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Minireview

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Antitumor effects of energy restriction-mimetic agents: thiazolidinediones

Abstract: Distinct metabolic strategies used by cancer cells to gain growth advantages, such as shifting from oxidative phosphorylation to glycolysis, constitute a basis for their selective targeting as a novel approach for cancer therapy. Thiazolidinediones (TZDs) are ligands for the nuclear transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) and they are clinically used as oral hypoglycemic agents. Accumulating evidence suggests that the ability of TZDs to suppress cancer cell proliferation through the interplay between apoptosis and autophagy was, at least in part, mediated through PPARγ-independent mechanisms. This review highlights recent advances in the pharmacological exploitation of the PPARγ-independent anticancer effects of TZDs to develop novel agents targeting tumor metabolism, including glucose transporter inhibitors and adenosine monophosphate-activated protein kinase, which have translational potential as cancer therapeutic agents.

Keywords: cancer; glucose starvation; glycolysis inhibition; peroxisome proliferator-activated receptor gamma (PPARγ); thiazolidinediones; Warburg effect.

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Introduction

The use of energy restriction-mimetic agents (ERMAs) to selectively target cancer cells based on the differential susceptibility of malignant *versus* normal cells to glycolysis inhibition has gained growing interest due to the promising results from animal and human trials (De Lena et al., 2001; Milane et al., 2011). Transformed cells shift from oxidative phosphorylation to glycolysis as the major source of energy production, even in the presence of adequate oxygen. This glycolytic shift is considered as an adaptive metabolic change that confers many survival advantages to cancer cells, the so-called Warburg effect (Hsu and Sabatini, 2008; Kaelin and Thompson, 2010). Tumor cells typically have a glycolysis rate up to 200 times higher than those of normal cells, and the produced lactate is used as a biosynthetic intermediate for the synthesis of nucleic acids, proteins, and fatty acids needed for rapid cell proliferation (Hsu and Sabatini, 2008; Holley et al., 2012). Thus, cancer cells are highly vulnerable to energy restriction through glycolysis inhibition. However, it is generally difficult to implement chronic caloric restriction through reduced energy intake in humans. ERMAs are used to cause a state of glucose starvation in cancer cells by inhibiting various aspects of glucose metabolism without caloric restriction. ERMAs have many putative targets, such as adenosine monophosphate-activated protein kinase (AMPK), phosphohexose isomerase, pyruvate kinase, hexokinase II, pyruvate dehydrogenase kinase and ATP citrate lyase (Omar et al., 2010).

Energy restriction-mimetic agents

Several agents have been developed to induce starvation-associated responses without dietary caloric restriction, such as 2-deoxyglucose (2-DG) which blocks glycolysis through the inhibition of phosphohexose isomerase (Sols and Crane, 1954; Tower, 1958), leading to depletion of ATP and glycolytic intermediates. 2-DG successfully inhibits

the growth of many types of tumors as a single agent or in combination with other chemotherapeutic agents (Omar et al., 2010). Resveratrol, (3, 4′, 5-trihydroxystilbene), a naturally occurring phytoalexin is one of the earliest identified ERMAs and is widely reported to possess both chemopreventive and chemotherapeutic activities in several cancers that are attributable, in part, to its energy restriction-mimetic effects (Bishayee, 2009; Lin et al., 2010). Many molecular targets have been identified for resveratrol; however, its exact underlying anticancer mechanism is not completely understood. Resveratrol modulates many signal transduction pathways associated with tumorigenesis, and it is likely to possess a collective mechanism of action, rather than just a single effect (Whitlock and Baek, 2012). The weak potency of resveratrol and 2-DG greatly challenges their clinical applications and highlights the need for more efficient ERMAs.

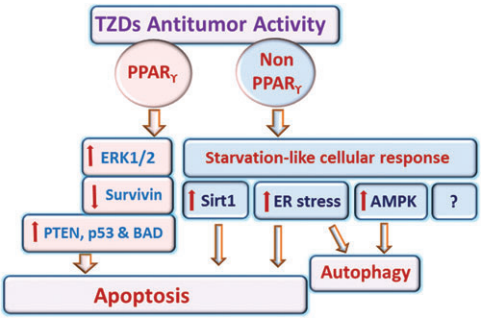

Figure 1 PPARγ-dependent and independent effects of thiazolidinedione (TZDs).
TZDs with PPARγ-dependent effects elicit their action through binding to PPARγ-response elements (PPREs), which requires initial heterotrimer formation of TZDs with retinoid X receptor and PPARγ proteins. This pathway resulted in insulin like effects. TZDs with PPARγ-independent effects induce starvation like cellular response that leads to autophagy through activation of adenosine monophosphate-activated protein kinase or apoptosis through transient induction of *Sirt1* and endoplasmic reticulum stress.

Antitumor activity of thiazolidinediones

Thiazolidinediones (TZDs), such as troglitazone, rosiglitazone, pioglitazone, and ciglitazone are high-affinity ligands for the nuclear transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) and they are clinically used as oral hypoglycemic agents in patients with type 2 diabetes mellitus (Panchapakesan et al., 2005). The activation of PPARγ by TZDs causes transcriptional activation of insulin-sensitive genes involved in glucose homeostasis in a manner mimicking the genomic effects of insulin (Olefsky, 2000; Wei et al., 2010). In addition, TZDs have been reported to decrease the risk of colorectal (Chen et al., 2013), lung and breast cancers in diabetic patients (Colmers et al., 2012). The antitumor activities of TZDs are mediated through the induction of cell cycle arrest, apoptosis, and redifferentiation (Jiang et al., 2004; Weng et al., 2006). While the exact antiproliferative mechanisms of TZDs remain elusive, accumulating evidence indicates that TZDs have both PPARγ-dependent and -independent mechanisms (Figure 1) (Weng et al., 2006). PPARγ-dependent mechanisms include the induction of pro-apoptotic proteins, phosphatase and tensin homolog (PTEN), p53, and BAD; and decreasing the level of the anti-apoptotic proteins Bcl-2, Bcl-xL, and survivin (Blanquicett et al., 2008), accompanied by the down-regulation of ERK1/2, which induce apoptosis via the mitochondrial pathway (Li et al., 2006). The PPARγ-independent action of TZDs, which targets multiple signaling pathways, is mediated through the energy restriction mimetic effect and the induction of starvation-associated cellular responses (Wei et al., 2009, 2010; Omar et al., 2012).

Energy restriction-dependent antiproliferative activity of thiazolidinediones

Troglitazone and ciglitazone, in relatively high doses, mimic glucose starvation and elicit cellular responses characteristic of energy restriction *in vitro* and *in vivo* against many types of cancer cells, thereby providing a rationale for developing TZDs as chemotherapeutic or chemopreventive agents (Panigrahy et al., 2003; Wei et al., 2010). PPARγ-active TZDs, troglitazone and ciglitazone and the newly-developed PPARγ-inactive derivatives, STG28, and CG12, have been shown to induce hallmark energy restriction-induced cellular responses in different cancer cell lines (Wei et al., 2010). The energy restriction-induced cellular responses of TZDs include decreased glycolytic rate, induction of the *silent information regulator 1* gene (*Sirt1*), activation of AMPK, and induction of endoplasmic reticulum stress (ER stress) (Wei et al., 2010). *Sirt1* regulates a broad spectrum of non-histone signaling proteins via deacetylation and plays a crucial role in mediating the induction of apoptosis by ERMAs through the activation of the ubiquitin E3 β-transducin repeat containing protein (β-TrCP)-facilitated proteolysis (Wei et al., 2010). Activated β-TrCP facilitates proteasomal degradation of the transcription factors β-catenin, cyclin

D1, and Sp1, and leads to the transcriptional repression of their respective target genes (Panigrahy et al., 2003; Wei et al., 2010). TZDs also facilitate the activation of AMPK, an intracellular fuel sensor, as an energy-restriction cellular response (Wei et al., 2010). AMPK activation promotes autophagy through two mechanisms: inhibition of mTOR complex1, an autophagy inhibitor, and activation of autophagy initiating kinase1 (ULK1) (Egan et al., 2011; Kim et al., 2011; Shang et al., 2011). Another energy restriction cellular response to TZDs is the induction of ER stress that is known to initiate both apoptosis and autophagy (Szegezdi et al., 2006; Sano et al., 2012).

Pharmacological exploitation and structural optimization of thiazolidinediones

The dissociation of PPARγ-independent antitumor activity of TZDs from PPARγ activity was confirmed by structural modifications (Shiau et al., 2005). For example, the introduction of a double bond adjoining the terminal thiazolidinedione ring of troglitazone and ciglitazone abrogates the PPARγ ligand activity and the resulted derivatives, Δ2TG and Δ2CG (structures shown in Figure 2) exhibit higher antitumor potency relative to their parent compounds (Shiau et al., 2005). Moreover, Δ2TG and Δ2CG retain the ability of their parent compounds to target many key signaling effectors governing the cell cycle regulation and apoptosis (Huang et al., 2005; Wei et al., 2008). The pleiotropic mode of action of these compounds arises from their ability to mimic the condition of glucose deprivation by inhibiting glucose transporters (Wei et al., 2010).

From a translational perspective, these findings provide a mechanistic rationale for the use of Δ2CG, a ciglitazone derivative, as a scaffold to develop a novel class of glucose transporter inhibitors (Wang et al., 2012a). Permutation of Δ2CG, followed by modifications at the terminal phenolic and hydrophobic moieties, lead to the discovery of glucose transporter inhibitor compounds CG-5, CG-12 and CG-30 (Figure 2), which exhibit at least an-order-of-magnitude higher potency relative to Δ2CG. Homology modeling analysis suggests that compound CG-30 inhibits glucose entry via its ability to bind to the GLUT1 channel at a site distinct from that of glucose; and that the higher potency of compound CG-30 might be attributable to the two additional terminal CF3 functions that aid electrostatic interactions with the binding pocket (Wang et al., 2012a).

CG-5 induces cellular responses in cancer cells similar to that caused by glucose deprivation (Lin et al., 2012). It increases the expression levels of a multitude of DNA methylation-silenced tumor suppressor genes, such as *GADD45a*, *GADD45b*, *LAMB3*, *BASP1*, *GPX3*, *IGFBP3*, and *GSTP1*, and decreases the expression levels of tumor/invasion-promoting genes such as *CD44*, *S100A4*, and *TACSTD2*. The epigenetic actions of CG-5 are mediated by transcriptional inhibition of DNA methyl transferase 1 and reduced expression of both Sp1 and E2F1 (Lin et al., 2012).

CG-12, another novel PPARγ-inactive ERMA with enhanced anti-proliferative activity, elicits hallmark

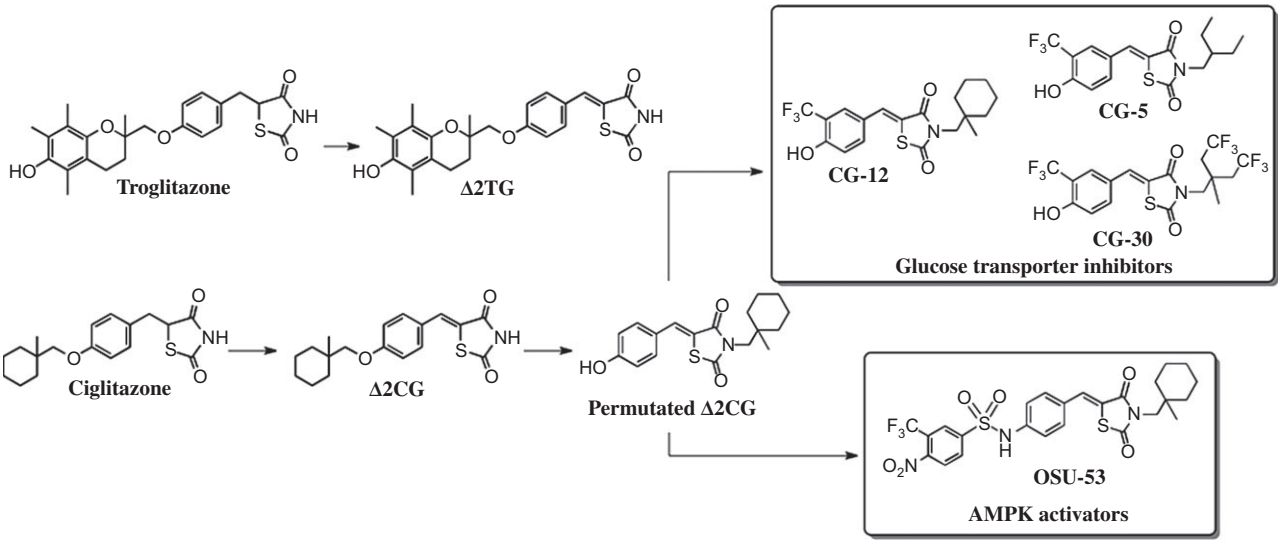

Figure 2 Chemical structures of troglitazone, and ciglitazone, and their respective PPARγ-inactive Δ2 derivatives (Δ2TG, Δ2CG, permutated Δ2CG, CG-12, CG-5, CG-30, and OSU-53).

cellular responses characteristic of energy restriction and induces apoptosis in transformed cells (Chen et al., 2011; Wei et al., 2012a). The anti-proliferative activity of CG-12 is mediated through activation of the intracellular fuel sensor (AMPK), ER stress, epigenetic activation of *Krueppel-like factor 6* tumor suppressor gene expression, and down-regulation of E3 ubiquitin ligase S-phase kinase-associated protein 2 (Skp2) (Chen et al., 2011; Wei et al., 2012a). Initial *in vitro* studies showed that CG-12 exhibited higher anti-proliferative activity than resveratrol in the human breast adenocarcinoma MCF-7 and the human prostate cancer LNCaP cell lines (Wei et al., 2010). However, more studies are needed to compare the *in vivo* antitumor activities and clearly reveal the exact mechanism of action of CG-12.

OSU-53, a direct adenosine monophosphate-activated protein kinase activator

The activation of AMPK and induction of ER stress by TZDs are key targets for selective cancer cell killing during caloric restriction (Saito et al., 2009; Omar et al., 2012). In addition to PPARγ, the role of AMPK in regulating energy homeostasis and insulin sensitivity is well recognized (Kahn et al., 2005; Hardie, 2007). It was demonstrated that the unique ability of the TZD family of PPARγ agonists to mediate AMPK activation was independent of their PPARγ activity (Guh et al., 2010) (Figure 1). Consequently, Δ2CG was pharmacologically exploited to develop novel AMPK activators, which led to the development of OSU-53 (Guh et al., 2010) (Figure 2). Evidence indicates that OSU-53 is a potent direct activator of AMPK (half maximal effective concentration in activating recombinant AMPK, 0.3 μM) by binding to the autoinhibitory domain (Lee et al., 2011). Beyond AMPK-mediated suppressive effects on mTOR signaling and lipogenesis, OSU-53 also targets multiple AMPK downstream pathways, such as the phosphatase 2A-dependent dephosphorylation of Akt that circumvents the feedback activation of Akt that results from mTOR inhibition (Lee et al., 2011). In addition, OSU-53 modulates energy homeostasis by shifting the metabolism to oxidation by suppressing fatty acid biosynthesis and increasing the expression of key regulators of mitochondrial biogenesis, such as a PPARγ coactivator 1α and the transcription factor nuclear respiratory factor 1 (Lee et al., 2011). Daily oral administration of OSU-53 effectively suppresses MDA-MB-231 xenograft tumor growth in nude mice, indicating its oral bioavailability (Lee et al., 2011).

Opportunities and challenges

The unique antiproliferative mechanism of TZDs, through the interplay between autophagy and apoptosis, underlies the potential of their combination with other antitumor agents to foster a novel therapeutic strategy. The induction of multiple starvation-associated responses, which mimic the actual glucose starvation condition, counteracts the abilities of cancer cells to resist chemotherapeutic agents via metabolic adaptation. Metabolomics, the study of the metabolic network in cancer to enhance disease understanding, can be used as an important tool for identifying the susceptible phenotype for each type of tumor metabolism-targeted combination (Wang et al., 2012b; Wei et al., 2012b). Lapatinib-resistant breast cancer, which is usually associated with poor prognosis, is a possible candidate for the use of the combination therapy with TZDs since it is sensitive to glucose deprivation and has enhanced rates of glucose processing (Locasale, 2012). Similarly, ovarian cancer cells while resistant to many conventional antitumor agents are sensitive to glucose deprivation, suggesting a new clinical strategy for personalized ovarian cancer therapy (Priebe et al., 2011). However, the heterogeneous nature of metabolics in the tumor microenvironment during the course of therapy may render the cells less sensitive to glucose deprivation (Cairns et al., 2011). In prostate cancer, for example, energy generation through fatty acid oxidation might become an alternative bioenergetic pathway that can limit the tumor's sensitivity to pharmacological intervention using ERMAs (Liu, 2006).

It warrants attention that the pleiotropic mechanism of action of TZDs, like many other anticancer agents, while offering therapeutic advantages against cancer cells, might impose adverse effects on normal cells (Omar et al., 2009). Hepatotoxicity was reported for 2-DG so the US Food and Drug Administration has suspended its clinical trial for advanced prostate cancer (NCT00633087) (Omar et al., 2010). Consequently, *in vivo* studies are thus required to determine the possible untoward effects of these compounds. In addition, these ERMAs lack the comprehensive pharmacokinetic studies that are required as a critical preceding step to clinical trials. In light of the translational potential of TZDs in fostering effective strategies for cancer treatment, the development of more effective members of TZDs and the elucidation of their mechanism of action and safety margins merit continued investigations.

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