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Review - Part of the Special Issue: Metabolism 2014 – Alterations of metabolic pathways as therapeutic targets

Energy restriction mimetic agents to target cancer cells: Comparison between 2-deoxyglucose and thiazolidinediones

Sandra Kuntz [a,b], Sabine Mazerbourg [a,b], Michel Boisbrun [c,d], Claudia Cerella [e], Marc Diederich [e,f], Isabelle Grillier-Vuissoz [a,b], Stephane Flament [a,b,*]

[a] Université de Lorraine, CRAN, UMR 7039, Vandœuvre-lès-Nancy, F-54506, France
[b] CNRS, CRAN, UMR 7039, Vandœuvre-lès-Nancy, F-54506, France
[c] Université de Lorraine, SRSMC, UMR 7565, Vandœuvre-lès-Nancy, F-54506, France
[d] CNRS, SRSMC, UMR 7565, Vandœuvre-lès-Nancy, F-54506, France
[e] Laboratoire de Biologie Moléculaire et Cellulaire du Cancer. Hôpital Kirchberg, L-2540, Luxembourg
[f] Department of Pharmacy, College of Pharmacy, Seoul National University, Seoul 151-742, Korea

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The use of energy restriction mimetic agents (ERMAs) to selectively target cancer cells addicted to glycolysis could be a promising therapeutic approach. Thiazolidinediones (TZDs) are synthetic agonists of the nuclear receptor peroxisome proliferator-activated receptor (PPAR)γ that were developed to treat type II diabetes. These compounds also display anticancer effects which appear mainly to be independent of their PPARγ agonist activity but the molecular mechanisms involved in the anticancer action are not yet well understood. Results obtained on ciglitazone derivatives, mainly in prostate cancer cell models, suggest that these compounds could act as ERMAs. In the present paper, we introduce how compounds like 2-deoxyglucose target the Warburg effect and then we discuss the possibility that the PPARγ-independent effects of various TZD could result from their action as ERMAs.

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Abbreviations: Δ2-TGZ, Δ2-Troglitazone; TGZ, Troglitazone; TZD, Thiazolidinediones; RGZ, Rosiglitazone; 2-DG, 2-deoxyglucose; ER, endoplasmic reticulum; CGZ, Ciglitazone; UPR, unfolded protein response.

* Corresponding author. Tel.: +33 383684005.
E-mail address: stephane.flament@univ-lorraine.fr (S. Flament).

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1. Warburg effect

As observed by Otto Warburg in the 1920s, the metabolic properties of cancer cells differ markedly from those of normal cells. Indeed, cancer cells have elevated rates of glucose consumption and high lactate production but unlike normal cells, lactate production occurs even in the presence of oxygen. This is known as aerobic glycolysis or Warburg Effect [1]. High glucose uptake of cancer tissues is clinically used to diagnose cancer and to monitor tumor response to treatment by imaging uptake of ^{18}F-deoxyglucose with PET scan [2]. Increased Warburg effect drives both tumor growth and metastatic potential and is associated with poor prognosis [3].

Glycolysis is the metabolic pathway that converts glucose into pyruvate by a determined sequence of ten enzyme-catalyzed reactions (Fig. 1). The first phase is an energy investment phase, which uses two adenosine 5′-triphosphate (ATP) molecules to phosphorylate glucose by hexokinase (HK) and fructose 6-phosphate by phosphofructokinase (PFK). The second phase is an energy production phase during which two molecules of glyceraldehyde 3-phosphate lead to two molecules of pyruvate with the production of 4 ATP molecules. The phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway, that mediates the physiological role of insulin in normal cells, plays an important role in coupling the energy status of the cell and its growth. In addition to direct available amino-acids into protein synthesis, this pathway regulates glucose uptake and utilization since it can not only regulate glucose transporter (GLUT) expression, but also enhance glucose capture by HK and stimulate PFK activity [4].

In normal cells, after glycolysis, pyruvate enters in the mitochondrial tricarboxylic acid cycle that produces NADH which fuels oxidative phosphorylation to maximize ATP production (Fig. 1). In this case, the complete oxidation of glucose to CO_2 and H_2O leads to the production of 36 ATP molecules. When the ability of normal proliferating cells to produce ATP from glucose is compromised, they can undergo cell cycle arrest and reactivate catabolic metabolism [5]. Indeed, signaling pathways exist to monitor energy status. In case of a decline in ATP production, adenylate kinases convert two molecules of adenosine diphosphate (ADP) to one ATP and one AMP (adenosine 5′-monophosphate). This has two consequences: it allows the maintenance of a viable ATP/ADP ratio on the one hand, and it leads to accumulation of AMP on the other hand. This compound binds to AMP-activated kinase (AMPK) and alters its conformation resulting in AMPK activation by its upstream regulator, the tumor suppressor protein liver kinase B1 (LKB1), via phosphorylation of AMPK at Thr^{172}. Subsequently, AMPK phosphorylates several targets to improve energy charge in cells [6]. For instance, AMPK phosphorylates and activates tuberous sclerosis complex (TSC) 1 and 2 resulting in mTOR signaling down-regulation and activation of autophagy. Interestingly, there is another connection between these two pathways: AKT phosphorylates and inhibits TSC1/2 and AMPK also phosphorylates and inhibits acetyl CoA carboxylase (ACC) 1 and 2. This is important because these enzymes catalyze the first step of fatty acids synthesis.

In cancer cells, aerobic glycolysis and conversion of pyruvate to lactate produce only 2 ATP molecules. This observation raises the question why an apparently less efficient metabolism, at least in terms of ATP production, would be interesting for rapidly

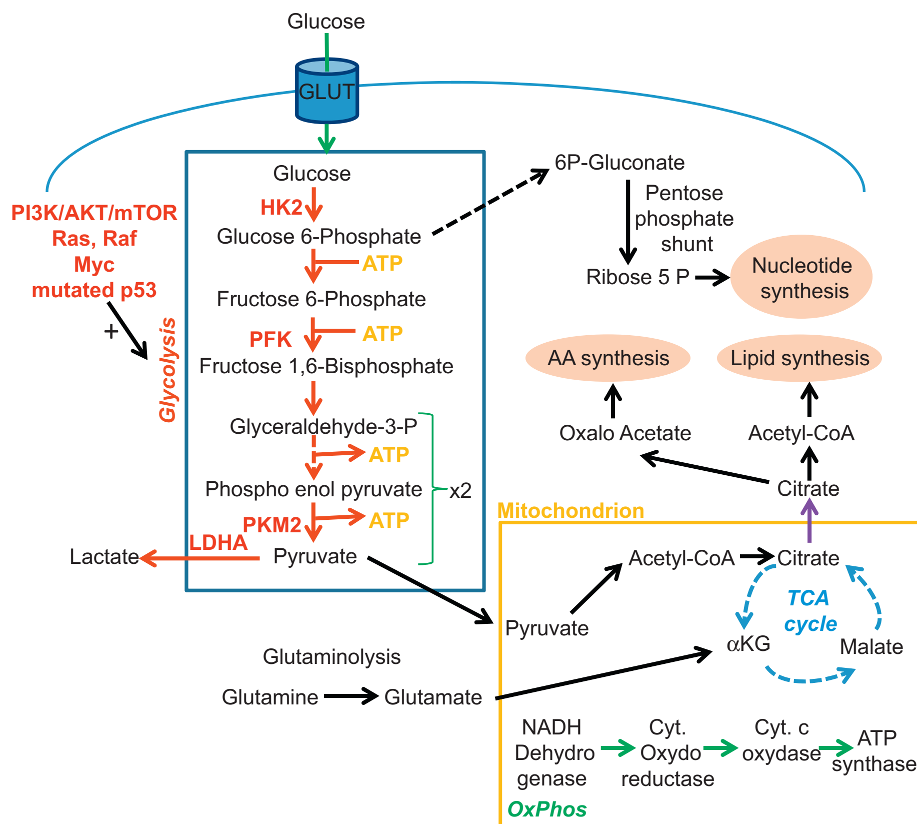

Fig. 1. Schematic representation of the main metabolic pathways discussed in this review. A simplified view of glycolysis that occurs in the cytoplasm and leads from glucose to pyruvate is depicted. The tricarboxylic acid (TCA) cycle and oxidative phosphorylation that both take place in mitochondria are also shown. The red arrows indicate the flux enhanced in cancer cells with the formation of lactate even in the presence of O_2 (aerobic glycolysis or Warburg effect). The links with some other pathways involved in the synthesis of amino acids (AA), nucleotides and lipids are also indicated. Dashed lines illustrate multistep events. See text for details. GLUT = glucose transporter, HK = hexokinase 2, PFK = phosphofructo kinase, LDHA = lactate deshydrogenase A, αKG = α ketoglutarate.

proliferating cancer cells. In fact, cancer cell metabolism is adapted to facilitate uptake and incorporation of nutrients into macromolecular precursors such as acetyl-CoA for fatty acid synthesis, glycolytic intermediates for nonessential amino acids, and ribose for nucleotides. Experiments using ^{13}C–nuclear magnetic resonance spectroscopy measurements showed that cultured glioblastoma cells convert as much as 90% of glucose and 60% of glutamine into lactate or alanine [7]. This probably explains the selective advantage provided by the Warburg effect.

One explanation for the Warburg effect is the tumor microenvironment that selects for metabolic alterations. When the early tumor grows, local blood vessels are not sufficiently developed, leading to hypoxia and stabilization of the hypoxia-inducible factor (HIF)-1α. HIF initiates a transcriptional program that provides solutions to hypoxic stress [8]. Cancer cell metabolism shifts towards glycolysis by an increased expression of glucose transporters, glycolytic enzymes and inhibitors of mitochondrial metabolism, because a decreased dependence on aerobic respiration becomes advantageous.

Another idea is that metabolic changes could be driven by oncogenes or tumor suppressors [9–11]. For instance, the oncogenes Ras and Raf, when mutated, are associated with increased expression of GLUT1 and promote glycolysis [12,13] (Fig. 1). A second example is the PI3 K/AKT/mTOR pathway whose aberrant activation is observed in many cancer types [14]. It reprises its role in glucose uptake and utilization in the cancer setting (Fig. 1). MYC transcription factor up-regulates the expression of various metabolic genes including the M2 isoform of muscle-type pyruvate kinase (PK-M2), and also stimulates glucose uptake [15,16] (Fig. 1). Regarding tumor suppressor proteins, wild-type protein p53 is able to repress the expression of GLUT1/4 and to stimulate the expression of TP53-induced glycolysis and apoptosis regulator (TIGAR) that functions as a fructose 2,6-biphosphatase, reducing the level of fructose 2,6-biphosphate that is an allosteric activator of PFK, thus directing the metabolic flux towards the pentose phosphate pathway (Fig. 1) [17,18]. Hence, loss of p53 that occurs in more than 50% of all human cancers, results in various metabolic changes that stimulate glycolysis. It is now well established that the Warburg effect results from an intricate network of signaling pathways that control both tumor cell growth and cancer metabolism [9].

2. Targeting cancer cell metabolism with 2-deoxyglucose

The existence of a cancer-specific metabolism and the fact that many cancer cells display a greater sensitivity to glucose-deprivation-induced cytotoxicity than normal cells explain why dietary energy restriction is a potent inhibitor of carcinogenesis. Nevertheless, in Human, it is difficult to sustain chronic caloric restriction through reduced energy intake. It is better to use ERMAs in order to cause a state of glucose starvation in cancer cells without limiting caloric intake. This approach has raised much interest in the development of glycolytic inhibitors as potential anticancer agents [19,20]. An interesting compound is 2-deoxyglucose (2-DG), a glucose analogue in which the C-2 hydroxyl group is replaced by hydrogen. Glucose and 2-DG are phosphorylated by hexokinase but 2-DG 6-phosphate cannot be further metabolized to fructose 6-phosphate by phosphoglucose isomerase, thus causing ATP depletion [21]. A second metabolic effect of 2-DG could be the noncompetitive inhibition of hexokinase by 2-DG 6-phosphate [22]. In addition to inhibition of the glycolytic pathway, 2-DG competes with glucose for the GLUT [23].

Several studies have shown that 2-DG affected glycolytic rate in cancer cells as expected. For instance, in LNCaP prostate cancer cells, a 50% decrease of the glycolytic rate was observed after 2 hours of treatment with 5 mM 2-DG. This event was associated with a 50–70% reduction of NADH production and lactate formation after 24 h [24]. 2-DG also systematically decreased ATP levels in various cell lines. For example, in the murine T cell lymphoma cell line, ATP levels dropped 60–70% 30 min after 2-DG treatment [25].

2.1. Anticancer effects of 2-DG

In vivo and *in vitro* studies in many cell lines showed that 2-DG had antitumor activity. Indeed, proliferation of the breast cancer cell lines MDA-MB468, MCF-7 and SKBR3 was affected by 2-DG (at concentrations between 4–12 mM) [26,27]. Interestingly, adriamycin-resistant MCF-7 cells (ADR) did not survive after 5 days of culture in the presence of a low concentration of 2-DG (1 mM). This finding correlates well with the three-fold faster glycolytic rate and the greater glucose requirement of ADR cells [26]. Tagg et al. confirmed the 2-DG-induced inhibition of proliferation in MCF-7 cells and observed a similar effect in the prostate cancer cell line LNCaP with an IC_{50} of 8.1 mM and 6.7 mM respectively [28]. Under hypoxia, the anticancer effect of 2-DG was enhanced by 20 to 25% in both cell lines. Under normoxia, even if glucose utilization is blocked by 2-DG, other sources (fats, proteins) can be used to produce ATP via oxidative phosphorylation. These results could explain why tumor cells showed resistance to 2-DG under normoxia, but became responsive under hypoxia in the absence of oxidative phosphorylation [29]. Then, alteration of the mitochondrial function enhanced 2-DG anticancer potential. In MCF-7 and MDA-MB-231 breast cancer cells, 2-DG (1–20 mM) alone did not demonstrate a significant inhibitory effect on colony formation. In combination with mitochondria-targeting drugs (MTD: Mito-CP and Mito-Q), 2-DG greatly inhibited the clonogenic growth of MCF-7 and MDA-MB-231 breast cancer cells, but not of non-tumorigenic MCF-10A cells. Indeed, MCF-10A were able to increase their glycolytic function in response to Mito-CP and were more resistant when co-treated with 2-DG [30]. This combinatorial strategy could be extended to other anticancer agents. Thus, combination with the microtubule disruptor STX140 (2-methoxyestradiol-bis-sulfamate, 0.1 μM) improved the efficiency of 2-DG in LNCaP cells [28]. 2-DG also sensitized gliomas and other cancer cells to radiations [31–34].

In animal models, 2-DG inhibited the growth of a methylcholanthrene-induced rat fibrosarcoma [35]. Similarly, liver tumor growth was delayed in rat treated with 2-DG [36]. 2-DG alone also induced a significant growth delay of human pancreatic MIA PaCa-2 cancer cells implanted in nude mice [37]. In contrast, other xenografted tumors (osteosarcoma, non-small-cell lung carcinoma, breast cancer cells MDA-MB-231) and Ehrlich ascites tumors were insensitive to 2-DG treatment. Wang *et al.* identified a dual-specific phosphatase, laforin, as a factor conferring resistance to apoptosis under energy deprivation [38]. Heterogeneous expression levels of laforin could explain differences in cellular susceptibility to energy deprivation [38].

Although 2-DG was not always effective as a single agent *in vivo*, it was able to enhance chemosensitivity and radiosensitivity of cancer cells in combination therapies. Several combinations were successful in several xenograft models: 2-DG/adriamycin (doxorubicin) for human osteosarcoma, 2-DG/paclitaxel (microtubule disruptor) for non-small cell lung cancer, 2-DG/STX140 (another microtubule disruptor) for breast (MCF-7) and prostate (LNCaP) cancer, 2-DG/etoposide (topoisomerase inhibitor) for Ehrlich ascites tumors (EAT), 2-DG/Mito-CP for breast cancer (MDA-MB-231-luc) [28,30,39,40]. Taken together, these *in vivo* results demonstrate that the combination of 2-DG with various chemotherapeutic agents clearly increased the efficiency of each agent. Several hypothesis could explain these results: (1) chemotherapeutic agents display antiangiogenic activity; tumor cells became

more hypoxic and more sensitive to 2-DG treatment. (2) Depletion of ATP caused by glycolytic inhibition prevents the reparation of damaged DNA. (3) Decreased ATP levels limit the activity of efflux pumps leading to intracellular drug accumulation[39].

2.2. 2-DG induces apoptosis

Apoptosis is morphologically defined by chromatin condensation and formation of apoptotic bodies. This process can be activated by two main pathways [41]. Apoptotic stimuli, such as oxidative stress or DNA damage, activate the intrinsic pathway that involves signaling through the mitochondria whose outer membrane permeability is regulated by members of the Bcl-2 (B Cell Lymphoma-2) family such as Bax (Bcl-2-associated X protein) and Bak (Bcl-2-homologous antagonist-killer) proapoptotic proteins and Bcl-2 and Bcl-X_L (B-cell lymphoma extra-large) antiapoptotic proteins. As a result, cytochrome c is released from the mitochondria into the cytosol leading to apoptosome formation, cleavage and activation of initiator caspase-9 that eventually cleaves effector caspases-3, -6 and -7. The extrinsic pathway is initiated through activation of cell surface death receptors (DR) which belong to the tumor necrosis factor (TNF) receptor superfamily. Ligand binding induces receptor trimerisation and cytosolic FADD (Fas-associated death domain) adaptor protein recruitment, leading to the formation of the Death Inducing Signaling Complex (DISC). In turn, caspases-8 and -10 are recruited and activated, leading to cleavage of downstream effectors procaspases-3 and -7. The cleavage of Bid (Bcl-2 interacting protein domain) links the two apoptotic pathways. Truncated Bid (t-Bid), activated by caspase-8, is essential for the insertion of Bax into the mitochondrial membrane leading to cytochrome c release and caspase-9 activation [42].

Several reports concluded that 2-DG affected cancer cells via apoptosis [24,27,29,43–47]. For instance, in murine T cell lymphoma cell lines (TCL), the cleavage of caspase-3 and PARP (poly(ADP-ribose) polymerase) observed after 2-DG treatment was inhibited by Q-VD-OPh pan-caspase inhibitor. However, this pan-caspase inhibitor had little effect on cell death induced by 2-DG, suggesting that cell death was not dependent on caspase activation. However, overexpression of the anti-apoptotic factor Bcl-2 dramatically enhanced survival of 2-DG-treated TCL cells. Co-immunoprecipitation experiments demonstrated that Bcl-2 multimerizes with the BH3 (Bcl-2 homology 3)-only proteins Bim (Bcl-2-interacting mediator of cell death) and Bmf (Bcl-2 modifying factor), up-regulated after 2-DG exposure. Then, the complexes Bcl-2/Bim or Bcl-2/Bmf could be involved in the activation of Bax at the mitochondrial level [25].

2-DG is not always effective as a single agent but acts as a potent enhancer of cancer cell death in combination treatments. In the prostate cancer cell line LNCaP, combination of 2-DG (8 mM) and the microtubule disruptor STX140 significantly induced apoptosis (monitored by annexin V labelling) with no effect on cell cycle [28]. In the same cell line, a treatment with 2-DG (1 mM) combined to metformin led to apoptosis after 48 h: the authors witnessed cleavage of caspase-3 and were able to inhibit the effect by the pan-caspase inhibitor Z-VAD-FMK [48]. In this case, apoptosis was dependent on AMPK phosphorylation and p53 expression. In colon and in ovarian cancer cells, 2-DG potentiated apoptosis induced by cisplatin [46,49]. In myeloid leukaemia cells U937 and in breast carcinoma cells MCF-7, 2-DG treatment (5 mM) enhanced apoptosis induced by a CD95 agonist antibody and TNF-related apoptosis-inducing ligand (TRAIL). 2-DG alone did not have considerable effect on cell death. In combination, the observed cell death was dependent on caspase activation, since it was completely blocked by the caspase inhibitor Z-VAD-FMK. Caspase-8 activation was the first detectable event facilitated by glucose deprivation after incubation of U937 cells with CD95 antibody, followed by cytochrome c release, Bax translocation and caspases-3 and -9 cleavage. The origin of the sensitization to death receptor-triggered apoptosis in U937 and MCF-7 cells deprived of glucose could not be determined [43]. 2-DG (10 mM) also sensitized MDA-MB-231 to TRAIL-induced apoptosis with reduction of mitochondrial membrane potential, caspase-8 and -3 processing. 2-DG up-regulated TRAIL receptor 2 and down-regulated receptor-interacting protein kinase 1 (RIP1), a critical event to induce sensitization to TRAIL in breast cancer cells [50].

2.3. 2-DG induces autophagy

In case of reduced external nutrient supply or increased energy demands, eukaryotic cells start autophagy, a catabolic process that involves the transport of cellular components (macromolecules and organelles) to the lysosomal compartment *via* double-membrane vesicles, called autophagosomes. In the context of disease, autophagy is often seen as an adaptive response to survival, whereas in other cases it appears to promote cell death [51].

2-DG has been shown to induce autophagy in various cell lines [24,48,52–55]. Different mechanisms by which 2-DG elicited autophagy have been described. As a consequence of changes in the ATP/AMP ratio, autophagy could be promoted by the energy sensor AMP-dependent AMPK. Phosphorylation of the AMPKα Thr^{172} was observed in a large panel of cell lines after 2-DG treatment [48,49,56–60]. In lung cancer cell lines, AMPK activation was LKB1-dependent and followed by the inhibition of mTOR activity and the decreased phosphorylation of its downstream effector p70S6 Kinase, a translational regulator [56,57]. A similar pathway was described in the prostate cancer cell line LNCaP and in glioma cell lines when exposed to 2-DG [48,58]. In glioma cell lines T98G and LN-229, the level of induced autophagy could be correlated to the activity of elongation factor-2 (eEF-2) kinase, a calcium/calmodulin-dependent enzyme that phosphorylates eEF-2, leading to loss of affinity of this elongation factor for the ribosome and to termination of protein elongation. The silencing of eEF-2 kinase reduced 2-DG-activated autophagy by more than 50% [58]. 2-DG-induced autophagy could also be linked to endoplasmic reticulum (ER) stress. In human pancreatic epithelial carcinoma cells (MIA PaCa2), ER calcium efflux activated the CaMKKβ (Ca^{2+}/calmodulin-dependent kinase kinase β) which targeted AMPKα at Thr^{172} [52,53]. In most cases, autophagy was associated with resistance to apoptosis and the cytotoxicity of 2-DG could be enhanced by autophagy inhibition [45,48,54].

2.4. 2-DG induces sirt1/β-TrCP-dependent proteolytic events

Besides ATP levels, glucose deprivation generated a decrease in the NADH/NAD^+ ratio. The increase in NAD^+ levels activated the NAD-dependent deacetylase sirtuin Sirt1 (silent information regulator 1). Sirt1 promotes chromatin compaction and repression of gene expression leading to inhibition of protein translation [61]. In the breast cancer cell line MCF-7, the levels of Sirt1 were significantly increased after exposure to 2-DG in a dose and time-dependent manner. In LNCaP cells, 2-DG induced a decrease in the intracellular NADH levels, with a maximum after 24 h treatment, as well as an increase in Sirt1 protein expression [24]. Sirt1 increased β-transducin repeat-containing protein (β-TrCP)-facilitated proteolysis through β-TrCP stabilization followed by the degradation of its substrates cyclin D1 and Sp1. Indeed, transfection with the dominant-negative form of β-TrCP completely reversed 2-DG-induced proteolysis of cyclin D1 and Sp1. Down-regulation of Sp1 was followed by decreased expression of histone deacetylases (HDAC) and H3K4 (histone 3 lysine 4) demethylases.

Then, energetic stress increased histone H3 acetylation and H3K4 methylation in the promoter region of the *Kruppel-like factor 6* (*KLF6*) gene. This epigenetic activation of KLF6 led to the expression of its downstream pro-apoptotic targets ATF3 (activating transcription factor 3), Noxa, DAPK2 (death-associated protein kinase 2) [62]. Other epigenetic regulations controlled by DNA methyltransferase 1 (DNMT1) were described in LNCaP cells treated during 48 hours with 2-DG or in glucose-starved cells [63]. Sp1 down-regulation was also associated with the reduced expression of the E3 ubiquitin ligase S-phase kinase-associated protein 2 (Skp2), which consequently stabilized β-TrCP in prostate and breast cancer cells exposed to 2-DG. Under glucose deprivation conditions, Wei et al. demonstrated that apoptosis associated with Sirt1-dependent β-TrCP stabilization was under the control of an Skp2-β-TrCP-Sp1 feedback loop [64].

2.5. 2-DG induces ER stress

Increasing evidence showed that energy restriction could lead to ER stress [53]. The ER is an important site for calcium (Ca^{2+}) storage and it is also the organelle responsible for synthesis, folding and trafficking of proteins. Alterations of Ca^{2+} levels or N-glycosylation machinery induce ER stress leading to misfolded or unfolded protein accumulation to which the organelle responds by an evolutionary conserved adaptive mechanism known as the Unfolded Protein Response (UPR). Misfolded or unfolded proteins titrate the chaperone glucose-regulated protein 78 (GRP78/BiP) away from three proximal sensors of the UPR: (1) the activated PKR-like ER kinase (PERK) which phosphorylates the eukaryotic initiation factor 2α (eIF2α) on Ser^{51} to slow down protein translation, (2) the activated inositol-requiring enzyme 1α (IRE-1α) which gains endoribonuclease activity to cleave the Xbox-binding protein 1 (XBP-1) mRNA, resulting in the synthesis of a highly active transcription factor and (3) the activating transcription factor 6 (ATF6) which translocates to the Golgi where it is cleaved and then binds ER stress response elements within the nucleus. These transcription factors allow the expression of genes encoding chaperones to increase the protein folding activity in the ER [65]. However, when ER function is strongly impaired and cannot be rescued by the UPR, ER stress-mediated apoptosis is initiated.

Glucose deprivation could lead to UPR since glucose is required for protein glycosylation. If proteins could not be correctly glycosylated, misfolded protein accumulated and the unfolded protein response could be engaged [29]. Furthermore, due to the lack of a hydroxyl group on its C-2 carbon, 2-DG equally mimics glucose as well as mannose, an essential component involved in N-linked glycosylation in the ER. Mannose is at least 10 times less concentrated in the cells than glucose. As a result, 2-DG could interfere with N-glycosylation at therapeutic doses and it could replace mannose thus increasing ER stress [29]. In pancreas carcinoma Mia PaCa2 and breast cancer SKBR3 cells, 2-DG induced UPR (up-regulation of GRP78, GRP94, and CHOP (C/Ebp-Homologous Protein) expressions) and apoptosis. In both cell lines, mannose reversed UPR when cells had been treated with low concentrations of 2-DG. At higher doses of 2-DG, mannose addition was less efficient. These data suggested that in some cellular types, at moderate dose, 2-DG cytotoxicity could be the consequence of the N-linked glycosylation alteration and activation of UPR. At higher concentration, 2-DG could activate the UPR pathway and inhibit glycolysis, both contributing to the cytotoxic effect [29,66]. In both cell lines, mannose reversed UPR when cells were treated with low concentrations of 2-DG. At higher doses of 2-DG, mannose addition was less efficient. These data suggested that in some cellular types, at moderate doses, 2-DG cytotoxicity could be the consequence of alterations of N-linked glycosylation and activation of UPR. At higher concentrations, 2-DG could activate the UPR pathway and inhibit glycolysis, both contributing to the cytotoxic effect [29,66]. In murine T cell lymphoma cell lines (TCL), ER stress and UPR activation by 2-DG was demonstrated with up-regulation of several UPR target genes (Gadd153/CHOP, Gadd34, GRP78, Edem) and cleavage of Xbp1 mRNA. Mannose transiently blocked the 2-DG-induced UPR, BH3-only protein Bim up-regulation and cell death, but it had no effect on ATP depletion. As previously described, Zagorodna *et al.* proposed that ER stress was essential for induction of TCL cell death with up-regulation of CHOP leading to increased expression of Bim and inhibition of anti-apoptotic functions of Bcl2 [25]. Nevertheless, in some cases, ER stress was also protective against 2-DG cytotoxicity [66–68].

3. Thiazolidinediones

Thiazolidinediones (TZD), including Troglitazone (TGZ, Sankyo), Rosiglitazone (RGZ, GlaxoSmithKline) and Pioglitazone (PGZ, Takeda Pharmaceuticals), constitute a family of synthetic compounds characterized by a thiazolidine-2,4-dione ring(Fig. 2). TZD are agonists of the Peroxisome Proliferator Activated Receptor gamma (PPARγ), a ligand-activated transcription factor belonging to the steroid hormone receptor superfamily, that were clinically used for the treatment of noninsulin-dependent type 2 *Diabetes mellitus* [69]. Despite the interest of TZD for the treatment of diabetes, side effects of these drugs led to their progressive withdrawal from the market. The clinical use of TGZ was stopped because of severe hepatotoxic effects. RGZ was withdrawn from the European markets because of increasing concerns about its cardiovascular safety. PGZ was also withdrawn from the market in France due to the observation of an increase in bladder cancer.

3.1. Anticancer effects of TZD

In addition to their anti-diabetic activity, TZD possess anticancer properties demonstrated *in vitro* and *in vivo* using various models. Despite promising preclinical results, clinical trials did not always display clear beneficial effects. Nevertheless, on advanced prostate cancer, a phase II trial showed that TGZ treatment

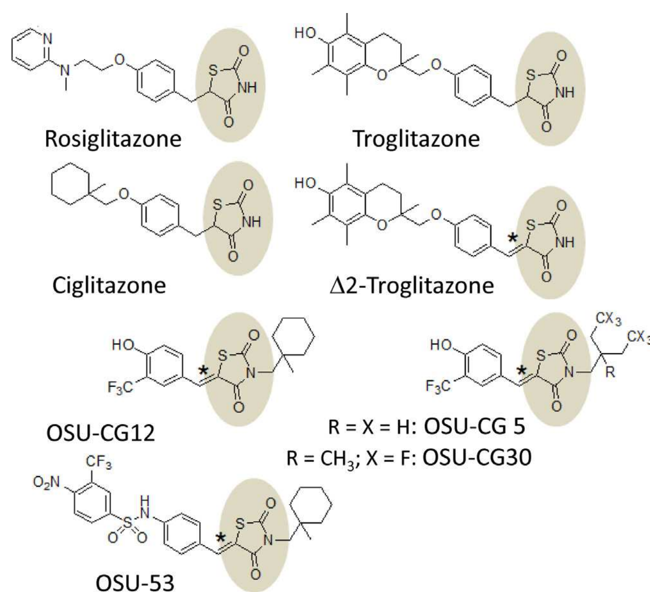

Fig. 2. Chemical structure of the main TZD discussed in this review. These molecules including rosiglitazone (RGZ) possess thiazolidine-2,4-dione rings (highlighted by the grey circle). Δ2-TGZ is a PPARγ-inactive derivative of Troglitazone (TGZ) that differs from its parent compound by a double bond (*) adjoining the TZD ring. OSU-CG5, OSU-CG12, OSU-CG30 and OSU-CG53 are Δ2 derivatives of ciglitazone (CGZ).

stabilized the prostate-specific antigen (PSA) serum concentration [70]. Moreover, a survey trial for diabetic patients showed a significant decrease of pancreatic cancer cases for those treated with RGZ compared to controls [71]. A meta-analysis including about 30,000 patients reported an overall lower incidence of cancer in diabetic patients treated with RGZ [72]. Another meta-analysis suggested that use of TZD was associated with a modest but significantly decreased risk of lung, colorectal and breast cancers [73]. Recently, a six year population-based cohort study showed a decrease in cancer risk (breast, brain, colorectal, ear-nose-throat, kidney, liver, lung, lymphatic, prostate, stomach, and uterus) in diabetic patients using TZD, and the association was dose-dependent [74].

The anticancer effects of TZD can be associated with several processes including cell differentiation, cell cycle arrest and cell death. However, the involvement of PPARγ in these anticancer effects of TZD is still unclear since many PPARγ-independent events have been reported. *In vitro*, the PPARγ-independence was demonstrated by several experiments [75]. Often, the authors could not demonstrate a correlation between the anticancer effect of TZDs and PPARγ levels. Besides, TZD anticancer action was still observable even in the presence of PPARγ antagonists or in cells where PPARγ expression was abrogated by RNA interference. *In vivo* results are also in agreement with a PPARγ-independent mechanism of action. Indeed, in a study showing a modest effect of RGZ in patients with thyroid cancer, there was no relationship between the level of PPARγ and the response to RGZ, suggesting a potential PPARγ-independent mechanism [76]. This was also in agreement with the fact that a phase I clinical trial did not reveal any beneficial effects of an association between RGZ and the RXR selective compound Bexarotene in patients with refractory cancer [77].

Since most of the anticancer effects of TZD appeared to be PPARγ-independent, several derivatives of the Δ2 family were synthesized. Such derivatives have a double bound adjoining the terminal thiazolidine-2,4-dione ring and lack PPARγ agonist activity, but still display anticancer effects (Fig. 2). For instance, Δ2-TGZ affected the viability of breast cancer cells [78]. Several derivatives of Δ2-TGZ that were functionalized on the terminal hydroxyl group of the chromane moiety increased the effect on breast cancer cell viability [79]. Some Δ2-TGZ derivatives also appeared interesting since they displayed good antiproliferative activities towards breast cancer cells and low toxicity towards human hepatocytes [80]. Compared to their respective parent compound, Δ2-TGZ and Δ2-CGZ inhibited prostate cancer cell proliferation more efficiently in both PPARγ-expressing PC-3 cells and PPARγ-deficient LNCaP cells [81]. OSU-CG12 is an inactive PPARγ derivative of Δ2-CGZ, in which a permutational rearrangement of the terminal methylcyclohexylmethyl moiety, led to an inverted molecule where the TZD ring was at the center of the molecule, and in which the phenyl ring was functionalized with a trifluoroacetate group (Fig. 2) [82]. OSU-CG12 affected the viability of LNCaP prostate cancer cells with an IC_{50} around 6 μM whereas it displayed poor toxicity towards nonmalignant prostate epithelial cells [24]. OSU-CG5, an OSU-CG12 derivative in which the terminal methylcyclohexyl ring was replaced by a 3-pentyl moiety (Fig. 2), was more potent in suppressing cell viability in LNCaP cancer cells [63]. OSU-CG5 was more potent than its parent compound OSU-CG12 in suppressing LNCaP cancer cells viability (IC_{50} = 4.5 μM versus 6 μM) [63]. When administrated orally to male transgenic adenocarcinoma of the mouse prostate (TRAMP) mice, OSU-CG5 also suppressed prostate epithelial proliferation and preneoplastic lesions [83]. Optimisation of OSU-CG5 led to compound OSU-CG30 where two terminal methyl functions of the hydrophobic side chain were replaced by CF_3 groups (Fig. 2). The effect of OSU-CG30 on the viability of LNCaP prostate cancer cells was higher than those of OSU-CG12 (IC_{50} = 1.5 μM) while no cytotoxicity was observed on normal prostate and mammary epithelial cells [84]. The introduction of an additive phenylsulfonamide on the OSU-CG12 compound led to the new derivative OSU-53 (Fig. 2) [85]. This compound inhibited the viability and clonogenic growth of MDA-MB-231 and MDA-MB-468 breast cancer cells whereas nonmalignant MCF-10A cells were unaffected [85]. In MDA-MB-231 tumor-bearing mice, daily oral administration of OSU-53 (50 and 100 mg/kg) suppressed tumor growth by 47–49% [86].

3.2. TZD induce apoptosis

In prostate cancer cells, Δ2-TGZ and Δ2-CGZ were more effective than TGZ and CGZ in inducing cytochrome c release and DNA fragmentation whereas marginal effect was observed with potent PPARγ agonists RGZ and PGZ and their Δ2 derivatives [81]. The induction of apoptosis by TZD is caspase-dependent and depends of intrinsic and extrinsic pathway activation. For example, TZD18, a dual PPARα/PPARγ agonist that inhibits cell proliferation in a PPARγ-independent manner, induced apoptosis of SD1 and BV173 leukemic cells by cleavage of caspases-9 and -8. This effect was disrupted by the pan-caspase inhibitor Z-VAD-FMK [87]. In bladder cancer cells T24 and RT4, TGZ induced the cleavage of caspase-9, -8 and -3 independently of PPARγ, and specific caspase inhibitors abolished TGZ-induced apoptosis [88]. Similar results were obtained with CGZ on T24 bladder cancer cells [89]. In MCF-7 and MDA-MB-231 breast cancer cells, Δ2-TGZ changed mitochondrial membrane potential and induced cleavage of PARP and caspase-7, events that were abolished in the presence of the pan-caspase inhibitor Z-VAD-FMK [90]. TZD activated the intrinsic apoptotic pathway by modulating expression of Bcl-2 family members. In human leukaemia cells, TZD18 up-regulated the proapoptotic protein Bax whereas the expression of the anti-apoptotic Bcl-2 remained unchanged [87]. TZD18 also up-regulated Bax and Bak expression in MCF-7 and MDA-MB-231 breast cancer cells [91]. TGZ increased the Bax/Bcl2 mRNA ratio in renal cell carcinoma whereas the expression level of Bcl-2 members was not altered in PC-3 prostate cancer cells [81,92]. Nevertheless, TGZ, CGZ and their Δ2 counterparts inhibited the anti-apoptotic function of Bcl-2 and Bcl-X_L by disrupting their heterodimerization with Bax, leading to cytochrome c release and caspase-9 activation [81]. In the PPARγ-deficient cell line LNCaP, Bcl-X_L overexpression protected cells against TGZ and Δ2-TGZ-induced apoptosis [81]. The recently identified membrane G protein-coupled receptor 40 (GPR40) can be activated by TZD [93]. This induction leads to osteocyte apoptosis after Bax recruitment to the outer mitochondrial membrane.

The anticancer action of OSU-CG12 in prostate and breast cancer cells was associated with apoptosis induction evidenced by the cleavage of PARP [24]. This was in agreement with an increase in the proapoptotic proteins ATF3, Noxa and DAPK2 [62]. PARP cleavage was also observed in LNCaP cells exposed to OSU-CG30 [84]. In the breast cancer cell lines MDA-MB-231 and MDA-MB-468, the induction of apoptosis by OSU-53 was suggested by the cleavage of PARP and increases in the sub-G1 apoptotic population [86]. These authors also observed PARP cleavage *in vivo* in MDA-MB-231 tumors of nude mice treated with OSU-53. This compound did not induce PARP cleavage in the control cells MCF-10A. OSU-53 also induced

As observed with 2-DG, TZD could also be used in combination treatments. For instance, TZD sensitized tumor cells to TRAIL-induced apoptosis [88,94–97]. In lung cancer cells, the cleaved forms of PARP and caspase-8, -9 and -3 were easily detected after a treatment with TRAIL and TZD compared to treatments with TRAIL or TZD alone [96]. TZD promotes TRAIL-induced apoptosis by the increase of DR5 expression and down-regulation of c-FLIP (cellular

Flice-like inhibitor protein) or survivin [88,95–97]. In lung cancer cells, overexpression of c-FLIP and silencing of DR5 expression by RNA interference abrogated the enhancement of TRAIL-induced apoptosis by PPARγ ligand [96]. Moreover, TGZ and CGZ up-regulated TRAIL expression in TRAIL-resistant T24 bladder cancer cells and potentiated TRAIL-induced apoptosis through activation of death receptor signaling pathway [88,89].

3.3. TZD induce autophagy

In HeLa cells, TGZ promoted autophagy, manifested by AMPK phosphorylation, LC3-II accumulation and degradation of a selective substrate of autophagy, sequestome 1 (SQSTM1/p62), which precedes and contributes to caspase-dependent apoptosis [98]. TGZ also promoted autophagosome formation and accumulation of LC3-II in porcine aortic endothelial cells [99]. This process was correlated with AMPK phosphorylation and was independent of PPARγ. TGZ and RGZ could also induce autophagy by PPARγ-activation in MDA-MB-231 breast cancer cells [100]. In H295R adrenocortical cancer cells, RGZ inhibited cell proliferation through both PPARγ-dependent and PPARγ-independent mechanisms and triggered an autophagic process associated with increased levels of p-AMPK and to the expression of beclin-1 [101]. Autophagy-mediated cell death by RGZ was dependent on the cellular context since this process was not observed in SW13 adrenocortical cancer cells. RGZ-induced autophagic process in H295R cancer cells seemed to be related to an increase in oxidative stress mediated by reactive oxygen species (ROS) production with disruption of the mitochondrial membrane potential [101]. NAF-1 (Nutrient-deprivation autophagy factor-1) and CDGSH iron sulfur domain 1 protein (mitoNEET), two members of NEET fold (Asn-Glu-Glu-Thr) protein family, play a key role in the maintenance of mitochondrial integrity as well as cellular iron and ROS homeostasis. NAF-1 and mitoNEET accumulate in MCF-7, MDA-MB-468 and HCC-70 human epithelial breast cancer cells compared to control MCF-10A breast cancer cells. The knockdown of these proteins using small hairpin (sh)RNA in MCF-7 and MDA-MB-231 breast cancer cells results in a significant decrease in cell proliferation and tumor growth, a decrease in mitochondrial membrane potential, an accumulation of ROS in mitochondria and activation of autophagy [102]. NAF-1 and mitoNEET could be mitochondrial targets of TZD [103–105].

In LNCaP prostate cancer cells, OSU-CG12 induced autophagy as illustrated by LC3-II accumulation into autophagic vacuoles [24]. OSU-CG12 induced AMPK phosphorylation after 10 min of exposure followed by down-regulation of mTOR and p70S6 K phosphorylation. Inhibition of the function of AMPK by expressing a dominant-negative form or by a pharmacological agent prevented LC3-I to LC3-II conversion and autophagy [24]. This inhibition of autophagy reduced the effect of OSU-CG12 on cell viability of LNCaP cells exposed, whereas it did not affect PARP cleavage [24].

OSU-53 induced a protective autophagy that attenuated its antiproliferative potency [86]. Indeed, cell viability was less affected by this compound when MDA-MB-231 breast cancer cells expressed a dominant negative form of AMK. In this context, co-treatment with the autophagy inhibitor chloroquine increased the *in vitro* antiproliferative activity and the *in vivo* tumor-suppressive effects of OSU-53 [86].

3.4. Some TZD act as ERMAs

A few TZD have been shown to act as ERMAs. For instance, this hypothesis was validated for OSU-CG12 in prostate cancer cells LNCaP [24]. High levels of supplemental glucose protected these cells against OSU-CG12-induced cell death. This compound triggered cellular responses characteristic of energy restriction in LNCaP cells and MCF-7 breast cancer cells [24]. These responses could be achieved at 5 μM compared to 5 mM for 2-DG [24]. OSU-CG12 decreased glycolytic rate and intracellular levels of lactate and NADH. As a result of the changes in the ATP/AMP ratio, OSU-CG12 also induced AMPK activation. In less than 20 min of OSU-CG12 exposure, there was a modest decrease in $[^3H]$2-DG uptake. In RT-PCR analyses performed after 24 h of treatment with OSU-CG12, there was a decrease in mRNA levels of hexokinase 2 and phosphofructokinase-1, the first two enzymes of the glycolytic pathway.

OSU-CG5 was also more potent to suppress $[^3H]$-2DG uptake in these cells (IC_{50} = 6 μM versus 9 μM for OSU-CG12). Optimization of OSU-CG5 led to OSU-CG30 that exhibited high potency in blocking glucose uptake into LNCaP cells with IC_{50} of 2.5 μM compared to 6 μM and 9 μM for OSU-CG5 and OSU-CG12 respectively [84]. Modeling analysis revealed that OSU-CG30 inhibits glucose entry *via* its ability to bind to the GLUT1 channel at a site distinct from that of glucose [84].

OSU-53 induced increased AMPK phosphorylation levels and a decrease in the phosphorylation of p70S6 K in C-26 colon adenocarcinoma cells [85]. Radiometric kinase assays performed with a recombinant AMPK α1β1γ2 showed that OSU-53 directly stimulated kinase activity with an EC_{50} of 0.3 μM compared to 8 μM for AMP [86]. In breast cancer cells, OSU-53 inhibited the viability and clonogenic growth not only of MDA-MB-468 (LKB1 positive) but also of MDA-MB-231 (LKB1 negative) with nearly equal potency whereas nonmalignant MCF-10A cells were unaffected. This result was in agreement with a direct activation of AMPK rather than a LKB1 mediated process. OSU-53 also targeted multiple AMPK downstream pathways [86].

The key starvation-associated responses to these compounds include transient Sirt1 induction and proteolytic events, ER stress, each of which mediates a distinct signaling pathway culminating in the anti-proliferative effects (Fig. 3).

3.5. TZD induce sirt1/β-TrCP-dependent proteolytic events

As observed in cells exposed to 2-DG, the transient increase of Sirt1 expression in cells treated with OSU-CG12 played a crucial role in mediating apoptosis induction. Sirt1 induced the accumulation of β-TrCP through its stabilization [24] by down-regulation of β-TrCP-specific E3 ligase Skp2 expression resulting in decreased ubiquitin-dependent degradation of β-TrCP [64]. β-TrCP facilitated proteasomal degradation of a series of cell cycle and apoptosis regulatory proteins, including β-catenin, cyclin D1 and Sp1

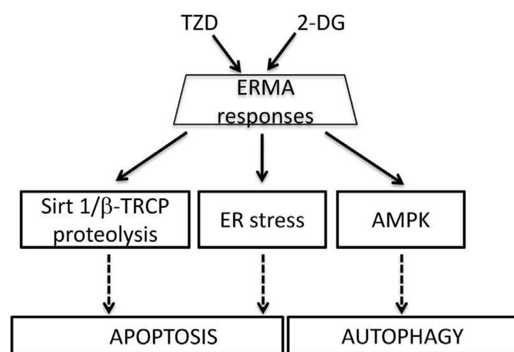

Fig. 3. Responses induced by 2-DG and TZD. Although they act through different initial mechanisms, both 2-DG and some TZD induce a reduction of the glycolytic rate. In cancer cells, they trigger apoptosis and autophagy, the latter being either protective in case of 2-DG and OSU-53 or involved in the cytoxicity in case of OSU-CG12. Sirt1/β-TRCP proteolytic events, ER stress and AMPK activation are early events typical of these two types of ERMAs.

[24,106,107]. As observed with 2-DG, the down-regulation of Sp1 facilitated the transcriptional repression of histone deacetylases and H3K4 demethylases resulting in epigenetic activation of the tumor suppressor KLF6 which plays a role in apoptosis induction [62].

Like OSU-CG12, its derivative OSU-CG5 up-regulated DNA methylation-silenced tumor suppressor genes and down-regulated methylated tumor/invasion-promoting genes. These epigenetic effects were the result of transcriptional repression of DNMT-1 [63]. OSU-CG30 also activated ERMAs-associated cellular responses such as β-TrCP-mediated protein degradation [cyclinD1, Sp1] and epigenetic activation of KLF6, both leading to apoptosis [84].

3.6. TZD induce ER stress

As observed in cells exposed to 2-DG, OSU-CG12 also induced ER stress. The phosphorylation of eIF2α at Ser^{51} appeared clearly after 6 h of treatment (10 μM). After 48 h of exposure to 5 μM of OSU-CG12, LNCaP cells showed an up-regulation of IRE-1α and the chaperone GRP78. An up-regulation of CHOP was also observed at this time, but it seemed to appear only after treatment with higher doses (10–20 μM). The silencing of CHOP had no effect on the susceptibility to the antiproliferative action of OSU-CG12 and on PARP cleavage [24].

OSU-CG12 showed higher anti-proliferative potencies than resveratrol and 2-DG. Indeed, the energy restriction-associated responses could be achieved at 5 μM compared to 100 μM and 5 mM for resveratrol and 2-DG respectively [24]. Moreover, OSU-CG12 displayed low toxicity to nonmalignant prostate epithelial cells and no effect on the levels of β-TrCP or Sp1 could be observed in these cells. ER stress did not appear as a mediator of OSU-CG12-induced apoptosis.

OSU-CG5 increased the levels of ER stress response proteins GRP78 and GADD153/CHOP in colorectal cancer cells HCT-116 and Caco-2 [108].

3.7. Future prospects

It might be interesting to determine if other TZD, and especially those of the Δ2 family that act in a PPARγ-independent manner, also exert their anticancer effects via an energy restriction mimetic activity. The fact that TGZ or Δ2-TGZ induce cellular responses similar to those of 2-DG in addition to apoptosis and autophagy, including Sirt1/β-TrCP-dependent proteolytic events and ER stress, could be in agreement with this idea. Indeed, the occurrence of apoptosis and autophagy in response to TGZ or Δ2-TGZ treatment was also reported in several studies performed in several cellular models [75,90,98–100]. Besides, several teams demonstrated that TGZ or Δ2-TGZ trigger ER stress in various cancer cell lines [75]. Proteolytic events, especially cyclin D1 degradation, have also been described as a common effect of TGZ or Δ2-TGZ [79,109]. It will be important in the future to determine if nutrient stress sensors, glycolytic rate and lactate production are affected by these compounds. We recently identified Δ2-TGZ derivatives that affect cancer cells more efficiently and display a lower toxicity towards hepatocytes than TGZ [80,110]. These derivatives could replace 2-DG which displayed hepatotoxicity leading the FDA to suspend its clinical trial for advanced prostate cancer [111]. Such TZD could have an interest for cancer therapy, especially in some resistant forms (such as lapatinib-resistant breast cancer, or ovarian cancer resistant to many conventional anticancer agents) that are sensitive to glucose deprivation [112,113]. As observed for 2-DG, these compounds could also improve at low dose the efficiency of chemotherapy or radiotherapy and further lead to personalization of cancer treatment [114].

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