Future ONCOLOGY

EDITORIAL

Potential targets of energy restriction mimetic agents in cancer cells



Hany A Omar*[1,2], Mai F Tolba[3,4] & Maha M Saber-Ayad[2,5]

Unlike normal cells, cancer cells often shift their metabolism from oxidative phosphorylation to aerobic glycolysis as an adaptive response to intermittent hypoxia and the robust demand for energy production, the so-called Warburg effect described in 1924 [1]. However, the high need of glucose and the lack of flexibility in modifying energy resources make cancer cells extremely vulnerable to glucose starvation and energy restriction [2,3]. Targeting cancer cells by energy-restriction mimetic agents has gained a growing interest due to their ability to provide the benefits of dietary energy restriction without reducing caloric intake by patients [4]. Understanding the features and potential targets of the recently developed energy-restriction mimetic agents will help to develop new approaches in early diagnosis and effective cancer therapy.

KEYWORDS
• AMPK • cancer • energy restriction
• Warburg effect

Energy-restriction mimetic agents main classes & proposed targets

Many energy-restriction mimetic agents (ERMAs) have been developed since the introduction of dietary energy restriction (DER) as a strategy in targeting cancer. The competitive inhibitor of glucose metabolism, 2-deoxyglucose (2-DG), was among the early studied ERMAs and it works via the activation of AMP-activated protein kinase and Sirt-1 and the inhibition of Akt [5]. 2-DG was not only effective in preventing carcinogenesis, but also in targeting cancer stem cells, which are dependent on fermentative glycolysis such as breast cancer [6].

Thiazolidinediones were then introduced to mimic energy restriction by increasing the expression of Sirt1 that plays a crucial role in mediating the induction of apoptosis through the activation of β-TrCP-facilitated proteolysis [7]. The action of thiazolidinediones as ERMAs suggested the interplay between autophagy and apoptosis as a key contributor to their antiproliferative activities. Interestingly, the antiproliferative effect of this drug class is independent of its PPAR-γ stimulatory action [8]. Herein, we are highlighting the

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[1]Department of Pharmacology, Faculty of Pharmacy, Beni-Suef University, Egypt
[2]Sharjah Institute for Medical Research, College of Pharmacy, University of Sharjah, Sharjah, UAE
[3]Department of Pharmacology & Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt
[4]Biology Department, School of Science & Engineering, American University in Cairo, New Cairo, Egypt
[5]Department of Pharmacology, Faculty of Medicine, Cairo University, Kasr Al Ainy, Egypt
*Author for correspondence: Tel.: +002 010 0088 2828; Fax: +002 082 231 7958; omar.22@buckeyemail.osu.edu

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updates regarding ERMAs' targets, including AMPK, tumor suppressor genes, glucose transporters and glycolysis.

• Activation of AMPK

AMP-activated protein kinase is an attractive target for cancer therapy. Activation of AMPK can induce cytotoxic effects through modulating multiple mechanisms. Epithelial–mesenchymal transition (EMT) is a key player in tumor metastasis via conferring an invasive phenotype [9]. Activation of AMPK using a small molecule C19 triggered GSK3-β-induced degradation of the downstream Hippo transducer TAZ leading to repression of EMT [10]. Exposure of cancer cells to OSU-53, which is a novel allosteric AMPK activator led to suppression of EMT via the modulation of Akt/MDM2/Foxo3 pathway [11]. In addition, the exposure to AMPK activators such as metformin and amino-imidazole-4-carboxamide ribonucleotide reversed the cells' mesenchymal phenotype [11]. Several studies indicated that AMPK activation leads to enhanced apoptosis in cancer cell lines of different origin [12,13].

Mammalian target of rapamycin (mTOR) is considered a key nutrient sensor that regulates cell growth and fate via synchronizing a multitude of upstream signaling pathways and environmental triggers [14]. AMPK activation inhibits mTOR signaling in ovarian tumors from mice maintained on a calorie restricted diet. This sheds a light on the possible role of energy metabolism in the pathogenesis of ovarian cancer [15]. In hormone-refractory prostate cancer, the novel anthraquinone derivative CC-36 exhibited antiproliferative activity via the activation of AMPK and liver kinase B1 leading to abrogation of mTOR signaling [16].

• Activation of KLF6 tumor suppressor gene

KLF6 is a zinc-finger tumor suppressor that is frequently mutated in various types of cancers [17]. The activation of KLF6 is another mechanism for the induction of apoptosis by ERMAs. Studies conducted by Chen *et al.*, in prostate cancer cells showed that ERMAs as OSU-CG12 epigenetically regulates KLF6 through increasing histone H3 acetylation and histone H3 lysine 4 trimethylation at the promoter region [18].

• Activation of silenced tumor suppressor genes

The epigenetic effects of ERMAs such as OSU-CG12 and its optimized derivative, CG5 have been attributed to their ability to decrease the methylation of silenced-tumor suppressor genes via the downregulation of DNA methyltransferase 1 (DNMT1) and DNMT3A expression [19]. OSU-CG5 and glucose deprivation not only differentially upregulate the expression of some DNA methylation – tumor suppressor genes, but also downregulate methylated tumor invasion/promoting genes. OSU-CG-5 was able to induce multiple components of the starvation-associated response, mimicking the actual glucose starvation, as previously shown by *in vitro* studies [8]. Combining OSU-CG5 with glucose deprivation increased the expression levels of a number of DNA methylation-silenced tumor suppressor genes, and decreased the expression of tumor/invasion-promoting genes [19]. The selectivity of epigenetic action of ERMAs is a determinative point in targeting cancer cells compared with the global reactivation of genes caused by epigenetic modifiers such as 5-aza-deoxycytidine [20].

• Glucose transporters inhibition

Inhibition of glucose uptake by ERMAs was identified as one of several mechanisms of its cytotoxic effect on colorectal cancer cell lines. CG5 showed a dose-dependent inhibition of fluorescent glucose analog 2NBDG uptake, which was parallel to its effect on cell viability, suggesting a possible link between both cellular events [21].

Another therapeutic advantage of CG-5 is a potential role to overcome pancreatic cancer resistance to chemotherapeutic agents. Gemcitabine-resistant pancreatic cancer cells can sharply increase the expression of ribonucleotide reductase M2 catalytic subunit (RRM2) upon exposure to gemcitabine through E2F1-mediated transcriptional activation. This upregulation of RRM2, induced by gemcitabine, represents a DNA-damage response that can increase the DNA repair capability of the cancer cells, leading to resistance [2].

• Hexokinase II & gylcolysis blockade

Hexokinase-II expression status was found to be downregulated in cisplatin-resistant ovarian and lung cancer cell lines. Exposure of these cells to glycolysis inhibitors as 2-deoxyglucose led to enhanced cisplatin cytotoxicity [22]. It is noteworthy that $CD8^+$ T-cell activation in the presence of 2-deoxyglucose resulted in boosted intratumoral T-cell reactions and enhanced their

antitumor functionality [23]. This was attributed to the notion that alterations in energy metabolism through glycolysis blockade directs activated T cells to become long-term memory cells instead of exhibiting terminal effector differentiation.

Opportunities & challenges

Agents that target tumor cell metabolism have been used successfully in human cancer therapy. A number of drugs were designed to specifically decrease the level of glutamine, a key nutrient, for treatment of acute lymphoblastic leukemia and other cancers [24]. The development of anticancer drugs targeting cell metabolism is challenged by their potential toxicity to normal cells [9]. Although some ERMAs were proven to be effective in preclinical experiments, the US FDA has stopped a clinical trial on 2-DG on prostate cancer due to the potential risk of hepatotoxicity [3].

Preliminary data about the safety of the currently available ERMAs such as OSU-CG5 is promising. The agent is well tolerated on chronic oral administration without any overt toxicity on metabolically active organs with naturally high glycolytic rates. Compared with resveratrol, OSU-CG5 shows a remarkable effect on prostate and colorectal cancers besides its ability to overcome gemcitabine resistance in pancreatic cancer with high safety margins [2,21,25]. However, the limited availability of data from other ERMAs underscores the urgent need for more comprehensive studies regarding their toxicity profile.

Another challenge in the development of effective ERMAs is the ability of cancer cells to compensate for the affected target, a phenomenon known as redundancy that usually triggers resistance [26,27]. Theoretically, the potential role of ERMAs as adjuvant chemotherapeutic agents or in combination with classical anticancer chemotherapy should enhance the activity and minimize the resistance. Despite an appreciable step has been taken in the exploration of ERMAs as anticancer agents, more agents need to be designed to fill the highlighted gaps in the way of building up a promising millstone in fighting cancer.

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