Review Article

PPARs: Interference with Warburg’ Effect and Clinical Anticancer Trials

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The metabolic/cell signaling basis of Warburg’s effect (“aerobic glycolysis”) and the general metabolic phenotype adopted by cancer cells are first reviewed. Several bypasses are adopted to provide a panoramic integrated view of tumoral metabolism, by attributing a central signaling role to hypoxia-induced factor (HIF-1) in the expression of aerobic glycolysis. The cancer metabolic phenotype also results from alterations of other routes involving ras, myc, p53, and Akt signaling and the propensity of cancer cells to develop signaling aberrances (notably aberrant surface receptor expression) which, when present, offer unique opportunities for therapeutic interventions. The rationale for various emerging strategies for cancer treatment is presented along with mechanisms by which PPAR ligands might interfere directly with tumoral metabolism and promote anticancer activity. Clinical trials using PPAR ligands are reviewed and followed by concluding remarks and perspectives for future studies. A therapeutic need to associate PPAR ligands with other anticancer agents is perhaps an important lesson to be learned from the results of the clinical trials conducted to date.

1. Introduction

Nowadays, cancer therapy offers strategies that do not primarily target nuclear DNA integrity, repair, duplication, or synthesis. These approaches address an event that is specific to cancer cells (inhibition/neutralization of overexpressed tyrosine kinase, for instance) or disrupt universal features of cancer development such as neovascularization. Though the therapeutic target should ideally be essential in cancer cells but not in normal cells, treatment may in turn restore sensitivity or remove resistance to physiological processes such as the apoptotic pathways. Various mechanisms underlying the anticancer actions of PPAR effects and ligands have previously been developed in other issues of this journal [1–7], as well as some controversial activity, notably regarding PPARβ/δ-driven effects [8–10].

Besides neovascularization, other characteristics common to many cancers are currently targeted by “mitocans” (drugs destabilizing tumoral mitochondria to induce cell death by cytotoxicity or apoptosis) [11, 12] and what might be called “metabocans” (drugs disrupting tumoral metabolism), acronyms of “mitochondria and cancer” and “metabolism and cancer”, respectively. The compounds covered by these acronyms may, however, overlap.

The desired endpoint of any anticancer therapy is a combination of optimal efficacy, minimal side effects, and prevention of resurgence. In practice, it is sometimes far from being met, some cancers being still incurable or hardly resolvable. The optimization of this goal resides in targeting features distinguishing more categorically cancer cells from normal cells. Encouraging examples have been provided by tyrosine kinase-directed antibodies or inhibitors which despite chemoresistance have served as templates to boost the development of novel anticancer drugs that target, for instance, breast cancers overexpressing HER-2 surface receptor or chronic myeloid leukemia overexpressing BCR-ABL.
tyrosine kinase, a fusion gene product [13]. The anticancer activity of drugs antagonizing neovascularization by interfering for instance with vascular endothelial growth factor (VEGF) signaling represents another development in cancer-targeted therapy [14]. Mitocans also currently represents a promising approach [11]. Disrupting cancer cell metabolism to induce cell death (via apoptosis, necrosis, or both) represents another elegant approach. “Metabolic therapy of cancer,” a concept aimed at controlling malignant behavior, was discussed before apoptosis came onto the scene [15, 16]. It would now be better to speak of metabolism disruption-driven cell death. Several drugs could be referred to as mitocans, metabocans, or aberrocans (disruption of biased signaling), for instance, monoclonal antibodies or kinase inhibitor-based drugs, and many other such drugs are being developed at present [17]. A major difficulty is targeting cancer cell signaling aberrance(s) without affecting kinase functions that are of crucial importance for normal cells.

Cancer cells express a metabolic phenotype that is distinct from normal cells as emphasized by Figure 1 which illustrates the contributions of glucose oxidation to ATP synthesis in normal cells under normoxia and in hypoxic/anoxic or cancer cells (cancer cells will be considered as having lazy mitochondria throughout this review) [18, 19]. In contrast to the normal aerobic glucose metabolism pathway which uses mitochondrial oxidation, cancer cells develop Warburg’s effect [20, 21], in which aerobic glycolysis is very much increased and for which drug-driven disruption might lead to minimal side effects. Because Warburg’s effect involves most if not all cancers, its disruption in a way and extent that cannot be counterbalanced by cancer cells might then resolve the malignant process, independently of its origin.

The ubiquity of Warburg’s effect in tumors has been evidenced by positron emission tomography scan imagery of 18F-deoxyglucose (FDG-PET), a glucose analogue transported and phosphorylated in cells without further metabolism for several decades. The tight link existing between tumoral status and FDG-PET data might confirm the pertinence of any therapeutic strategy aimed at disrupting tumoral metabolism. Interestingly, 2-deoxy-D-glucose and analogues are currently being developed as a drug template for treating cancer by competing with the metabolic feature that it was
first used to demonstrate when used in its labeled form (18F-deoxyglucose) in FDG-PET. More precisely, 2-deoxy-D-glucose presents anticancer properties and may potentiate the efficacy of prototype anticancer drugs [22].

Targeting tumoral metabolism in a way that cannot be counterbalanced by cancer cells is not, however, an easy task. Pragmatically, this strategy requires a general integrated view of tumoral metabolism because it is not a single metabolic step that is altered but the entire energetic metabolism that works on a pattern profoundly affected in cancer (versus normal) cells. This metabolic modus vivendi results from permissive alterations in cell signaling among which HIF-1 routes. Although it would be an oversimplification to consider that tumoral metabolism is close to anaerobic metabolism, it may help in understanding how, step by step, it is organized in comparison with normal metabolism.

An appraisal of this organization in relation to Warburg's effect is therefore provided in the following two chapters by explaining step by step the metabolic and signaling articulations that exist between tumoral glycolysis and cancer mitochondria, and then the particular role of tumoral pyruvate kinase. The properties of PPARs in relation with Warburg's effect and clinical trials using PPARs as anticancer agents, all mechanisms comprised, will be then reviewed.

2. Tumoral Glycolysis and Mitochondria

2.1. General Characteristics. Different patterns of glucose metabolism are observed in normal cells in normoxia and hypoxia/anoxia. Under oxygen, one glucose molecule is oxidized in the cytosol into two pyruvates which enter mitochondria for decarboxylation by pyruvate dehydrogenase. This aerobic oxidation of glucose yields approximated 36 molecules of ATP. Hypoxic/anoxic normal cells develop only the glycolytic contribution to glucose oxidation, converting one glucose into two pyruvates that are then reduced locally into lactates by lactate dehydrogenase. This reaction recycles the NAD+ required for glycolysis to proceed. The net result is here two (instead of 36) molecules of ATP formed by oxidation of one molecule of glucose (Figure 1).

Normoxic oxidation of glucose in cancer cells resembles that observed in hypoxic/anoxic normal cells. This similarity is emphasized when they are referring to as aerobic (Warburg's effect) and anaerobic glycolysis, respectively. The tumoral metabolic phenotype results from alterations in several regulatory pathways including p53, myc, ras, Akt, and HIF-1 signaling pathways [23–26]. The biased nature of signaling pathways, especially the HIF-1 signaling pathway, the role of pyruvate kinase and the fact that cancer cells have to cope with hypoxia influence tumoral metabolism and provide a general outline for the process. The ability of cancer cells to function like anaerobic cells despite normoxia might explain their extraordinary tolerance to anoxia.

2.2. Cell Signalling Involving HIF-1. The anaerobic-like metabolic phenotype observed in normoxic cancer cells may result from biased sensing of oxygen by the HIF-1 signaling pathway. HIF-1 inactivation and activation pathways [27–29] are illustrated in Figure 2. In normal cells, oxygen blocks the activation of HIF-1 signaling. Exposure of cells to oxygen downregulates functional HIF-1 by restricting the availability of its α subunit. More precisely, molecular oxygen is sensed by cell membrane NADPH oxidase which reduces it to superoxide. This species oxidatively damages the HIF-1α subunit, initiating degradation by the proteasome (Figure 2). Functional HIF-1, following heterodimerization of the α and β HIF-1 subunits in the cytosol, undergoes nuclear translocation and activates target genes. Molecular oxygen normally "paralyzes" HIF-1 signaling by inducing depletion of its α subunit. In hypoxic/anoxic normal cells, the α subunit is little oxidized/degraded, favoring functional HIF-1, nuclear translocation, and gene activation. These events give rise to the glycolytic phenotype in which, in contrast to oxidative phenotype, mitochondrial oxidations do not contribute to glucose oxidation. Normal cells develop oxidative and glycolytic phenotypes in normoxic and anoxic conditions, respectively.

In normoxic cancer cells, HIF-1 inactivation is disrupted, and hence HIF-1 signaling is enhanced, giving a rise to a glycolytic phenotype despite the presence of oxygen. Figure 2(b) details hydroxylation and the subsequent steps of the inactivation pathway. In normal normoxic cells, oxygen contributes to HIF-1 inactivation by initiating superoxide-driven oxidative damage to the HIF-1α subunit (see Figure 2(a)) and by promoting hydroxylation steps (also considered as oxygen sensors). In cancer cells, formation of the complex involving von Hippel Lindau protein (mutations affecting the E3 ubiquitin complex ligase gene) may be deficient [30]. Mutations may also affect the succinate dehydrogenase and/or fumarase genes [31, 32], and the resulting succinate accumulation alters hydroxylation steps by product inhibition. These genes (von Hippel Lindau protein, succinate dehydrogenase, and fumarase genes) represent tumor suppressor genes, inborn errors of which favor cancer development [31, 32].

2.3. Metabolism Compartmentalization Induced by HIF-1 Signaling. Permanent activation of the HIF-1 pathway and some other signaling pathways in cancer cells enhance the expression of genes encoding proteins involved not only in tumoral angiogenesis and substrate supply (for instance, erythropoietin and VEGF) (see Figure 2(a)) but also in the glycolytic phenotype (Figure 3). Tumoral glucose metabolism increases cytosolic NADH which is oxidized back to NAD+ by cytosolic lactate dehydrogenase which converts pyruvate into lactate (Figure 3). Figure 3(b) illustrates how tumoral glycolysis starts at the mitochondrial outer membrane where hexokinase type II (HKII) interacts with the voltage-dependent anionic channel (VDAC), also located in this membrane, via a binding domain [33].

2.4. Metabolic Impact of Tumoral Glycolysis. The oxidation of glucose to pyruvate (glycolysis) yields less energy (only 2 ATPs instead of 36 ATPs, see above) than glucose oxidation
to CO₂ (glycolysis plus mitochondrial oxidations). Glycolytic mobilization of ATP as developed by cancer cells is, however, faster than in normal cells. Therefore, despite a lower recovery, energy mobilization is faster in tumoral cells as attested by the increased uptake of ¹⁸F-deoxyglucose observed in FDG-PET scans of patients with malignant tumors.

Normal cell mitochondria are positively charged by the respiratory chain-driven proton gradient. In contrast, cancer cell (lazy) mitochondria are negatively charged on account of the accumulation of negative molecules due to the closed state of VDAC.

In normal mitochondria, VDAC is open, allowing the exchange of small solutes (pyruvate and other negatively charged compounds with a molecular weight inferior to 1.5 KDa) [34]. In cancer cell mitochondria, VDAC is closed by a rise in cytoplasmic NADH and its interaction with HKII [34], therefore, inhibiting the exchange of small solutes. The VDAC-HKII complex can dissociate and VDAC may reopen subsequently following an increase in the levels of glucose-6-phosphate which is produced by glucokinase or hexokinases. Figure 3(c) presents various therapeutic opportunities based on these differences between cancer and normal cells.
3. Tumoral Pyruvate Kinase

The ultimate goal of sustained glycolytic rates in cancer cells is not only to provide an advantageous mode of energy mobilization that still works when the cell needs to move or when oxygen in the environment is low. It is also to ensure anaplerosis of nucleic acid synthesis and other biosynthetic pathways by supplying ribose phosphate moieties. This supply is provided by articulations existing between glycolysis and the pentose phosphate pathway, with the development...
**Figure 4:** Tetrameric M2 pyruvate kinase-driven fuel-generating (green panel) and dimeric M2 pyruvate kinase-driven biosynthetic precursor-generating (red panels) glycolysis (yellow panel) in cancer cells. Tumoral M2 pyruvate kinase exists in a dimeric inactive form that blocks pyruvate and ATP formation from glucose. It induces the accumulation of energy-rich phosphometabolites found upstream in the glycolytic pathway and off which biosynthetic processes may branch. Interconversion to the active tetrameric form of the enzyme may occur when the glucose supply is high, leading to a rise in fructose 1,6 bisphosphate which stimulates this tetrameric conversion. When glucose levels are high, cancer cells may then produce energy at the same time as supplying biosynthetic pathways. In this situation, the rise in glycolytic intermediary rich energy phosphometabolites results not from a block located downstream of their production but from an increased load of glycolysis by glucose. When glucose levels fall again, the subsequent decrease in fructose 1,6 bisphosphate results in recruitment of the dimeric inactive form of M2 pyruvate kinase. In this case, both energy and pyruvate production (and hence formation of lactate) by the tumor may derive from the catabolism of aminoacids such as glutamine and serine. The latter sets of metabolic reactions, by analogy with glycolysis for glucose to lactate production, are referred to as glutaminolysis and serinolysis, respectively. The supply of these aminoacids to the tumor is associated at distance with notably muscle proteolysis, explaining the progression of patients towards a cachectic state when the tumor gains in growth and development. Cachexy may be also favored by energy wasting associated to uncoupling of mitochondria in some cancer cell lines. Except with tumors such as insulinoma and hepatoma, for instance, no hypoglycaemia is, however, induced in patients since a sustained production of lactate is ensured by the tumor from these aminoacids. Lactate may be recycled to glucose by gluconeoeformator cells, mainly hepatocytes (Cori’s cycle). Biosynthetic pathways branching off glycolysis include sialic acid, nucleic acid, aminoacid, ether glycerolipid, and ester glycerolipid anabolic pathways. The latter pathway is not emphasized here by inclusion in a red panel because in many cancer cell lines glycerol phosphate dehydrogenase is deficient thus reducing the availability of glycerol 3-phosphate and limiting incorporation of neoformed fatty acids into lipids. Fatty acid synthase is often overexpressed, and, along with the removal of fatty acids (known for immunosuppressive properties) outside the cell, it allows tumoral cells to cope with the massive rise in glycolysis-driven NADH and proton (H⁺) formation (glyceraldehyde 3-phosphate dehydrogenase step), avoiding excess acidification and consequent cell death. The threshold for reversible interconversion of tetrameric to dimeric M2 pyruvate kinase may be lowered by oncogenes in favor of the dimeric form. As mentioned in the text, the tetrameric active form is part of the glycolytic complex (a complex which groups most glycolylic enzymes for optimal metabolic function and energy production) whereas the dimeric form separates from this glycolytic complex.

Several sensors enable cells to adapt cellular growth and proliferation to nutrient supply. Pyruvate kinase, which is responsible for the net ATP formation during glycolysis, represents such a key sensor. It is, for instance, inhibited by ATP (high when nutrient supply is high) and activated by AMP and Pi (high when nutrient supply is low), directing differently phosphoenolpyruvate (and hence glucose) towards biosynthetic pathways and ATP formation, respectively. Cells have developed an elegant means to avoid pyruvate kinase inhibition when the glucose supply is low and on the opposite pyruvate kinase activation when the glucose supply is high. This regulator, which couples the glucose cell supply of a nonoxidative pentose phosphate cycle. Ribose phosphate supply and lactate formation from glucose are distinct exclusive endpoints. When glycolytic intermediates enter the pentose phosphate route (to form ribose 1-P and hence ribose 6-P) or other biosynthetic pathways branching off from glycolysis, their carbon skeleton can no longer be used for pyruvate and lactate formation. Reciprocally, when glucose is converted to pyruvate (2 pyruvates per glucose), it can no longer be used for ribose phosphate synthesis and other biosynthetic processes. Because proliferative cells need energy, cell death would occur if no regulatory mechanisms were implemented when nutrient supply is limited.
to pyruvate kinase activity, is fructose 1,6-biP, a potent physiological activator of pyruvate kinase [35]. Fructose 1,6-
biP is itself dependent on fructose 2,6-biP, the powerful
stimulator of phosphofructokinase [36].

Pyruvate kinase exists in various isoforms, L in the liver
and kidneys (gluconeogenic metabolism), R in red blood
globules; M1 in muscles and the brain (tissues in which rapid
mobilization of energy may be required), and M2 in the
lungs and tissues with nucleogenic metabolism (increased
mobilization of energy may be required), and M2 in the
and tumoral cells [35]. Normal cell and tumoral
M2 isoforms differ in their quaternary structures which
are tetrameric and prominently dimeric, respectively [35].
Tetrameric (normal) and dimeric (tumoral) forms of M2
pyruvate kinase exhibit distinct kinetic properties and induce
distinct processes. Tetrameric M2 pyruvate kinase favors
the conversion of phosphoenolpyruvate to pyruvate and
net glycolytic ATP production, driving glycolytic phospho-
metabolites towards fuel production. In contrast, dimeric
(tumoral) M2 pyruvate kinase is inactive in the presence
of physiological concentrations of phosphoenolpyruvate
and does not promote net ATP formation so glycolytic
phosphometabolites are channeled towards biosynthetic
processes including nucleic acid, aminoacid, sialic acid, and
phospholipid biosynthesis.

Therefore, in tumoral cells exhibiting high glucose
consumption rates, the inactive dimeric form of M2 pyruvate
kinase allows glycolytic phosphometabolites to accumulate
and subsequently be used for biosynthesis. Ribose 5-P
synthesis branches off from glycolysis via the transketo-
lase/transaldolase reaction (nonoxidative pentose phosphate
cycle) because the oxidative pentose phosphate cycle is
inhibited by high levels of fructose 1,6 biP (consecutive to
increased glucose supply and reduced pyruvate kinase activ-
ity) [35]. The role of M2 pyruvate kinase in cancer has been
reviewed in detail elsewhere [35]. In cancer cells, the shift
from dimeric to tetrameric M2 pyruvate kinase is dependent
on fructose 1,6 BiP levels; according to a threshold-driven
regulation mechanism the enzyme is converted from the
dimeric to the tetrameric form when concentrations exceed
the threshold and inversely when concentrations are below
the threshold. The threshold itself is subject to modulation
by signaling molecules such as oncogene products which may
lower the threshold [35]. The contribution of the dimeric
and tetrameric forms of tumoral M2 pyruvate kinase to
Warburg's effect is illustrated in Figure 4.

4. PPARs, Metabolism, and Inflammation

PPARs are nuclear receptors which influence many aspects
of cell physiology. Their action is pleiotropic and impacts
in diverse ways the signalome, the metabolome, and the cell
cycle. The three PPAR isoforms have metabolic effects and
anti-inflammatory properties. Metabolic effects of PPARs
result notably from the transactivation properties of ligands
involving the PPAR-RXRα heterodimer, whereas the anti-
inflammatory effects of ligands result mainly from the
ability of activated PPARs to combine with transcription
factors involved in inflammation signaling [37]. Figure 5
illustrates this dual ability of PPARs to control the acti-
vation of metabolic proteins by heterodimerizing with
RXRα and hence binding to DNA, and to downregulate
inflammatory pathways by interacting with so-called redox
transcription factors without further binding to DNA of
the PPAR/inflammatory transcription factor complex. These
two types (metabolic and anti-inflammatory) of effects
induced by PPARs could contribute to Warburg's effect.
Nevertheless, although cumulative evidence supports the
ability of metabolic events such as those induced by PPARs
to interfere with Warburg's effect, the impact of anti-
inflammatory events similar to those achievable by PPARs
and their ligands on Warburg's effect has been pointed to
recently and is still little documented.

5. PPARs and Metabolism of Inflammatory
Fatty Acid Derivatives

The link between PPARs and eicosanoid metabolism is
strong, tight, and reciprocal. Indeed, whereas eicosanoid
metabolism may form physiological PPAR ligands [38],
PPARs themselves regulate eicosanoid metabolism. As illus-
trated in Figure 6, at least three physiological PPAR ligands
are issued from arachidonate metabolism, namely LTβ4,
PGL2 and 15-deoxy-PGJ2 which activate PPARα, β/δ, and γ,
respectively. By their transrepressive activity, the activation
of PPARs prevents induction of COX2 via a physiological
feedback loop. This loop limits the additional production of
arachidonate-derived inflammatory mediators in response to
oxidative stress (generated for instance by the recruitment
of inflammatory cells) by controlling the level of induction
of COX2 [37]. As COX2 activity increases, more physio-
logical ligands of PPARβ/δ and PPARγ are produced which
potentiate the transrepressive activity of these isoforms on
inflammatory signaling-driven stimulation of COX2 gene
expression (in practice, agonists of each of the three main
PPAR isoforms may induce this antiinflammatory effect).

Physiological activation of PPARα by the LOX-derived
eicosanoid metabolite LTBA4 also takes place in the context of
a negative metabolic feedback loop when taking into account
the ability of this PPAR isoform to induce leukotriene-
inactivating pathways. These inactivating pathways may also
concern COX-derived metabolites and include peroxisomal
β-oxidation and fatty acid ω-hydroxylation. Prostaglandins
and leukotrienes may be inactivated by carbon chain short-
ening corresponding to one or two peroxisomal β-oxidation
cycles [39]. They may also be inactivated by hydroxylation
at the terminal carbon position of their fatty acid chain
by a fatty acid ω-hydroxylase (using NADPH+H+, O2, and
cytochrome P450 of the CYP4A or CYP4F subfamilies) [40,
41]. In rodents, the two pathways are activated by PPARα
whilst in humans peroxisomal β-oxidation does not seem to
be induced [39]. In contrast, fatty acid ω-hydroxylase activity
and CYP4A levels are enhanced by PPARα activation in the
humans [42].
6. PPARs, Inflammation, Angiogenesis, and Warburg’s Effect

The modulation of inflammatory events by PPARs in relation to Warburg’s effect is starting to be described. Though the role of inflammation in cancer has been largely documented, the relations between inflammation, and Warburg’s effect are still currently the topic of a limited number of scientific papers. Common pathogenesis events involving the production of oxidant species would lead to the concurrence of cancer cells with the Warburg’s effect phenotype and of an inflammatory microenvironment of the tumor which both favor cancer progression. In a recent paper, Pavlides et al. [43] elegantly illustrated this situation by showing that the loss of stromal caveolin-1 leads to oxidative stress and hypoxia, inducing HIF which favors Warburg’s effect and triggering NF-κB signaling which, via the activation of inflammatory pathways, induces inflammation. These cell signaling routes cause nitric oxide overproduction, mitochondrial dysfunction and ischemia mimic. Pavlides et al. [43] demonstrated that, in fact, mice lacking stromal caveolin-1 represented an animal model displaying the tumor stroma without the tumor, in other words the stromal ground which pathophysio- logically dialogs and interacts with Warburg phenotyped cancer cells during in situ cancer growth and progression. These results might indicate that stroma cell inflammation and Warburg phenotyped cancer cells coexist in a kind of symbiosis in which each cell type takes advantage of being in the presence of the other. Because of their anti-inflammatory properties, PPARs should, therefore, affect this symbiosis between cancer cells and their stromal microenvironment and hence might impair tumoral growth and cancer progression. It is possible that part of the anticancer mechanisms of PPAR ligands might lie in their capacity to disrupt this particular symbiosis.

Targeting tumor stroma by drugs not primarily referred to as anticancer drugs and including COX-2 inhibitors, mTOR antagonists and PPARγ agonists has been previously proposed [44–46]. PPARγ actually displays antiangiogenic properties which have been proposed to disrupt the symbio-
Arachidonic acid (AA) may generate various lipoxygenase (LOX) (hydroxyeicosatrienes, HETEs; hydroperoxyeicosatrienes; HPETEs, leucotrienes, LTs) and cyclooxygenase- (COX) (prostaglandins, PGs; thromboxanes, TXs) derived metabolites. Among these metabolites, LTB4, prostacyclin (PGI2), and 15-deoxy PGJ2 (PGJ2) represent ligands of each of the three PPAR isoforms, PPARα, β, and γ, respectively. Subsequent physiological activation of PPARs impacts the formation of such ligands via a negative feedback loop by increasing their degradation and lowering their formation. Indeed, PPARα activation stimulates microsomal ω-hydroxylase (in humans) and peroxisomal β-oxidation (in rodents, for instance but not in humans) and hence degradation of each of the precited PPAR ligands. Each of the PPARs may upregulate the activity of antioxidant enzymes and downregulate inflammatory proteins. Preventing induction of cyclooxygenase type 2 is a way to counteract inflammation-driven increase in arachidonic metabolites which are cyclooxygenase-dependent ligands of PPARs. The interest of a PPAR-based therapy in preventing the synergism between stromal cell inflammation and tumor development/invasion is explained in the text.
7. PPAR Ligand-Mediated Metabolic Changes Influencing Cancer Development

The anticancer properties of several PPAR ligands and effects have been described in experimental models and more recently in human patients [5, 79, 80]. Several putative underlying mechanisms have been reported, addressing essentially cancer cell signalling, cycle, fate, and life/survival balance determinants [1, 3, 79, 80]. To a lesser extent, the abilities of PPARα to disrupt the metabolic events that typically take place in cancer cells and the tightly related changes induced by cancer cell signalling, cycle, fate, and life/survival balance mechanisms have been reported, addressing essentially cancer cell signalling, cycle, fate, and life/survival balance determinants [1, 3, 79, 80]. In this respect, the general anticancer effects exerted by PPARα on cellular metabolism and inflammation were recently reviewed by Grabacka and Reiss [84]. The anticancer effects of interest highlighted by these authors included PPAR cooperation with AMP-dependent protein kinase, repression of AKT-driven oncogenicity, inhibition of cell proliferation, transrepression of inflammatory transcription factors, and PPAR transactivation properties leading to overexpressed UCPs and “forced” metabolic catastrophe [84]. In the present review, special attention is paid to the metabolic changes that directly result from PPAR activation and ligands and that interfere with Warburg’s effect. The aspects presented here are far from exhaustive and those developed in this section and in a larger manner in this review may be complemented by aspects developed in the other articles mentioned throughout this review.

General therapeutic interventions that interfere with tumoral metabolism have been described above and illustrated in Figure 3(c). In this figure, the metabolic basis for targeting mitochondrial and not nuclear DNA is emphasized. As also mentioned above, 18F-deoxyglucose used in PET scan imagery can enter the cell where it is phosphorylated into its phosphate derivative without being further processed. 2-Deoxy-D-glucose may mimic the dissociative effect that glucose-6-phosphate exerts on the hexokinase II/VDAC complex. This type of glucose analogues is currently subject to pharmacological development, and targeting the dissociation of the hexokinase-VDAC complex is an emerging anticancer therapy [85].

7.1. PPARα Metabolic Changes and Warburg’s Effect. Though PPARα agonists were initially described to convey anti-apoptotic properties [86–90], PPARα-driven proapoptotic mechanisms have been also described [91–93]. Mechanisms by which the metabolic action of PPARα might interfere with the Warburg’s effect and induce a pro-apoptotic issue are illustrated in Figure 7. This figure provides the reader with a sketch in which direct metabolic effects presented thereafter about PPARα and ligands move to lead to anticancer activity.

Figure 7 is an attempt to group under the same scenario several of PPAR and PPAR ligand-mediated direct effects on intermediary metabolism, notably those induced by PPARα. The scenario is based on integration of several PPAR-driven metabolic features depicted in this figure (for the underlying cell signaling pathways, see the literature cited in this review).

Referring therefrom directly to the steps numbered in Figure 7, these events include (1) the enhanced cell synthesis and levels of coenzyme A (PPARα) along with (2) increased mitochondrial acyl-CoA synthetase (ACS) activities (PPARα) favours (3) the formation of long-chain fatty acyl-CoAs for which the accumulation (4) is strengthened by deficiency of their removal via glycerol esterification (deficient glycerol 3P dehydrogenase in cancer cells), (5) and is known to inhibit hexokinase forms (metabolic regulation), (6) The inhibition of hexokinase II leads to (7) its detachment from VDAC which consequently (8) becomes “re-opened” restoring transfer of a lot many of small water metabolites (particularly those negatively charged and with a molecular weight inferior to 1.5 kDa) from a part to another of mitochondrial outer membrane. (9) More particularly, long-chain acyl-CoA esters (which are relatively soluble in water in comparison to unesterified fatty acids, have a molecular weight lesser than 1.5 kDa, and are negatively charged because of the content of CoA in phosphate functions) may via opened VDAC enter mitochondrial intermembranar space. (10) In this space fatty acyl-CoA are converted to their acyl-carnitine esters through action of carnitine palmitoyltransferase type I (CPT1) for which catalytic activity facing mitochondrial intermembrane space is enhanced as a result of
and FADH2), and doing so induces an increased electron flux pathway generates cofactors in their reduced forms (NADH notably) upregulated by PPARs. The intramitochondrial oxidation enzymes which are (acyl-CoA dehydrogenases, β-oxidation of long-chain acyl-CoA requires entry of CoA esters first in intermembrane space via transit by VDAC). (11) Fatty acyl-carnitines enter mitochondrial matrix via carnitine acylcarnitine translocase (CACT) located in mitochondrial inner membrane. (12) They are then converted back to CoA esters by carnitine palmitoyltransferase 2 (also upregulated by PPAR ligands) to undergo chain shortening by (13) Mitochondrial β-oxidation enzymes which are (acyl-CoA dehydrogenases, notably) upregulated by PPARs. The intramitochondrial pathway generates cofactors in their reduced forms (NADH and FADH2), and doing so induces an increased electron flux towards impaired respiratory chain. (14) The NADH (and protons) which accumulate locally as a result of their enhanced production (mitochondrial β-oxidation) and impaired management (deficient respiration): (14a) may be transferred via oxalate-malate shuttle system to cytosol and (14b) subsequent additional rise in cytoplasmic compartment (14c) may hamper seriously glycolysis to proceed at the level of glyceraldehyde dehydrogenase (NADH-forming) step. (15) The intramitochondrial β-oxidation-driven rise in producing reduced cofactors along with impaired respiratory electron chain transfer results in generation of free radicals and other oxidant species. This result is further strengthened by the sudden general boosting of mitochondrial metabolism which may emerge from unlocking VDAC and hence supply of mitochondrial oxidations by massive amounts of small metabolites (see events contained in the oval associated with an arrow pointing close to number 15). (16) This intramitochondrial boosting of metabolism, oxidative stress, and electron flux create conditions favourable to trigger apoptosis. (17) These intramitochondrial (17a) along with other pro-apoptotic events (including (17b), VDAC in its free form and then its potential availability for permeability transition pore, and (17c), down-regulation of anti-apoptotic factors by PPARγ ligands) (18) may act on proapoptotic/antiapoptotic balance towards apoptosis. (19) Impaired respiratory chain (RC) favours intramitochondrial free radical formation and notably direct transfer of electrons to molecular oxygen to form superoxide radical anion via radical intermediates of electron transfer chain.

Regarding the dissociation of the hexokinase-VDAC complex mentioned above to be an emerging anticancer issue, it is well known that the diverse hexokinase forms can be inhibited by the CoA esters of long-chain fatty acids [94, 95]. Two metabolic effects induced by PPARs (PPARα) favor the synthesis of long-chain fatty acyl-CoAs: upregulation of mitochondrial fatty acyl-CoA synthetase [96–98] and enhanced cell biogenesis and levels of its cofactor coenzyme A [99]. The latter PPAR effect is consecutive to the upregulation of pantothenate kinase 1 which catalyzes the rate-limiting step of coenzyme A synthesis. These two metabolic features explain how synthesis of long-chain acyl-CoAs is increased following activation of PPARs although one should not overlook the possibility that PPARβ/δ isoform may up-regulate another cellular acyl-CoA-synthetase which is involved in lipid biosynthesis [100]. The PPAR-driven increase in cell fatty acyl-CoA levels is further strengthened.

**Figure 7:** Potential anticancer value of metabolic changes interfering with Warburg’s effect and mediated essentially by PPARα (the metabolic events numbered in the figure are explained in the text).
secondarily to upregulation by PPARα [101] and PPARγ [102] of acyl-CoA binding protein which is known to stimulate acyl-CoA synthetase activity by removing (binding) the enzyme product [103, 104]. This increase in long-chain acyl-CoAs is also favored by the relative lack of glycerol 3-P which normally branches off glycolysis via glycerol 3P dehydrogenase, the latter being deficient in cancer cells [35] as mentioned above. The impairment of this glycerol esterification pathway shifts the acyl-CoA esterification/oxidation balance towards oxidation.

Long-chain fatty acyl-CoAs produced by mitochondria are formed in the vicinity of the VDAC-HKII complex since in cancer cells mitochondrial acyl-CoA synthetase and this complex are both located in the mitochondrial outer membrane. As a result of their inhibitory properties towards hexokinase forms, a local rise in the concentration of long-chain acyl-CoAs should logically inhibit HKII. This effect might be also induced by CoA esters of the pharmacological carboxylic ligands of PPARs. Previously described CoA esters of PPAR ligands include fenofibroyl-CoA, nafenopin-CoA, ciprolfibroyl-CoA, and bezafibroyl-CoA [105–107].

Importantly, inhibition of HKII activity is classically known to induce its dissociation from VDAC. VDAC, which is closed during its interaction with HKII, then reopens when hexokinase detaches. Since VDAC is involved in the transport of long-chain acyl-CoAs through the mitochondrial intermembrane space, the opening of this channel unlocks the access of long-chain acyl-CoA to the mitochondrial intermembrane space. In this space, long-chain acyl-CoAs are converted to their carnitine esters by mitochondrial outer membrane carnitine palmitoyltransferase 1 which has its catalytic center facing intermembrane space in contrast to its malonyl-CoA-binding site which is located at the cytosolic aspect of the mitochondrial outer membrane [108, 109]. This acyltransferase may be stimulated following PPAR activation for several reasons, including upregulation by PPARα and γ agonists [110–112] and the PPARα-driven release of the inhibition exerted by malonyl-CoA. The release of the inhibitory action of malonyl-CoA on carnitine palmitoyltransferase 1 involves the contribution of PPARα toward the downregulation of acyl-CoA carboxylase (malonyl-CoA forming enzyme) [113] and the upregulation of malonyl-CoA decarboxylase (malonyl-CoA catabolizing enzyme) [114]. Other PPARα-driven metabolic changes which contribute to stimulate carnitine-dependent entry of fatty acids in mitochondria are the upregulation of both carnitine synthesis and its transport across the cell membrane [115, 116].

Long-chain acyl-carnitines are transferred from the mitochondrial intermembrane space to the mitochondrial matrix via the action of carnitine acylcarnitine translocase which belongs to the mitochondrial inner membrane. Within mitochondria, fatty acylcarnitines are converted back to their CoA esters by carnitine palmitoyltransferase 2 which is also the product of an upregulated target gene of PPARα [117]. Fatty acyl-CoAs produced by this acyltransferase are oxidized on the inner side of the mitochondrial inner membrane (very long-chain acyl-CoA dehydrogenase and trifunctional protein) and finally in the matrix. Intramitochondrial β-oxidation enzymes, very long-chain [118] and medium-chain acyl-CoA dehydrogenases [119] are themselves also upregulated by PPARα ligands.

In cancer cells with relatively inactive mitochondria, stimulation of both the supply of acyl-CoA and increased β-oxidation rates boosts the metabolism in these organelles. The huge increase in the electron flux towards the respiratory chain, often impaired in cancer cells, cannot be handled adequately by tumoral mitochondria resulting in a rise in free radicals and other oxidant species. This oxidative stress may then trigger mitochondria-induced apoptosis.

The anticancer potentialities of these PPAR effects concern cancer cells with so-called lazy mitochondria and may not address all cancer cell lines. Indeed, some cancer cell lines exhibit enhanced mitochondrial β-oxidation rates with increased UCP-driven uncoupled accelerated electron transfer rates. In these cases, it has been proposed to be opportune, on the opposite, to act therapeutically by inhibiting [120] rather than stimulating mitochondrial fatty acid oxidation. In cancer cells, the pro-apoptotic basis for “forcing” mitochondrial fatty acid oxidation to proceed at substantial rates might be relatively close to the anticancer mechanisms underlying the effects of mitochondrial membrane permeating compounds such as dichloracetate and pyruvate methyl ester (see above in the text, Figure 3(c)). These two mitocans, by restoring substantial intramitochondrial pyruvate oxidation, are thought to boost the electron flux towards the respiratory chain and hence, in these circumstances, induce an oxidative stress which triggers mitochondrial apoptosis. In this perspective, mitochondrial β-oxidation-inducing PPAR ligands could be also classified as mitocans. Importantly, increased plasma ketone body levels may result from PPAR ligand-driven stimulation of mitochondrial β-oxidation in ketone body-producing organs. Increased exposure of cancer cells to circulating or local ketones might also boost the electron flux towards mitochondrial respiration at the level of complex II (ketolysis involves succinyl-CoA; acetoacetate CoA transferase and produces succinate). Whether in cancer cell mitochondria such a load on the ketolytic route might trigger apoptosis remains, however, to be elucidated.

### 7.2. PPARγ Metabolic Changes and Warburg’s Effect

The pro-apoptotic properties of PPARγ and its ligands may also favor the commitment of cancer cells towards apoptosis. The ligands may act via mechanisms either dependent or independent of PPAR. These mechanisms directly address key signaling players of pro-apoptotic routes and were recently reviewed [83].

Regarding mitochondria and apoptosis, PPARγ agonists were also recently described to probably target, via PPAR-independent mechanisms, adenylate nucleotide transporters (ANT) [121]. The mitochondrial permeability transition pore complex also recruits VDAC and seems to require the channel to be available in a form dissociated from HKII.

An interesting point is the increase in fatty acid synthesis which in many cancer cell lines is accompanied by increased fatty acid synthase (FASN) capacity and contributes to tumoral cell development [122–125]. Increased fatty acid
content represents a reservoir of precursors for signaling molecules that may promote cancer development. As developed elsewhere [126], free fatty acids including those generated by FASN may be toxic for cells. To overcome fatty acid-driven lipotoxicity, cancer cells overexpress enzymes involved in triacylglycerol synthesis, a pathway which removes cellular fatty acids and stores them in a mobilizable and less toxic form (see [126]). In this respect, it has been suggested that a “lipogenetic benefit” results from an unexpected crosstalk between the tyrosine kinase HER2 (human epidermal growth factor receptor) and FASN [127–133]. In cancer cells, this cross-talk is the basis for alleviating fatty acid-driven toxicity by coupling triacylglycerol synthesis to free-fatty acid formation [130, 134, 135], actually increasing aerobic glycolysis or Warburg’s effect by pull effect (the pull effect refers to the ability of a metabolic step or pathway to stimulate the step or pathway that precedes it, the principle being similar to the favored displacement of the equilibrium of a chemical reaction towards the product when it is removed, for instance, by evaporation or chelation, from the reaction medium). PPARγ- and PPARγ-binding proteins are in these conditions upregulated by overexpressed HER2 and activate the lipogenetic triacylglycerol synthesis pathway [130, 134, 135]. Very importantly, this collaboration between HER2 and FASN also takes place out of a pathological context and is of physiological relevance in adipogenesis, that is, proliferation and differentiation of adipocyte cell precursors [130, 136].

7.3. PPARβ/δ Metabolic Changes and Warburg’s Effect. Like other PPAR isoforms, PPARβ/δ exerts antiinflammatory and metabolic properties. The clinical use of PPAR ligands only currently emerges, and this shed lights on the physiological activity of this nuclear receptor. Part of the effects of PPARβ/δ overlaps those exhibited by either PPARα or PPARγ and includes adipocyte differentiation and improved insulin resistance, stimulated fatty acid oxidation in target tissues (heart and skeletal muscle) [67]. For instance, specific PPARβ/δ agonists may increase HDL cholesterol or HDL/LDL cholesterol ratio, and may decrease excess circulating triglycerides and insulin levels, and, like agonistic PPARα and PPARγ ligands, can counteract some of the aspects of the metabolic syndrome [67, 137–140]. The events depicted in Figure 7 for PPARα might also partially apply to PPARβ/δ inasmuch its activation may increase mitochondrial fatty acid oxidation in tissues through changes paralleling somewhat those exerted by PPARα and including upregulations of carnitine palmitoyltransferase type I, carnitine acylcarnitine translocase, and long-chain acyl-CoA dehydrogenase [141, 142]. In this respect, PPARβ/δ has been shown to enable a metabolic shift from glucose to fatty acid utilization [143]. In this respect also, PPARβ/δ has been described to enable metabolic compensation in deficient PPARα conditions [144].

Besides PPARα-like effects, PPARβ/δ also displays PPARγ-like effects in targeting the white adipocytes, favoring cell differentiation, fatty acid oxidative capacity, and insulin sensitivity of adipocytes [67].
7.4. PPAR-Dependent and Independent Metabolic Changes Induced by Ligands. An essential point determining the exact pathophysiological roles of PPARs and hence their therapeutic potentialities is to distinguish receptor from “extra-PPAR” effects of PPAR ligands. This point has been reviewed by Scatena et al. [145]. These authors highlighted the inhibition of the respiratory chain, notably complex I, as extra-PPAR activities of ligands thus underlining a weak inhibitory effect for PPAR ligand fibrates associated with both glucose and fatty acid oxidations and low differentiating properties. In contrast, PPARy ligand thiazolidinediones which mediate stronger inhibition of complex I associated with essential glucose utilization and strong cell differentiating activity. The authors also recall that PPAR ligands were initially described as nongenotoxic carcinogens, at least in rodents. Despite such effects, these ligands appear sometimes but not always to be able to influence cancer development in a way favorable for patients.

7.5. PPAR, Metabolic Syndrome and Cancer. As illustrated in Figure 8, the tissue distribution and physiological functions of the various PPARs put these nuclear receptors in a privileged position to counteract, through partially overlapping mechanisms, various aspects of the metabolic syndrome. Moreover, cumulated actions of these receptors, as could be achieved by PPAR panagonists, might theoretically juggle all of the aspects of the metabolic syndrome [146]. On the other hand, metabolic syndrome (defined as a combination of several of the four following traits dyslipidemia, high fasting glycemia, hypertension, and obesity) is currently perceived as a condition which strongly promotes cancer progression [147]. Therefore, the activation of PPARs by preventing or treating the metabolic syndrome removes one important condition promoting tumoral growth though other anticancer mechanisms may be shared by PPARs. As indicated throughout this manuscript, PPAR activation may also trigger signaling that, in contrast, favors tumoral growth. So, the general problem inherent to PPARs and use of PPAR ligands in cancer therapy lies in the fact that pleiotropic effects of these nuclear receptors encompass both cancer brake and accelerator mechanisms. The fact that distinct signaling may be involved in pro- and anticancer properties of PPAR offers the hope to use successfully PPAR ligands in cancer therapy in combination with other active anticancer drugs that overcome the PPAR pro-oncogenic effects. This issue is, however, complicated by the fact that the biological activity of PPAR may be modulated in a cell-or-tissue specific manner and for a same PPAR by the ligand, a phenomenon referred to literature as SPPARM (selective PPAR modulation) [146], suggesting that PPAR effect in cancers might be cancer dependent. Despite some limits in a wide use of PPAR ligands to treat cancers, clinical trials have been already initiated in this field in recent years. A nonexhaustive presentation of these trials is given in the next section.

8. Clinical Trials with Anticancer PPAR Ligands

Clinical trials for evaluating anticancer therapies based on targeting PPAR signaling have been developed against different cancers. For this purpose, drugs that mostly act on the y isoform of PPARs have been used, not necessarily elucidating whether the drugs work via PPAR-dependent mechanisms or via PPAR-independent mechanisms due to their chemical structure. The main results obtained to date are given in Table 1. This table is commented below, and the studies described in this table may be completed by general reviews that further stress the therapeutic potential of thiazolidinediones as anticancer drugs, the antineoplastic effects of PPARy and its role as an antioncogene, the synergetic effects of retinoids in cancer therapy and finally an explanation for the mechanisms underlying the modulation of cancer cell phases [171–181].

In liposarcoma, two phase II trials with PPARy agonists (either troglitazone or rosiglitazone) [148, 149] indicated cell differentiation of the solid tumors without, however, correlation between drug-induced PPARy activity in the tumor and the clinical outcome.

Prostate cancer has been the subject of several clinical trials, and the tumoral growth of human prostate cancer cell lines has also been studied [150–155]. Thiazolidinediones, PPARy agonists, troglitazone and rosiglitazone, led to conflictual results with two encouraging trials and one trial showing no advantage over the placebo [154]. The deleterious effect of the PPARy expression and variants were also studied, indicating no association between the Pro12Ala polymorphism and prostate cancer [151], suggesting therefore that PPARy does not promote prostate cancer development [154]. A study with the LTB4 receptor antagonist LY29311 also known for its PPARy activating properties failed to demonstrate any efficacy when used in combination with the anticancer drug gemcitabine in advanced prostatic carcinoma [155].

Colo-rectal cancer was also targeted by a clinical phase II trial using the PPARγ agonist thiazolidinedione troglitazone against chemotherapy resistant metastatic colorectal cancer [156]. No objective or negative tumor response was observed in this and other studies [156–158]. Interestingly, in the scope of the Bezafibrate Infarctus Prevention (BIP) study, some experimental support was obtained to suggest preventive effects for bezafibrate (a PPAR panagonist) against the development of colon cancer [159].

A phase II clinical trial using troglitazone in metastatic breast cancer refractory to chemotherapy or hormonal therapies suggested moderate efficacy of this PPAR γ agonist [160]. At the same time, preclinical studies indicated that in breast cancer cell lines PPARα expression is dependent on the estrogen receptor and represents a marker for sensitivity/resistance to histone deacetylase inhibitors [161]. When PPARγ signalling is increased in breast cancer, it impacts the balance between cell death and cell proliferation in favor of tumoral growth [162].

Studies in leukemia suggested that PPARy regulates apoptosis at the level of caspase 8, and its coactivator DRIP205
Table 1: Clinical trials and some preclinical studies for evaluation of PPARs and their ligands in cancer development and anticancer therapy.

| References                      | Nuclear receptor | Treatment                                      | Clinical phase | Number of patients | Human tumors or cell types | Main conclusions of the authors                                                                 |
|---------------------------------|------------------|------------------------------------------------|----------------|--------------------|----------------------------|-------------------------------------------------------------------------------------------------|
| Demetri et al., 1999 [148]      | PPARγ            | Troglitazone (per os, 1 × 800 mg/d, 6 weeks) | Phase II       | 3                  | High-grade liposarcomas    | Induction of cell differentiation in a human solid tumors                                      |
| Debrock et al., 2003 [149]      | PPARγ            | Rosiglitazone (4 mg/d for 1 year)              | Phase II       | 12                 | Liposarcoma                | Increased PPARγ activity: no correlation with clinical outcome                                 |
| Mueller et al., 2000 [150]      | PPARγ            | Troglitazone (per os, 2 × 400 mg/d, 12 weeks) | Phase II       | 41                 | Human prostate cancer      | Prolonged stabilization of PSA with PSA close to 0 in 1 patient                                 |
| Paltoo et al., 2003 [151]       | PPARγ Pro12Ala   | Impact of a gene polymorphism on prostate cancer development |                 | 193 (versus 188 controls) | Prostate cancer            | No association of prostate cancer and Pro12Ala polymorphism                                   |
| Xu et al., 2003 [152]           | PPARγ            | Tosiglitazone                                  | Predinical     |                    | Primary culture of human prostatic cancer cells                                               | Prodifferentiating properties of thiazolidinediones                                               |
| Dawson and Slovin, 2003 [153]   | Vit D PPARγ      | Review                                         |                |                    | Prostate cancers           |                                                                                                 |
| Smith et al., 2004 [154]        | PPARγ            | Rosiglitazone 2 × 4 mg/d (versus placebo 315 d) | Phase II       | 105                | Advanced pancreatic carcinoma | No advantage over placebo efficacy and PPARγ do not contribute to prostate cancer development   |
| Saif et al., 2009 [155]         | PPARγ agonist and LTB4 receptor antagonist | LY29311 (in combination with gemcitabine) | Phase II       | 67 (combined therapy versus 66 (gemcitabine alone) | Colorectal cancer | No benefit obtained by adding LY293111 to gemcitabine                                           |
| Kulke et al., 2002 [156]        | PPARγ            | Troglitazone per os 15d-PGJ2 pioglitazone       | Phase II       | 25                 | Chemoresistant colorectal metastatic cancer                                                  | No objective tumor response                                                                       |
| Choi et al., 2008 [157]         | PPARγ            | Bezafibrate Infarctus Prevention (BIP) study    | Predinical     |                    | APC-mutated HT-29 human colon cancer cells                                                   | PPARγ ligand promotes growth of APC-mutated HT-29 colon cancer cells                              |
| Dai and Wang, 2010 [158]        | PPARγ            | Bezafibrate Infarctus Prevention (BIP) study    | Predinical     |                    | Colorectal cancer                                                             | Mechanisms by which PPARγ impacts carcinogenesis in colorectal cancer                          |
| Tenenbaum et al., 2008 [159]    | All PPARs        | Panagonist bezafibrate retard 400 mg/d          | Predinical     | 3011 with coronary artery disease and no cancer | 1506 given bezafibrate 1505 given placebo | Experimental support for preventive effects of bezafibrate towards colon cancer                 |
| References | Nuclear receptor | Treatment | Clinical phase | Number of patients | Human tumors or cell types | Main conclusions of the authors |
|------------|------------------|-----------|----------------|-------------------|--------------------------|--------------------------------|
| Burstein et al., 2003 [160] | PPARγ | Troglitazone 800 mg/d for 6 months | Phase II | 22 | Breast cancer refractory to one chemotherapy or two hormonal therapies | Little apparent clinical effect in patients with treatment refractory metastatic breast cancer (1) ER dependence of PPARα (2) PPARα levels = marker of breast cancer cell resistance to histone deacylase inhibitors PPARγ signaling impacts balance between proliferation and apoptosis towards proliferation in breast cancer |
| Faddy et al., 2006 [161] | | | Predclinical | | | |
| Zaytseva et al., 2008 [162] | PPARγ1 | RNAi | Predclinical | | MCF-7 breast cancer cells | |
| Hasegawa et al., 2007 [163] | PPARγ | Fuligocondis B via increase in PGJ2 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) 15d-PGJ2 | Predclinical | | Leukemia cells | 15d-PGJ2 sensitizes TRAIL-resistant cells to TRAIL-independent on PPARγ |
| Tsao et al., 2010 [164] | PPARγ | Rosiglitazone 4 mg/d 1 week + 8 mg/d 7 weeks | Preclinical Phase I | 9 | Acute myelogenous leukemia cell lines from 9 patients | PPARγ regulates apoptosis via activation of caspase 8 and co-activator DRIP205 promotes cell differentiation by PPARγ |
| Kebebew et al., 2006 [165] | PPARγ | Rosiglitazone 8 mg/d for 6 weeks | Phase II | 10 patients | Differentiated thyroid cancer | Rosiglitazone may induce radioiodine uptake in some patients possibly via PPARγ-independent pathways Increase of radioiodine uptake in thyroid tumors possibly via PPARγ-independent mechanisms |
| Tepmongkol et al., 2008 [166] | PPARγ | | Phase II | 23 | Thyroid carcinoma | |
| Yao et al., 2006 [167] | HMG-CoA reductase PPARγ | Lovastatin + troglitazone | Predclinical | | Glioblastoma and lung cancer cell lines | Induction of P27 [Kip 1] (statines), E2F-1 (glitazone), + CDK2, cyclin A, Rb phosphorylation status |
| Hau et al., 2008 [168] | COX-2 inhibitors PPARγ | Rofecoxib pioglitazone in association with low-dose chemotherapy | Phase II | 44 | High-grade gliomas (glioblastomas or anaplastic glioma) | Moderate activity encouraging future utilization in highly selected patients |
| Schweitzer et al., 2010 [169] | PPARγ | Review | | | Head and neck cancers | Therapeutic use of PPARγ ligands in head and neck cancer |
| Botton et al., 2009 [170] | PPARγ | Ciglitazone versus other thiazolidinediones | Predclinical | | Melanoma cell lines | Effects on cycle arrest, p21, cyclin D1, pRB hypophosphorylation are better than with other thiazolidinediones |
was found to promote cell differentiation via PPARγ [164]. Sensitization of TRAIL-resistant cells to TRAIL was also reported for the natural PPARγ agonist 15d-PGJ2, however, independently of PPARγ signaling [163].

In thyroid cancer, the synthetic PPARγ agonist rosiglitazone was shown to enhance the uptake of radioiodine by thyroid tumors in a way apparently independent of PPARγ [165, 166]. Although this effect is not per se an anticancer mechanism, it is of therapeutic interest in potentiating the radioiodine-based chemotherapy of hyperthyroidism, thyroid, and other cancers. Interestingly, this potentiating effect indicates that rosiglitazone administration should be theoretically questioned in a context of defective nuclear power plants or in people living close to these plants.

PPARγ targeting in human glioma and glioblastoma has provided encouraging results in in vitro and in vivo studies when thiazolidinedione is combined with either a statin or a coxib. Yao and coworkers [167] have shown anticancer activity with a combination of lovastatin and troglitazone in glioblastoma and lung cancer cells. The anticancer properties of the exposure of cells to this dual treatment included the combined enhancement of intracellular levels of P27 [Kip 1] (usually induced by statins) and E2F1 (induced by glitazones) along with changes in the status of CDK2, cyclin A and Rb phosphorylation. A phase II study combining the PPARγ agonist pioglitazone and rofecoxib with low-dose chemotherapy in high-grade gliomas pointed out a moderate benefit and encourages the future use of this cocktail in highly selected patients [168].

Head and neck cancers were also challenged with PPARγ ligands with some benefit as reviewed elsewhere by Schweitzer et al. [169].

In melanoma, tumoral cell growth has been shown to be inhibited by the thiazolidinedione ciglitazone, in a way independent of PPARγ activation [170]. This antitumoral activity of ciglitazone has been further shown to involve down-regulation of chemokine CXCL1 and microphthalmia-associated transcription factor, MITF, two proteins overexpressed in human and playing a key role promoting its pathogenesis [182].

9. Conclusions and Perspective

This review has attempted to account for the rationale underlying the metabolic functioning of cancer cells in relation with Warburg's effect, and its corollaries in terms of metabolic vulnerability. More precisely, the metabolic behavior of cancer cells with lazy mitochondria was emphasized because it theoretically represents a nearly ideal target for PPARα agonists to reverse the cancer cell-driven metabolic lock of mitochondrial metabolism. Nevertheless, the perception of Warburg's effect currently evolves, and in this context defective mitochondrial oxidative capacity is not longer viewed as a mandatory component, substantial mitochondrial oxidative activities contributing in this context to cover cancer cell energetic needs. Anticancer metabolic and other effects presented throughout the text in relation with the Warburg's effect should be completed in more details with anticancer activities exerted by PPAR ligands in many realms other than metabolism, inflammation, and angiogenesis as for instance cell cycle, cell survival, cell maturation, cell differentiation, tumoral invasion, and apoptosis. In this review, the latter process has been further proposed to be sensitive to unlocking of mitochondrial metabolism and respiration induced by PPARα agonists. Surprisingly, clinical trials with PPARα ligands are still to be initiated, possibly because they were initially described to be nongenotoxic carcinogens that could mediate antiapoptotic properties [86–90]. Since then species differences [183] and PPARα-driven pro-apoptotic mechanisms [91–93] have been documented. In contrast, several trials with PPARγ ligands have been conducted to date. PPARγ and their ligands are shown in the literature to favor apoptosis via multiple actions on cell-signaling pathways. At the same time, they may also be able to promote anti-apoptotic pathways. This is now well documented for the PPARγ ligand troglitazone which promotes apoptosis via upregulation of the TRAIL death receptor, inhibition of the anti-apoptotic proteins FLIP, and downregulation of survivin [184]. In turn, troglitazone may also activate anti-apoptotic pathways, for instance, via enhanced phosphorylation of ERK and subsequently of BAD, resulting in increased availability of the anti-apoptotic proteins Bcl-2 and Bcl-XL to scavenge key pro-apoptotic mediators such as BAX [185]. The fact that in this case pro- and anti-apoptotic actions are mediated by separate signaling pathways offers the perspective of potentiating the former by inhibiting the second, and in practice, by combining troglitazone with an inhibitor of the events leading to BAX sequestration via the anti-apoptotic proteins mentioned above. The need for this association of PPAR ligands with other anticancer agents is perhaps one of the most important lessons to be learned from clinical trials based on the use of these ligands to treat cancer.

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