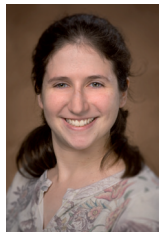
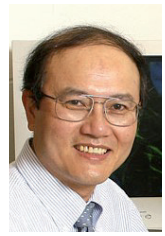
Energy restriction as an antitumor target



"…targeting tumor metabolism has emerged as a promising therapeutic … approach…"

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Editorial
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Molecular basis for targeting tumor metabolism in cancer therapy

The high need for energy in rapidly growing tumor cells links their survival to the robust availability of energy. In contrast to normal cells, transformed cells lack metabolic flexibility and switch to a glycolytic phenotype for energy production, an adaptive response to intermittent hypoxia that persists even in the presence of normal oxygen tension, the so-called Warburg effect [1–6]. This shift in energy production from oxidative phosphorylation to glycolysis is considered to be a fundamental property of cancer cells through the dysregulation of the pathways mediated by c-Myc and Akt [7–9]. This dependence on glycolysis for energy production has been linked to protection against the constitutive oxidative stress experienced by tumor cells [10–13]. The glycolytic switch can fuel the intracellular antioxidant machinery with reducing equivalents, such as NADPH, to raise tolerance to reactive oxygen species. In addition, the high rate of glycolytic flux associated with aerobic glycolysis enables tumor cells to divert intermediates of glycolysis into anabolic pathways for the synthesis of fatty acids, nucleotides and amino acids [2,4,14]. Recent evidence indicates that the glycolytic end product lactate serves as a biosynthetic intermediate for various cellular building blocks, thereby providing a growth advantage [15,16].

"The emerging view of cancers as a metabolic disease reveals opportunities for the development of new therapeutic strategies."

The microenvironment-independent reliance on glycolysis and increased consumption of glucose render cancer cells more vulnerable to inhibition of glycolysis than normal cells, which can utilize diverse fuel sources for energy production. Consequently, targeting tumor metabolism has emerged as a promising therapeutic or preventative approach, of which the proof of principle is evident from studies on the anticarcinogenic efficacy of chronic dietary energy restriction in various animal models [17–21]. Since chronic energy restriction proves to be difficult to implement as an antitumor strategy in humans, alternative approaches have been used to mimic the beneficial effects of energy restriction through interference with tumor metabolism. An early example of such an approach was nutritional metabolic therapy for brain cancer using the ketogenic diet, a high-fat, low-carbohydrate diet that shifts the prime substrate for energy metabolism from glucose to ketone bodies in order to disrupt tumor metabolism while maintaining the nutritional status of patients [22,23].

Tumor metabolism-targeted agents

More recently, the development of small molecule agents that target various aspects of glucose metabolism has been the focus of many investigations, which are summarized in this article, according to cellular target.

Glucose intake

Glufosfamide, a covalent conjugate of glucose with an ifosfamide mustard, is preferentially taken up by cancer cells and then metabolized to release a cytotoxic compound, isophosphoramide. Glufosfamide has undergone clinical trials in solid tumors, alone or in combination with gemcitabine, with low-to-modest activities [24,25].

Adenosine monophosphate-activated protein kinase

Agents that activate adenosine monophosphate-activated protein kinase (AMPK) and, thus, induce cell cycle senescence include amino-imidazole-4-carboxamide ribonucleotide (AICAR)

Keywords
■ cancer therapeutic agent ■ energy restriction ■ glycolysis ■ tumor metabolism ■ Warburg effect

and metformin and its analogs, phenformin and biguanide. AICAR is widely used experimentally to activate AMPK and inhibit the growth of tumor cells *in vitro* [26–28] and *in vivo* [26,27,29]. Epidemiologic data have suggested the chemopreventive potential of metformin in breast cancer [30,31], which is supported by its efficacy in suppressing breast xenograft tumor growth in immunocompromised mice [32]. At the molecular level, metformin suppresses cancer cell growth by inhibiting mTOR-dependent translation initiation through AMPK activation [33,34] or by the phosphorylating and inactivating acetyl-CoA carboxylase, accompanied by the suppression of fatty acid synthase, which leads to growth inhibition by blocking lipogenesis [28,35].

Glycolysis

Inhibitors of glycolysis include resveratrol, a phytoalexin with widely reported anticancer activity, which is attributable, in part, to its energy restriction mimetic effects [36–40]. Resveratrol also activates AMPK [41,42]. While many studies have demonstrated resveratrol's anticancer activity in both *in vitro* and *in vivo* (largely in the context of chemoprevention) models [36,43], resveratrol shows no activity against the growth of existing tumors, except those of the skin and GI tract [44], which is, in part, caused by its poor systemic bioavailability [45–47]. OSU-CG12, a PPAR-γ inactive ciglitazone derivative, is a new energy restriction mimetic agent with 20- and 1000-fold higher potency than resveratrol and 2-deoxyglucose (2-DG), respectively [39]. OSU-CG12 inhibits glucose metabolism through mechanisms at different molecular levels, including the cellular uptake of glucose, Akt signaling and the transcription of genes associated with glycolysis and energy metabolism. Investigation into additional mechanisms is ongoing.

Hexokinase II

Inhibition of the mitochondrial-bound hexokinase (HK) II by the indazole carboxylic acid lonidamine not only affects glucose metabolism, but also sensitizes cancer cells to apoptosis by facilitating the docking of Bax on the voltage-dependent anion channel, a HK II binding partner [48]. In Phase II trials, the combination of lonidamine and cytotoxic chemotherapy was active against advanced non-small-cell lung cancer and ovarian cancer [49,50]. However, as a single agent, lonidamine showed little activity against non-small-cell lung cancer or glioblastoma multiforme [51,52]. 3-bromopyruvate, another HK II inhibitor, is an alkylating agent with structural similarity to lactate, which may enter cancer cells on the same transporter that exports lactate, and then induce ATP depletion [53]. 3-bromopyruvate has demonstrated suppressive activities against hepatocellular carcinoma [54] and breast cancer [55], both *in vitro* and *in vivo*. 2-DG also inhibits HK II activity [56].

Phosphohexose isomerase

2-deoxyglucose blocks glycolysis through the inhibition of phosphohexose isomerase [57,58], leading to a depletion of ATP and glucose derivatives required for protein glycosylation. 2-DG also induces the unfolded protein response, as does low glucose stress [59,60], and inhibits the growth of rat fibrosarcoma [61], hepatocellular carcinoma [62,63] and other tumors, as a single agent or in combination with chemotherapeutics [64,65].

> "Further understanding of the signaling mechanisms underlying the antitumor effects of these tumor metabolism-targeted agents will help foster novel strategies for cancer therapy."

Pyruvate kinase

TLN-232 (or CAP-232) is a cyclic heptapeptide that targets the M2 splice isoform of pyruvate kinase, which has been reported to play an important role in cancer metabolism and tumor growth [66]. TLN-232 is currently undergoing a small Phase II study in metastatic melanoma [67].

Lactate dehydrogenase A

The treatment of P493 human lymphoma B cells with FX11, an inhibitor of lactate dehydrogenase A, reduces ATP levels and causes oxidative stress-induced cell death, and, thus, inhibits the progression of human lymphoma and pancreatic xenograft tumor growth [68].

Pyruvate dehydrogenase kinase

Dichloroacetate has been proposed as a novel and relatively nontoxic anticancer agent that can reverse the glycolytic phenotype in cancer cells through the inhibition of pyruvate dehydrogenase kinase [69]. Dichloroacetate has been used clinically for the treatment of lactic acidosis since 1969, and is currently undergoing clinical trials to evaluate its toxicity in cancer patients.

Monocarboxylate transporter 1

Inhibition of monocarboxylate transporter 1 by α-cyano-4-hydroxy-cinnamate induces a switch from lactate-fueled respiration to

glycolysis in oxygenated tumor cells, and, thus, suppresses lung and colon xenograft tumor growth [70].

ATP citrate lyase

The inhibition of ATP citrate lyase by SB2499 blocks cytosolic acetyl-CoA production and lipid synthesis, thereby inhibiting proliferation and survival of tumor cells displaying aerobic glycolysis *in vitro* and *in vivo* [71].

Opportunities & challenges

The emerging view of cancers as a metabolic disease reveals opportunities for the development of new therapeutic strategies. Many of the tumor metabolism-targeted agents described in this article exhibit *in vivo* efficacy alone or in combination with chemotherapeutic drugs in advanced cancers.

It is generally believed that interfering with energy metabolism causes ATP depletion and metabolic stress, leading to cell death. However, data from ours and other laboratories indicate that reducing glycolytic rate by energy restriction activates multiple signaling pathways, including those mediated by the NAD^+-dependent histone deacetylase sirtuin 1, AMPK and endoplasmic reticulum stress [39]. This complicated signaling network affects many aspects of cellular functions relevant to cell cycle regulation, survival and aggressive phenotype, culminating in cancer cell death through autophagy and apoptosis. Therefore, it is plausible to achieve synergy with other molecularly targeted agents, such as kinase inhibitors or histone deacetylase inhibitors, to kill cancer cells. Further understanding of the signaling mechanisms underlying the antitumor effects of these tumor metabolism-targeted agents will help foster novel strategies for cancer therapy.

Despite substantial advances in the preclinical development of these tumor metabolism-targeted agents, a number of issues warrant further investigation. Toxicity is common among many drugs associated with high doses required to attain *in vivo* efficacy and/or off-target pharmacological activities. For example, the US FDA has suspended the clinical trial of 2-DG for advanced prostate cancer (NCT00633087), and that of lonidamine for benign prostate hypertrophy owing to hepatic side effects [101]. In addition, not all cancer cells are susceptible to interference with energy metabolism. AMPK activators, such as AICAR and metformin, were reported to selectively inhibit p53-deficient tumor cell growth, suggesting that AMPK activation forces a metabolic conversion that $p53^{-/-}$ cells are unable to execute [29]. Therefore, it is important to define the determining factor for the resistant phenotype for each type of tumor metabolism-targeted agent.

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