G.; Sanson, H.; Frederick, V.; Castano, A.M.; Cerulo, L.; Rolland, D.C.M.; Mall, R.; Mokhtari, K.; Elenitoba-Johnson, K.S.J.; Sanson, M.; Huang, X.; Ceccarelli, M.; Lasorella, A.; Iavarone, A. A metabolic function of FGFR3-TACC3 gene fusions in cancer. *Nature.* **2018** Jan 11;553(7687):222-227. doi: 10.1038/nature25171. Epub 2018 Jan 3. PubMed PMID: 29323298; PubMed Central PMCID: PMC5771419.

[78] Grabacka, M.; Plonka, P.M.; Urbanska, K.; Reiss, K. Peroxisome proliferator-activated receptor alpha activation decreases metastatic potential of melanoma cells in vitro via down-regulation of Akt. *Clin Cancer Res.* 2006 May 15;12(10):3028-36. PubMed PMID: 16707598.

[79] Liu, D.C.; Zang, C.B.; Liu, H.Y.; Possinger, K.; Fan, S.G.; Elstner, E. A novel PPAR alpha/gamma dual agonist inhibits cell growth and induces apoptosis in human glioblastoma T98G cells. *Acta Pharmacol Sin.* **2004** Oct;25(10):1312-9. PubMed PMID: 15456533.

[80] Suchanek, K.M.; May, F.J.; Robinson, J.A.; Lee, W.J.; Holman, N.A.; Monteith, G.R.; Roberts-Thomson, S.J. Peroxisome proliferator-activated receptor alpha in the human breast cancer cell lines MCF-7 and MDA-MB-231. *Mol Carcinog.* **2002** Aug;34(4):165-71. PubMed PMID: 12203367.

[81] Abu Aboud, O.; Wettersten, H.I.; Weiss, R.H. Inhibition of PPARα induces cell cycle arrest and apoptosis, and synergizes with glycolysis inhibition in kidney cancer cells. *PLoS One.* **2013** Aug 7;8(8):e71115. doi: 10.1371/journal.pone.0071115. eCollection 2013. PubMed PMID: 23951092; PubMed Central PMCID: PMC3737191.

[82] Peters, J.M.; Cattley, R.C.; Gonzalez, F.J. Role of PPAR alpha in the mechanism of action of the nongenotoxic carcinogen and peroxisome proliferator Wy-14,643. *Carcinogenesis.* **1997** Nov;18(11):2029-33. PubMed PMID: 9395198.

[83] Fidoamore, A.; Cristiano, L.; Laezza, C.; Galzio, R.; Benedetti, E.; Cinque, B.; Antonosante, A.; d'Angelo, M.; Castelli, V.; Cifone, M.G.; Ippoliti, R.; Giordano, A.; Cimini, A. Energy metabolism in glioblastoma stem cells: PPARα a metabolic adaptor to intratumoral microenvironment. *Oncotarget.* **2017** Jul 7;8(65):108430-108450. doi: 10.18632/oncotarget.19086. eCollection 2017 Dec 12. PubMed PMID: 29312541; PubMed Central PMCID: PMC5752454.

[84] Yang, L.; Lin, C.; Wang, L.; Guo, H.; Wang, X. Hypoxia and hypoxia-inducible factors in glioblastoma multiforme progression and therapeutic implications. *Exp Cell Res.* **2012** Nov 15;318(19):2417-26. doi: 10.1016/j.yexcr.2012.07.017. Epub 2012 Aug 13. Review. PubMed PMID: 22906859.

[85] Persano, L.; Rampazzo, E.; Basso, G.; Viola, G. Glioblastoma cancer stem cells: role of the microenvironment and therapeutic targeting. *Biochem Pharmacol.* **2013** Mar 1;85(5):612-22. doi: 10.1016/j.bcp.2012.10.001. Epub 2012 Oct 11. Review. PubMed PMID: 23063412.

[86] Laurenti, G.; Benedetti, E.; D'Angelo, B.; Cristiano, L.; Cinque, B.; Raysi, S.; Alecci, M.; Cerù, M.P.; Cifone, M.G.; Galzio, R.; Giordano, A.; Cimini, A. Hypoxia induces peroxisome proliferator-activated receptor α (PPARα) and lipid metabolism peroxisomal enzymes in human glioblastoma cells. *J Cell Biochem.* **2011** Dec;112(12):3891-901. doi: 10.1002/jcb.23323. PubMed PMID: 21866563.

[87] Pelletier, J.; Bellot, G.; Gounon, P.; Lacas-Gervais, S.; Pouysségur, J.; Mazure, N.M. Glycogen Synthesis is induced in Hypoxia by the Hypoxia-Inducible Factor and Promotes Cancer Cell Survival. *Front Oncol.* **2012** Feb 28;2:18. doi: 10.3389/fonc.2012.00018. eCollection 2012. PubMed PMID: 22649778; PubMed Central PMCID: PMC3355943.

[88] Guo, D.; Bell, E.H.; Chakravarti, A. Lipid metabolism emerges as a promising target for malignant glioma therapy. *CNS Oncol.* **2013** May;2(3):289-99. Review. PubMed PMID: 24159371; PubMed Central PMCID: PMC3804348.

[89] Morihiro, Y.; Yasumoto, Y.; Vaidyan, L.K.,; Sadahiro, H.; Uchida, T.; Inamura, A.; Sharifi, K.; Ideguchi, M.; Nomura, S.; Tokuda, N.; Kashiwabara, S.; Ishii, A.; Ikeda, E.; Owada, Y.; Suzuki, M. Fatty acid binding protein 7 as a marker of glioma stem cells. *Pathol Int.* **2013** Nov;63(11):546-53. doi: 10.1111/pin.12109. PubMed PMID: 24274717.

[90] Ta, M.T.; Kapterian, T.S.; Fei, W.; Du, X.; Brown, A.J.; Dawes, I.W.; Yang, H. Accumulation of squalene is associated with the clustering of lipid droplets. *FEBS J.* **2012** Nov;279(22):4231-44. doi: 10.1111/febs.12015. Epub 2012 Oct 22. PubMed PMID: 23013491.

[91] Perroud, B.; Ishimaru, T.; Borowsky, A.D.; Weiss, R.H. Grade-dependent proteomics characterization of kidney cancer. *Mol Cell Proteomics.* **2009** May;8(5):971-85. doi: 10.1074/mcp.M800252-MCP200. Epub 2009 Jan 21. PubMed PMID: 19164279; PubMed Central PMCID: PMC2689781.

[92] Shah, Y.M.; Morimura, K.; Yang, Q.; Tanabe, T.; Takagi, M.; Gonzalez, F.J. Peroxisome proliferator-activated receptor alpha regulates a microRNA-mediated signaling cascade responsible for hepatocellular proliferation. *Mol Cell Biol.* **2007** Jun;27(12):4238-47. Epub 2007 Apr 16. PubMed PMID: 17438130; PubMed Central PMCID: PMC1900062.

[93] Wang, C.; Lisanti, M.P.; Liao, D.J. Reviewing once more the c-myc and Ras collaboration: converging at the cyclin D1-CDK4 complex and challenging basic concepts of cancer biology. *Cell Cycle.* **2011** Jan 1;10(1):57-67. Epub 2011 Jan 1. Review. PubMed PMID: 21200143; PubMed Central PMCID: PMC3048075.

[94] Cairns, R.A.; Harris, I.S.; Mak, T.W. Regulation of cancer cell metabolism. *Nat Rev Cancer.* **2011** Feb;11(2):85-95. doi: 10.1038/nrc2981. Review. PubMed PMID: 21258394.

[95] Diaz-Moralli, S.; Tarrado-Castellarnau, M.; Miranda, A.; Cascante, M. Targeting cell cycle regulation in cancer therapy. *Pharmacol Ther.* **2013** May;138(2):255-71. doi: 10.1016/j.pharmthera.2013.01.011. Epub 2013 Jan 26. Review. PubMed PMID: 23356980.

[96] Kamarajugadda, S.; Becker, J.R.; Hanse, E.A.; Mashek, D.G.; Mashek, M.T.; Hendrickson, A.M.; Mullany, L.K.; Albrecht, J.H. Cyclin D1 represses peroxisome proliferator-activated receptor alpha and inhibits fatty acid oxidation. *Oncotarget.* **2016** Jul 26;7(30):47674-47686. doi: 10.18632/oncotarget.10274. PubMed PMID: 27351284; PubMed Central PMCID: PMC5216970.

[97] Fu, M.; Rao, M.; Bouras, T.; Wang, C.; Wu, K.; Zhang, X.; Li, Z.; Yao, T.P.; Pestell, R.G. Cyclin D1 inhibits peroxisome proliferator-activated receptor gamma-mediated adipogenesis through histone deacetylase recruitment. *J Biol Chem.* **2005** Apr 29;280(17):16934-41. Epub 2005 Feb 14. PubMed PMID: 15713663.

[98] Hanse, E.A.; Mashek, D.G.; Becker, J.R.; Solmonson, A.D.; Mullany, L.K.; Mashek, M.T.; Towle, H.C.; Chau, A.T.; Albrecht, J.H. Cyclin D1 inhibits hepatic lipogenesis via repression of carbohydrate response element binding protein and hepatocyte nuclear factor 4α. *Cell Cycle.* **2012** Jul 15;11(14):2681-90. doi: 10.4161/cc.21019. Epub 2012 Jul 15. PubMed PMID: 22751438; PubMed Central PMCID: PMC3409010.

[99] Le, A.; Lane, A.N.; Hamaker, M.; Bose, S.; Gouw, A.; Barbi, J.; Tsukamoto, T.; Rojas, C.J.; Slusher, B.S.; Zhang, H.; Zimmerman, L.J.; Liebler, D.C.; Slebos, R.J.; Lorkiewicz, P.K.; Higashi, R.M.; Fan, T.W.; Dang, C.V. Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells. *Cell Metab.* **2012** Jan 4;15(1):110-21. doi: 10.1016/j.cmet.2011.12.009. PubMed PMID: 22225880; PubMed Central PMCID: PMC3345194.

[100] Fu, M.; Wang, C.; Rao, M.; Wu, X.; Bouras, T.; Zhang, X.; Li, Z.; Jiao, X.; Yang, J.; Li, A.; Perkins, N.D.; Thimmapaya, B.; Kung, A.L.; Munoz, A.; Giordano, A.; Lisanti, M.P.; Pestell, R.G. Cyclin D1 represses p300 transactivation through a cyclin-dependent kinase-independent mechanism. *J Biol Chem.* **2005** Aug 19;280(33):29728-42. Epub 2005 Jun 10. PubMed PMID: 15951563.

[101] Knudsen, K.E. Cyclin D1 goes metabolic: dual functions of cyclin D1 in regulating lipogenesis. *Cell Cycle.* **2012** Oct 1;11(19):3533-4. doi: 10.4161/cc.22039. Epub 2012 Sep 5. PubMed PMID: 22951541; PubMed Central PMCID: PMC3478301.

[102] Chakravarthy, M.V.; Pan, Z.; Zhu, Y.; Tordjman, K.; Schneider, J.G.; Coleman, T.; Turk, J.; Semenkovich, C.F. "New" hepatic fat activates PPARalpha to maintain glucose, lipid, and cholesterol homeostasis. *Cell Metab.* **2005** May;1(5):309-22. PubMed PMID: 16054078.

[103] Chakravarthy, M.V.; Zhu, Y.; López, M.; Yin, L.; Wozniak, D.F.; Coleman, T.; Hu, Z.; Wolfgang, M.; Vidal-Puig, A.; Lane, M.D.; Semenkovich, C.F. Brain fatty acid synthase activates PPARalpha to maintain energy homeostasis. *J Clin Invest.* **2007** Sep;117(9):2539-52. PubMed PMID: 17694178; PubMed Central PMCID: PMC1937501.

[104] Horiguchi, A.; Asano, T.; Asano, T.; Ito, K.; Sumitomo, M.; Hayakawa, M. Fatty acid synthase over expression is an indicator of tumor aggressiveness and poor prognosis in renal cell carcinoma. *J Urol.* **2008** Sep;180(3):1137-40. doi: 10.1016/j.juro.2008.04.135. Epub 2008 Jul 18. PubMed PMID: 18639282.

[105] Abu Aboud, O.; Donohoe, D.; Bultman, S.; Fitch, M.; Riiff, T.; Hellerstein, M.; Weiss, R.H. PPARα inhibition modulates multiple reprogrammed metabolic pathways in kidney cancer and attenuates tumor growth. *Am J Physiol Cell Physiol.* **2015** Jun 1;308(11):C890-8. doi: 10.1152/ajpcell.00322.2014. Epub 2015 Mar 25. PubMed PMID: 25810260; PubMed Central PMCID: PMC4451352.

[106] Kurokawa, T.; Shimomura, Y.; Bajotto, G.; Kotake, K.; Arikawa, T.; Ito, N.; Yasuda, A.; Nagata, H.; Nonami, T.; Masuko, K. Peroxisome proliferator-activated receptor α (PPARα) mRNA expression in human hepatocellular carcinoma tissue and non-cancerous liver tissue. *World J Surg Oncol.* **2011** Dec 15;9:167. doi: 10.1186/1477-7819-9-167. PubMed PMID: 22168458; PubMed Central PMCID: PMC3260121.

[107] Chen, Y.; Wang, Y.; Huang, Y.; Zeng, H.; Hu, B.; Guan, L.; Zhang, H.; Yu, A.M.; Johnson, C.H.; Gonzalez, F.J.; Huang, M.; Bi, H. PPARα regulates tumor cell proliferation and senescence via a novel target gene carnitine palmitoyltransferase 1C. *Carcinogenesis.* **2017** Apr 1;38(4):474-483. doi: 10.1093/carcin/bgx023. PubMed PMID: 28334197.

[108] Wolfgang, M.J.; Kurama, T.; Dai, Y.; Suwa, A.; Asaumi, M.; Matsumoto, S.; Cha, S.H.; Shimokawa, T.; Lane, M.D. The brain-specific carnitine palmitoyltransferase-1c regulates energy homeostasis. *Proc Natl Acad Sci U S A.* **2006** May 9;103(19):7282-7. Epub 2006 May 1. PubMed PMID: 16651524; PubMed Central PMCID: PMC1564279.

[109] Reilly, P.T.; Mak, T.W. Molecular pathways: tumor cells Co-opt the brain-specific metabolism gene CPT1C to promote survival. *Clin Cancer Res.* **2012** Nov 1;18(21):5850-5. doi: 10.1158/1078-0432.CCR-11-3281. Epub 2012 Sep 5. Review. PubMed PMID: 22952346.

[110] Nath, A.; Chan, C. Genetic alterations in fatty acid transport and metabolism genes are associated with metastatic progression and poor prognosis of human cancers. *Sci Rep.* **2016** Jan 4;6:18669. doi: 10.1038/srep18669. PubMed PMID: 26725848; PubMed Central PMCID: PMC4698658.

[111] Mascaró, C.; Acosta, E.; Ortiz, J.A.; Marrero, P.F.; Hegardt, F.G.; Haro, D. Control of human muscle-type carnitine palmitoyltransferase I gene transcription by peroxisome proliferator-activated receptor. *J Biol Chem.* **1998** Apr 10;273(15):8560-3. PubMed PMID: 9535828.

[112] Brandt, J.M.; Djouadi, F.; Kelly, D.P. Fatty acids activate transcription of the muscle carnitine palmitoyltransferase I gene in cardiac myocytes via the peroxisome proliferator-activated receptor alpha. *J Biol Chem.* **1998** Sep 11;273(37):23786-92. PubMed PMID: 9726988.

[113] Martinez-Outschoorn, U.E.; Lin, Z.; Whitaker-Menezes, D.; Howell, A.; Lisanti, M.P.; Sotgia, F. Ketone bodies and two-compartment tumor metabolism: stromal ketone production fuels mitochondrial biogenesis in epithelial cancer cells. *Cell Cycle.* **2012** Nov 1;11(21):3956-63. doi: 10.4161/cc.22136. Epub 2012 Sep 19. PubMed PMID: 23082721; PubMed Central PMCID: PMC3507491.

[114] Saraon, P.; Cretu, D.; Musrap, N.; Karagiannis, G.S.; Batruch, I.; Drabovich, A.P.; van der Kwast, T.; Mizokami, A.; Morrissey, C.; Jarvi, K.; Diamandis, E.P. Quantitative proteomics reveals that enzymes of the ketogenic pathway are associated with prostate cancer progression. *Mol Cell Proteomics.* **2013** Jun;12(6):1589-601. doi: 10.1074/mcp.M112.023887. Epub 2013 Feb 26. PubMed PMID: 23443136; PubMed Central PMCID: PMC3675816.

[115] Chen, S.W.; Chou, C.T.; Chang, C.C.; Li, Y.J.; Chen, S.T.; Lin, I.C.; Kok, S.H.; Cheng, S.J.; Lee, J.J.; Wu, T.S.; Kuo, M.L.; Lin, B.R. HMGCS2 enhances invasion and metastasis via direct interaction with PPARα to activate Src signaling in colorectal cancer and oral cancer. *Oncotarget.* **2017** Apr 4;8(14):22460-22476. doi: 10.18632/oncotarget.13006. PubMed PMID: 27816970; PubMed Central PMCID: PMC5410236.

[116] Spaner, D.E. Oral high-dose glucocorticoids and ofatumumab in fludarabine-resistant chronic lymphocytic leukemia. *Leukemia.* **2012** May;26(5):1144-5. doi: 10.1038/leu.2011.329. Epub 2011 Nov 8. PubMed PMID: 22064354.

[117] Tung, S.; Shi, Y.; Wong, K.; Zhu, F.; Gorczynski, R.; Laister, R.C.; Minden, M.; Blechert, A.K.; Genzel, Y.; Reichl, U.; Spaner, D.E. PPARα and fatty acid oxidation mediate glucocorticoid resistance in chronic lymphocytic leukemia. *Blood.* **2013** Aug 8;122(6):969-80. doi: 10.1182/blood-2013-03-489468. Epub 2013 Jun 27. PubMed PMID: 23814018.

[118] Schulze, A.; Downward, J. Flicking the Warburg switch-tyrosine phosphorylation of pyruvate dehydrogenase kinase regulates mitochondrial activity in cancer cells. *Mol Cell.* **2011** Dec 23;44(6):846-8. doi: 10.1016/j.molcel.2011.12.004. PubMed PMID: 22195959.

[119] Pond, C.M. Adipose tissue and the immune system. *Prostaglandins Leukot Essent Fatty Acids.* **2005** Jul;73(1):17-30. Review. PubMed PMID: 15946832.

[120] Wolins, N.E.; Quaynor, B.K.; Skinner, J.R.; Tzekov, A.; Park, C.; Choi, K.; Bickel, P.E. OP9 mouse stromal cells rapidly differentiate into adipocytes: characterization of a useful new model of adipogenesis. *J Lipid Res.* **2006** Feb;47(2):450-60. Epub 2005 Nov 30. PubMed PMID: 16319419.

[121] Chandran, K.; Goswami, S.; Sharma-Walia, N. Implications of a peroxisome proliferator-activated receptor alpha (PPARα) ligand clofibrate in breast cancer. *Oncotarget.* **2016** Mar 29;7(13):15577-99. doi: 10.18632/oncotarget.6402. PubMed PMID: 26621841; PubMed Central PMCID: PMC4941262.

[122] Lupu, R.; Menendez, J.A. Targeting fatty acid synthase in breast and endometrial cancer: An alternative to selective estrogen receptor modulators? *Endocrinology.* **2006** Sep;147(9):4056-66. Epub 2006 Jun 29. Review. PubMed PMID: 16809439.

[123] Rakhshandehroo, M.; Knoch, B.; Müller, M.; Kersten, S. Peroxisome proliferator-activated receptor alpha target genes. *PPAR Res.* **2010**;2010. pii: 612089. doi: 10.1155/2010/612089. Epub 2010 Sep 26. PubMed PMID: 20936127; PubMed Central PMCID: PMC2948931.

[124] Lacasa, D.; Le Liepvre, X.; Ferre, P.; Dugail, I. Progesterone stimulates adipocyte determination and differentiation 1/sterol regulatory element-binding protein 1c gene expression. potential mechanism for the lipogenic effect of progesterone in adipose tissue. *J Biol Chem.* **2001** Apr 13;276(15):11512-6. Epub 2001 Jan 16. PubMed PMID: 11278421.

[125] Vander Heiden, M.G.; Cantley, L.C.; Thompson, C.B. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science.* **2009** May 22;324(5930):1029-33. doi: 10.1126/science.1160809. Review. PubMed PMID: 19460998; PubMed Central PMCID: PMC2849637.

[126] Grabacka, M.; Pierzchalska, M.; Reiss, K. Peroxisome proliferator activated receptor α ligands as anticancer drugs targeting mitochondrial metabolism. *Curr Pharm Biotechnol.* **2013**;14(3):342-56. Review. PubMed PMID: 21133850; PubMed Central PMCID: PMC3631438.

[127] Jan, C.I.; Tsai, M.H.; Chiu, C.F.; Huang, Y.P.; Liu, C.J.; Chang, N.W. Fenofibrate Suppresses Oral Tumorigenesis via Reprogramming Metabolic Processes: Potential Drug Repurposing for Oral Cancer. *Int J Biol Sci.* **2016** May 15;12(7):786-98. doi: 10.7150/ijbs.13851. eCollection 2016. PubMed PMID: 27313493; PubMed Central PMCID: PMC4910598.

[128] Li, X.M.; Patel, B.B.; Blagoi, E.L.; Patterson, M.D.; Seeholzer, S.H.; Zhang, T.; Damle, S.; Gao, Z.; Boman, B.; Yeung, A.T. Analyzing alkaline proteins in human colon crypt proteome. *J Proteome Res.* **2004** Jul-Aug;3(4):821-33. Erratum in: J Proteome Res. 2004 Nov-Dec;3(6):1300. Seehozer, Steven H [corrected to Seeholzer, Steven H]. PubMed PMID: 15359737.

[129] Huang, Y.P.; Chang, N.W. Proteomic analysis of oral cancer reveals new potential therapeutic targets involved in the Warburg effect. Clin *Exp Pharmacol Physiol.* **2017** Aug;44(8):880-887. doi: 10.1111/1440-1681.12774. PubMed PMID: 28453233.

[130] Tontonoz, P.; Nagy, L.; Alvarez, J.G.; Thomazy, V.A.; Evans, R.M. PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. *Cell.* **1998** Apr 17;93(2):241-52. PubMed PMID: 9568716.

[131] Rosen, E.D.; Sarraf, P.; Troy, A.E.; Bradwin, G.; Moore, K.; Milstone, D.S.; Spiegelman, B.M.; Mortensen, R.M. PPAR gamma is required for the differentiation of adipose tissue in vivo and in vitro. *Mol Cell.* **1999** Oct;4(4):611-7. PubMed PMID: 10549292.

[132] Desvergne, B.; Wahli, W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev.* **1999** Oct;20(5):649-88. Review. PubMed PMID: 10529898.

[133] Kotta-Loizou, I.; Giaginis, C.; Theocharis, S. The role of peroxisome proliferator-activated receptor-γ in breast cancer. *Anticancer Agents Med Chem.* **2012** Nov;12(9):1025-44. Review. PubMed PMID: 22583414.

[134] Pang, X.; Wei, Y.; Zhang, Y.; Zhang, M.; Lu, Y.; Shen, P. Peroxisome proliferator-activated receptor-γ activation inhibits hepatocellular carcinoma cell invasion by upregulating plasminogen activator inhibitor-1. *Cancer Sci.* **2013** Jun;104(6):672-80. doi: 10.1111/cas.12143. Epub 2013 Apr 8. PubMed PMID: 23461356.

[135] Srivastava, N.; Kollipara, R.K; Singh, D.K.; Sudderth, J.; Hu, Z.; Nguyen, H.; Wang, S.; Humphries, C.G.; Carstens, R.; Huffman, K.E.; DeBerardinis, R.J.; Kittler, R. Inhibition of cancer cell proliferation by PPARγ is mediated by a metabolic switch that increases reactive oxygen species levels. *Cell Metab.* **2014** Oct 7;20(4):650-61. doi: 10.1016/j.cmet.2014.08.003. Epub 2014 Sep 25. PubMed PMID: 25264247; PubMed Central PMCID: PMC4191999.

[136] Girnun, G.D.; Smith, W.M.; Drori, S.; Sarraf, P.; Mueller, E.; Eng, C.; Nambiar, P.; Rosenberg, D.W.; Bronson, R.T.; Edelmann, W.; Kucherlapati, R.; Gonzalez, F.J.; Spiegelman, B.M. APC-dependent suppression of colon carcinogenesis by PPARgamma. *Proc Natl Acad Sci U S A.* **2002** Oct 15;99(21):13771-6. Epub 2002 Oct 7. PubMed PMID: 12370429; PubMed Central PMCID: PMC129773.

[137] Reka, A.K.; Kurapati, H.; Narala, V.R.; Bommer, G.; Chen, J.; Standiford, T.J.; Keshamouni, V.G. Peroxisome proliferator-activated receptor-gamma activation inhibits tumor metastasis by antagonizing Smad3-mediated epithelial-mesenchymal transition. *Mol Cancer Ther.* **2010** Dec;9(12):3221-32. doi: 10.1158/1535-7163.MCT-10-0570. PubMed PMID: 21159608; PubMed Central PMCID: PMC3044476.

[138] Saez, E.; Tontonoz, P.; Nelson, M.C.; Alvarez, J.G.; Ming, U.T.; Baird, S.M.; Thomazy, V.A.; Evans, R.M. Activators of the nuclear receptor PPARgamma enhance colon polyp formation. *Nat Med.* **1998** Sep;4(9):1058-61. PubMed PMID: 9734400.

[139] Jansson, E.A.; Are, A.; Greicius, G.; Kuo, I.C.; Kelly, D.; Arulampalam, V.; Pettersson, S. The Wnt/beta-catenin signaling pathway targets PPARgamma activity in colon cancer cells. *Proc Natl Acad Sci U S A.* **2005** Feb 1;102(5):1460-5. Epub 2005 Jan 21. PubMed PMID: 15665104; PubMed Central PMCID: PMC547827.

[140] Yang, K.; Fan, K.H.; Lamprecht, S.A.; Edelmann, W.; Kopelovich, L.; Kucherlapati, R.; Lipkin, M. Peroxisome proliferator-activated receptor gamma agonist troglitazone induces colon tumors in normal C57BL/6J mice and enhances colonic carcinogenesis in Apc1638 N/+ Mlh1+/- double mutant mice. *Int J Cancer.* **2005** Sep 10;116(4):495-9. PubMed PMID: 15818612.

[141] Burstein, H.J.; Demetri, G.D.; Mueller, E.; Sarraf, P.; Spiegelman, B.M.; Winer, E.P. Use of the peroxisome proliferator-activated receptor (PPAR) gamma ligand troglitazone as treatment for refractory breast cancer: a phase II study. *Breast Cancer Res Treat.* **2003** Jun;79(3):391-7. PubMed PMID: 12846423.

[142] Saez, E.; Rosenfeld, J.; Livolsi, A.; Olson, P.; Lombardo, E.; Nelson, M.; Banayo, E.; Cardiff, R.D.; Izpisua-Belmonte, J.C.; Evans, R.M. PPAR gamma signaling exacerbates mammary gland tumor development. *Genes Dev.* **2004** Mar 1;18(5):528-40. PubMed PMID: 15037548; PubMed Central PMCID: PMC374235.

[143] Egerod, F.L.; Nielsen, H.S.; Iversen, L.; Thorup, I.; Storgaard, T.; Oleksiewicz, M.B. Biomarkers for early effects of carcinogenic dual-acting PPAR agonists in rat urinary bladder urothelium in vivo. *Biomarkers.* **2005** Jul-Aug;10(4):295-309. PubMed PMID: 16240504.

[144] Lecarpentier, Y.; Claes, V.; Duthoit, G.; Hébert, J.L. Circadian rhythms, Wnt/beta-catenin pathway and PPAR alpha/gamma profiles in diseases with primary or secondary cardiac dysfunction. *Front Physiol.* **2014** Nov 4;5:429. doi: 10.3389/fphys.2014.00429. eCollection 2014. Review. PubMed PMID: 25414671; PubMed Central PMCID: PMC4220097.

[145] Abbot, E.L.; McCormack, J.G.; Reynet, C.; Hassall, D.G.; Buchan, K.W.; Yeaman, S.J. Diverging regulation of pyruvate dehydrogenase kinase isoform gene expression in cultured human muscle cells. *FEBS J.* **2005** Jun;272(12):3004-14. PubMed PMID: 15955060.

[146] Jeong, Y.; Xie, Y.; Lee, W.; Bookout, A.L.; Girard, L.; Raso, G.; Behrens, C.; Wistuba, I.I.; Gadzar, A.F.; Minna, J.D.; Mangelsdorf, D.J. Research resource: Diagnostic and therapeutic potential of nuclear receptor expression in lung cancer. *Mol Endocrinol.* **2012** Aug;26(8):1443-54. doi: 10.1210/me.2011-1382. Epub 2012 Jun 14. PubMed PMID: 22700587; PubMed Central PMCID: PMC3404298.

[147] Reck, M.; Heigener, D.F.; Mok, T.; Soria, J.C.; Rabe, K.F. Management of non-small-cell lung cancer: recent developments. *Lancet.* **2013** Aug 24;382(9893):709-19. doi: 10.1016/S0140-6736(13)61502-0. Review. PubMed PMID: 23972814.

[148] Vadlapatla, R.K.; Vadlapudi, A.D.; Pal, D.; Mitra, A.K. Mechanisms of drug resistance in cancer chemotherapy: coordinated role and regulation of efflux transporters and metabolizing enzymes. *Curr Pharm Des.* **2013**;19(40):7126-40. Review. PubMed PMID: 23829373.

[149] Wang, M.; Li, G.; Yang, Z.; Wang, L.; Zhang, L.; Wang, T.; Zhang, Y.; Zhang, S.; Han, Y.; Jia, L. Uncoupling protein 2 downregulation by hypoxia through repression of peroxisome proliferator-activated receptor γ promotes chemoresistance of non-small cell lung cancer. *Oncotarget.* **2017** Jan 31;8(5):8083-8094. doi: 10.18632/oncotarget.14097. PubMed PMID: 28042952; PubMed Central PMCID: PMC5352384.

[150] Bouillaud, F. UCP2, not a physiologically relevant uncoupler but a glucose sparing switch impacting ROS production and glucose sensing. *Biochim Biophys Acta.* **2009** May;1787(5):377-83. doi: 10.1016/j.bbabio.2009.01.003. Epub 2009 Jan 20. Review. PubMed PMID: 19413946.

[151] Moon, E.J.; Giaccia, A. Dual roles of NRF2 in tumor prevention and progression: possible implications in cancer treatment. *Free Radic Biol Med.* **2015** Feb;79:292-9. doi: 10.1016/j.freeradbiomed.2014.11.009. Epub 2014 Nov 29. Review. PubMed PMID: 25458917; PubMed Central PMCID: PMC4339613.

[152] Cornic, M.; Delva, L.; Guidez, F.; Balitrand, N.; Degos, L.; Chomienne, C. Induction of retinoic acid-binding protein in normal and malignant human myeloid cells by retinoic acid in acute promyelocytic leukemia patients. *Cancer Res.* **1992** Jun 15;52(12):3329-34. PubMed PMID: 1317749.

[153] Hu, Z.B.; Ma, W.; Uphoff, C.C.; Lanotte, M.; Drexler, H.G. Modulation of gene expression in the acute promyelocytic leukemia cell line NB4. *Leukemia.* **1993** Nov;7(11):1817-23. PubMed PMID: 7901456.

[154] Yasugi, E.; Horiuchi, A.; Uemura, I.; Okuma, E.; Nakatsu, M.; Saeki, K.; Kamisaka, Y.; Kagechika, H.; Yasuda, K.; You, A. Peroxisome proliferator-activated receptor gamma ligands stimulate myeloid differentiation and lipogenensis in human leukemia NB4 cells. *Dev Growth Differ.* **2006** Apr;48(3):177-88. Erratum in: Dev Growth Differ. 2006 Jun;48(5):347. PubMed PMID: 16573735.

[155] David, C.J.; Chen, M.; Assanah, M.; Canoll, P.; Manley, J.L. HnRNP proteins controlled by c-Myc deregulate pyruvate kinase mRNA splicing in cancer. *Nature.* **2010** Jan 21;463(7279):364-8. doi: 10.1038/nature08697. Epub 2009 Dec 13. PubMed PMID: 20010808; PubMed Central PMCID: PMC2950088.

[156] Dayton, T.L.; Jacks, T.; Vander Heiden, M.G. PKM2, cancer metabolism, and the road ahead. *EMBO Rep.* **2016** Dec;17(12):1721-1730. Epub 2016 Nov 17. Review. PubMed PMID: 27856534; PubMed Central PMCID: PMC5283597.

[157] Lee, J.S.; Chu, I.S.; Heo, J.; Calvisi, D.F.; Sun, Z.; Roskams, T.; Durnez, A.; Demetris, A.J.; Thorgeirsson, S.S. Classification and prediction of survival in hepatocellular carcinoma by gene expression profiling. *Hepatology.* **2004** Sep;40(3):667-76. PubMed PMID: 15349906.

[158] Gan, F.Y.; Gesell, M.S.; Alousi, M.; Luk, G.D. Analysis of ODC and c-myc gene expression in hepatocellular carcinoma by in situ hybridization and immunohistochemistry. *J Histochem Cytochem.* **1993** Aug;41(8):1185-96. PubMed PMID: 7687263.

[159] Banerjee, S.S.; Feinberg, M.W.; Watanabe, M.; Gray, S.; Haspel, R.L.; Denkinger, D.J.; Kawahara, R.; Hauner, H.; Jain, M.K. The Krüppel-like factor KLF2 inhibits peroxisome proliferator-activated receptor-gamma expression and adipogenesis. *J Biol Chem.* **2003** Jan 24;278(4):2581-4. Epub 2002 Nov 7. PubMed PMID: 12426306.

[160] Choi, Y.; Oh, S.T.; Won, M.A.; Choi, K.M.; Ko, M.J.; Seo, D.; Jeon, T.W.; Baik, I.H.; Ye, S.K.; Park, K.U.; Park, I.C.; Jang, B.C.; Seo, J.Y.; Lee, Y.H. Targeting ODC1 inhibits tumor growth through reduction of lipid metabolism in human hepatocellular carcinoma. *Biochem Biophys Res Commun.* **2016** Sep 30;478(4):1674-81. doi: 10.1016/j.bbrc.2016.09.002. Epub 2016 Sep 2. PubMed PMID: 27592554.

[161] Kourtidis, A.; Jain, R.; Carkner, R.D.; Eifert, C.; Brosnan, M.J.; Conklin, D.S. An RNA interference screen identifies metabolic regulators NR1D1 and PBP as novel survival factors for breast cancer cells with the ERBB2 signature. *Cancer Res.* **2010** Mar 1;70(5):1783-92. doi: 10.1158/0008-5472.CAN-09-1550. Epub 2010 Feb 16. PubMed PMID: 20160030; PubMed Central PMCID: PMC2837372.

[162] Zhu, Y.; Qi, C.; Jain, S.; Rao, M.S.; Reddy, J.K. Isolation and characterization of PBP, a protein that interacts with peroxisome proliferator-activated receptor. *J Biol Chem.* **1997** Oct 10;272(41):25500-6. PubMed PMID: 9325263.

[163] Bertucci, F.; Borie, N.; Ginestier, C.; Groulet, A.; Charafe-Jauffret, E.; Adélaïde, J.; Geneix, J.; Bachelart, L.; Finetti, P.; Koki, A.; Hermitte, F.; Hassoun, J.; Debono, S.; Viens, P.; Fert, V.; Jacquemier, J.; Birnbaum, D. Identification and validation of an ERBB2 gene expression signature in breast cancers. *Oncogene.* **2004** Apr 1;23(14):2564-75. PubMed PMID: 14743203.

[164] Schaffer, J.E. Lipotoxicity: when tissues overeat. *Curr Opin Lipidol.* **2003** Jun;14(3):281-7. Review. PubMed PMID: 12840659.

[165] Kourtidis, A.; Srinivasaiah, R.; Carkner, R.D.; Brosnan, M.J.; Conklin, D.S. Peroxisome proliferator-activated receptor-gamma protects ERBB2-positive breast cancer cells from palmitate toxicity. *Breast Cancer Res.* **2009**;11(2):R16. doi: 10.1186/bcr2240. Epub 2009 Mar 19. PubMed PMID: 19298655; PubMed Central PMCID: PMC2688944.

[166] Wang. X.; Sun, Y.; Wong, J.; Conklin, D.S. PPARγ maintains ERBB2-positive breast cancer stem cells. *Oncogene.* **2013** Dec 5;32(49):5512-21. doi: 10.1038/onc.2013.217. Epub 2013 Jun 17. PubMed PMID: 23770845; PubMed Central PMCID: PMC3898098.

[167] March, H.N.; Rust, A.G.; Wright, N.A.; ten Hoeve, J.; de Ridder, J.; Eldridge, M.; van der Weyden, L.; Berns, A.; Gadiot, J.; Uren, A.; Kemp, R.; Arends, M.J.; Wessels, L.F.; Winton, D.J.; Adams, D.J. Insertional mutagenesis identifies multiple networks of cooperating

genes driving intestinal tumorigenesis. *Nat Genet.* **2011** Nov 6;43(12):1202-9. doi: 10.1038/ng.990. PubMed PMID: 22057237; PubMed Central PMCID: PMC3233530.

[168] Ahmad, I.; Mui, E.; Galbraith, L.; Patel, R.; Tan, E.H.; Salji, M.; Rust, A.G.; Repiscak, P.; Hedley, A.; Markert, E.; Loveridge, C.; van der Weyden, L.; Edwards, J.; Sansom, O.J.; Adams, D.J.; Leung, H.Y. Sleeping Beauty screen reveals Pparg activation in metastatic prostate cancer. *Proc Natl Acad Sci U S A.* **2016** Jul 19;113(29):8290-5. doi: 10.1073/pnas.1601571113. Epub 2016 Jun 29. PubMed PMID: 27357679; PubMed Central PMCID: PMC4961202.

[169] Kompare, M.; Rizzo, W.B. Mitochondrial fatty-acid oxidation disorders. *Semin Pediatr Neurol.* **2008** Sep;15(3):140-9. doi: 10.1016/j.spen.2008.05.008. Review. PubMed PMID: 18708005.

[170] Niu, Z.; Shi, Q.; Zhang, W.; Shu, Y.; Yang, N.; Chen, B.; Wang, Q.; Zhao, X.; Chen, J.; Cheng, N.; Feng, X.; Hua, Z.; Ji, J.; Shen, P. Caspase-1 cleaves PPARγ for potentiating the pro-tumor action of TAMs. *Nat Commun.* **2017** Oct 3;8(1):766. doi: 10.1038/s41467-017-00523-6. PubMed PMID: 28974683; PubMed Central PMCID: PMC5626701.

[171] Peters, J.M.; Lee, S.S.; Li, W.; Ward, J.M, Gavrilova O, Everett C, Reitman ML, Hudson LD, Gonzalez FJ. Growth, adipose, brain, and skin alterations resulting from targeted disruption of the mouse peroxisome proliferator-activated receptor beta(delta). *Mol Cell Biol.* **2000** Jul;20(14):5119-28. PubMed PMID: 10866668; PubMed Central PMCID: PMC85961.

[172] Chong, H.C.; Tan, M.J.; Philippe, V.; Tan, S.H.; Tan, C.K.; Ku, C.W.; Goh, Y.Y.; Wahli, W.; Michalik, L.; Tan, N.S. Regulation of epithelial-mesenchymal IL-1 signaling by PPARbeta/delta is essential for skin homeostasis and wound healing. *J Cell Biol.* **2009** Mar 23;184(6):817-31. doi: 10.1083/jcb.200809028. PubMed PMID: 19307598; PubMed Central PMCID: PMC2699156.

[173] Peters, J.M.; Shah, Y.M.; Gonzalez, F.J. The role of peroxisome proliferator-activated receptors in carcinogenesis and chemoprevention. *Nat Rev Cancer.* ***2012*** Feb 9;12(3):181-95. doi: 10.1038/nrc3214. Review. PubMed PMID: 22318237; PubMed Central PMCID: PMC3322353.

[174] Stephen, R.L.; Gustafsson, M.C.; Jarvis, M.; Tatoud, R.; Marshall, B.R.; Knight, D.; Ehrenborg, E.; Harris, A.L.; Wolf, C.R.; Palmer, C.N. Activation of peroxisome proliferator-activated receptor delta stimulates the proliferation of human breast and prostate cancer cell lines. *Cancer Res.* **2004** May 1;64(9):3162-70. PubMed PMID: 15126355.

[175] Aung, C.S.; Faddy, H.M.; Lister, E.J.; Monteith, G.R.; Roberts-Thomson, S.J. Isoform specific changes in PPAR alpha and beta in colon and breast cancer with differentiation. *Biochem Biophys Res Commun.* **2006** Feb 10;340(2):656-60. Epub 2005 Dec 20. PubMed PMID: 16378595.

[176] Buttitta, L.A.; Edgar, B.A. Mechanisms controlling cell cycle exit upon terminal differentiation. *Curr Opin Cell Biol.* **2007** Dec;19(6):697-704. Epub 2007 Nov 26. Review. PubMed PMID: 18035529; PubMed Central PMCID: PMC2700000.

[177] Yao, P.L.; Morales, J.L.; Zhu, B.; Kang, B.H.; Gonzalez, F.J.; Peters, J.M. Activation of peroxisome proliferator-activated receptor-β/δ (PPAR-β/δ) inhibits human breast cancer cell line tumorigenicity. *Mol Cancer Ther.* **2014** Apr;13(4):1008-17. doi: 10.1158/1535-7163.MCT-13-0836. Epub 2014 Jan 24. PubMed PMID: 24464939; PubMed Central PMCID: PMC3981956.

[178] Genini, D.; Garcia-Escudero, R.; Carbone, G.M.; Catapano, C.V. Transcriptional and Non-Transcriptional Functions of PPARβ/δ in Non-Small Cell Lung Cancer. *PLoS One.* **2012**;7(9):e46009. doi: 10.1371/journal.pone.0046009. Epub 2012 Sep 25. PubMed PMID: 23049921; PubMed Central PMCID: PMC3457940.

[179] Pedchenko, T.V.; Gonzalez, A.L.; Wang, D.; DuBois, R.N.; Massion, P.P. Peroxisome proliferator-activated receptor beta/delta expression and activation in lung cancer. *Am J Respir Cell Mol Biol.* **2008** Dec;39(6):689-96. doi: 10.1165/rcmb.2007-0426OC. Epub 2008 Jun 19. PubMed PMID: 18566335; PubMed Central PMCID: PMC3159083.

[180] Di-Poï, N.; Michalik, L.; Tan, N.S.; Desvergne, B.; Wahli, W. The anti-apoptotic role of PPARbeta contributes to efficient skin wound healing. *J Steroid Biochem Mol Biol.* **2003** Jun;85(2-5):257-65. PubMed PMID: 12943711.

[181] Pollock, C.B.; Yin, Y.; Yuan, H.; Zeng, X.; King, S.; Li, X.; Kopelovich, L.; Albanese, C.; Glazer, R.I. PPARδ activation acts cooperatively with 3-phosphoinositide-dependent protein kinase-1 to enhance mammary tumorigenesis. *PLoS One.* **2011** Jan 13;6(1):e16215. doi: 10.1371/journal.pone.0016215. PubMed PMID: 21297860; PubMed Central PMCID: PMC3020974.

[182] Narkar, V.A.; Downes, M.; Yu, R.T.; Embler, E.; Wang, Y.X.; Banayo, E.; Mihaylova, M.M.; Nelson, M.C.; Zou, Y.; Juguilon, H.; Kang, H.; Shaw, R.J.; Evans, R.M. AMPK and PPARdelta agonists are exercise mimetics. *Cell.* **2008** Aug 8;134(3):405-15. doi: 10.1016/j.cell.2008.06.051. Epub 2008 Jul 31. PubMed PMID: 18674809; PubMed Central PMCID: PMC2706130.

[183] Ito, K.; Carracedo, A.; Weiss, D.; Arai, F.; Ala, U.; Avigan, D.E.; Schafer, Z.T.; Evans, R.M.; Suda, T.; Lee, C.H.; Pandolfi, P.P. A PML–PPAR-δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance. *Nat Med.* **2012** Sep;18(9):1350-8. PubMed PMID: 22902876; PubMed Central PMCID: PMC3566224.

[184] Wang, X.; Wang, G.; Shi, Y.; Sun, L.; Gorczynski, R.; Li, Y.J.; Xu, Z.; Spaner, D.E. PPAR-delta promotes survival of breast cancer cells in harsh metabolic conditions. *Oncogenesis.* **2016** Jun 6;5(6):e232. doi: 10.1038/oncsis.2016.41. PubMed PMID: 27270614; PubMed Central PMCID: PMC4945742.

[185] Carracedo, A.; Weiss, D.; Leliaert, A.K.; Bhasin, M.; de Boer, V.C.; Laurent, G.; Adams, A.C.; Sundvall, M.; Song, S.J.; Ito, K.; Finley, L.S.; Egia, A.; Libermann, T.; Gerhart-Hines, Z.; Puigserver, P.; Haigis, M.C.; Maratos-Flier, E.; Richardson, A.L.; Schafer, Z.T.; Pandolfi, P.P. A metabolic prosurvival role for PML in breast cancer. *J Clin Invest.* **2012** Sep;122(9):3088-100. doi: 10.1172/JCI62129. Epub 2012 Aug 13. PubMed PMID: 22886304; PubMed Central PMCID: PMC3433768.

[186] Li, Y.J.; Sun, L.; Shi, Y.; Wang, G.; Wang, X.; Dunn, S.E.; Iorio, C.; Screaton, R.A.; Spaner, D.E. PPAR-delta promotes survival of chronic lymphocytic leukemia cells in energetically unfavorable conditions. *Leukemia.* **2017** Sep;31(9):1905-1914. doi: 10.1038/leu.2016.395. Epub 2017 Jan 4. PubMed PMID: 28050012.

[187] Sun, L.; Shi, Y.; Wang, G.; Wang, X.; Zeng, S.; Dunn, S.E.; Fairn, G.D.; Li, Y.J.; Spaner, D.E. PPAR-delta modulates membrane cholesterol and cytokine signaling in malignant B cells. *Leukemia.* **2018** Jan;32(1):184-193. doi: 10.1038/leu.2017.162. Epub 2017 May 30. PubMed PMID: 28555083.

[188] Jeong, E.; Koo, J.E.; Yeon, S.H.; Kwak, M.K.; Hwang, D.H.; Lee, J.Y. PPARδ deficiency disrupts hypoxia-mediated tumorigenic potential of colon cancer cells. *Mol Carcinog.* **2014** Nov;53(11):926-37. doi: 10.1002/mc.22144. Epub 2014 Mar 9. PubMed PMID: 24610641.

[189] He, T.C.; Chan, T.A.; Vogelstein, B.; Kinzler, K.W. PPARdelta is an APC-regulated target of nonsteroidal anti-inflammatory drugs. *Cell.* **1999** Oct 29;99(3):335-45. PubMed PMID: 10555149; PubMed Central PMCID: PMC3779681.

[190] Zuo, X.; Peng, Z.; Moussalli, M.J; Morris, J.S.; Broaddus, R.R.; Fischer, S.M.; Shureiqi, I. Targeted genetic disruption of peroxisome proliferator-activated receptor-delta and colonic tumorigenesis. *J Natl Cancer Inst.* **2009** May 20;101(10):762-7. doi: 10.1093/jnci/djp078. Epub 2009 May 12. PubMed PMID: 19436036; PubMed Central PMCID: PMC2684551.

[191] Qian, B.Z.; Pollard, J.W. Macrophage diversity enhances tumor progression and metastasis. *Cell.* **2010** Apr 2;141(1):39-51. doi: 10.1016/j.cell.2010.03.014. Review. PubMed PMID: 20371344; PubMed Central PMCID: PMC4994190.

[192] Schumann, T.; Adhikary, T.; Wortmann, A.; Finkernagel, F.; Lieber, S.; Schnitzer, E.; Legrand, N.; Schober, Y.; Nockher, W.A.; Toth, P.M.; Diederich, W.E.; Nist, A.; Stiewe, T.; Wagner, U.; Reinartz, S.; Müller-Brüsselbach, S.; Müller, R. Deregulation of PPARβ/δ target genes in tumor-associated macrophages by fatty acid ligands in the ovarian cancer microenvironment. *Oncotarget.* **2015** May 30;6(15):13416-33. PubMed PMID: 25968567; PubMed Central PMCID: PMC4537024.

[193] Zhu, P.; Tan, M.J.; Huang, R.L.; Tan, C.K.; Chong, H.C.; Pal, M.; Lam, C.R.; Boukamp, P.; Pan, J.Y.; Tan, S.H.; Kersten, S.; Li, H.Y.; Ding, J.L.; Tan, N.S. Angiopoietin-like 4 protein elevates the prosurvival intracellular O2(-):H2O2 ratio and confers anoikis resistance to tumors. *Cancer Cell*. **2011** Mar 8;19(3):401-15. doi: 10.1016/j.ccr.2011.01.018. PubMed PMID: 21397862.

[194] Zhu, P.; Goh, Y.Y.; Chin, H.F.; Kersten, S.; Tan, N.S. Angiopoietin-like 4: a decade of research. *Biosci Rep.* **2012** Jun;32(3):211-9. doi: 10.1042/BSR20110102. Review. PubMed PMID: 22458843.

[195] Martín-Martín, N.; Zabala-Letona, A.; Fernández-Ruiz, S.; Arreal, L.; Camacho, L.; Castillo-Martin, M.; Cortazar, A.R.; Torrano, V.; Astobiza, I.; Zúñiga-García, P.; Ugalde-Olano, A.; Loizaga-Iriarte, A.; Unda, M.; Valcárcel-Jiménez, L.; Arruabarrena-Aristorena, A.; Piva, M.; Sánchez-Mosquera, P.; Aransay, A.M.; Gomez-Muñoz, A.; Barrio, R.; Sutherland, J.D.; Carracedo, A. PPARδ Elicits Ligand-Independent Repression of Trefoil Factor Family to Limit Prostate Cancer Growth. *Cancer Res.* **2018** Jan 15;78(2):399-409. doi: 10.1158/0008-5472.CAN-17-0908. Epub 2017 Nov 29. PubMed PMID: 29187400.

[196] Aleshin, S.; Strokin, M.; Sergeeva, M.; Reiser, G. Peroxisome proliferator-activated receptor (PPAR)β/δ, a possible nexus of PPARα- and PPARγ-dependent molecular pathways in neurodegenerative diseases: Review and novel hypotheses. *Neurochem Int.* **2013** Oct;63(4):322-30. doi: 10.1016/j.neuint.2013.06.012. Epub 2013 Jun 25. Review. PubMed PMID: 23811400.