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Manipulation of Glucose and Hydroperoxide Metabolism to Improve Radiation Response

John M. Floberg, MD, PhD,* and Julie K. Schwarz, MD, PhD*,†,‡

Dysregulated glucose and redox metabolism are near universal features of cancers. They therefore represent potential selectively toxic metabolic targets. This review outlines the preclinical and clinical data for targeting glucose and hydroperoxide metabolism in cancer, with a focus on drug strategies that have the most available evidence. In particular, inhibition of glycolysis using 2-deoxyglucose, and inhibition of redox metabolism using the glutathione pathway inhibitor buthionine sulfoximine and the thioredoxin pathway inhibitor auranofin, have shown promise in preclinical studies to increase sensitivity to chemotherapy and radiation by increasing intracellular oxidative stress. Combined inhibition of glycolysis, glutathione, and thioredoxin pathways sensitizes highly glycolytic, radioresistant cancer models in vitro and in vivo. Although the preclinical data support this approach, clinical data are limited to exploratory trials using a single drug in combination with either chemotherapy or radiation. Open research questions include optimizing drug strategies for targeting glycolysis and redox metabolism, determining the appropriate timing for administering this therapy with concurrent chemotherapy and radiation, and identifying biomarkers to determine the cancers that would benefit most from this approach. Given the quality of preclinical evidence, dual targeting of glycolysis and redox metabolism in combination with chemotherapy and radiation should be further evaluated in clinical trials.

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Introduction

Increased glucose utilization is a nearly universal feature of cancers and was described by Warburg nearly a century ago.1,2 This has been proposed as an adaptation to hypoxia as malignant lesions outgrow their blood supply, and as a phenotype that is selected for in environments with scarce oxygen and glucose.3–5 It has also formed the basis for the widespread clinical use of [F-18]fluorodeoxy glucose positron emission tomography ([F-18]FDG-PET) in oncology as a tool for staging, prognosis, and monitoring treatment response.6,7 The mechanism of increased [F-18]FDG signal seen in cancers relative to normal tissues is related to increased transport by GLUT transporters and phosphorylation by hexokinases compared to most normal tissues. [F-18]FDG becomes trapped after its phosphorylation by hexokinases and does not proceed any further through glycolysis.8–10 [F-18]FDG-PET derived imaging metrics have been shown to be prognostic in lymphomas, head and neck, lung, and gynecologic cancers and numerous other cancer sites, and decreased [F-18]FDG signal during or following treatment is a favorable prognostic sign.11–17 These extensive clinical data suggest that increased glucose utilization is related to the aggressiveness of a cancer and how well it is able to tolerate standard therapies such as chemotherapy and radiation.

Altered redox metabolism, and particularly changes in glutathione and thioredoxin metabolism, have likewise been noted in many cancer types, and upregulation of these pathways has been linked to cancer progression.18 Cancer cells produce more reactive oxygen species (ROS) than noncancerous cells, and upregulate antioxidant systems, such as the glutathione and thioredoxin pathways, to manage this excess.

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of ROS, particularly hydroperoxide species.\textsuperscript{18-21} Glutathione, in particular has been shown to play an important role in cancer initiation, and the combination of inhibiting the glutathione and thioredoxin pathways has been shown to be toxic to a number of different cancer cells.\textsuperscript{18,22,23} Increased glycolysis and increased activity of the pentose phosphate pathway may also help cancer cells manage oxidative stress by providing reducing equivalents, for example nicotinamide adenine dinucleotide phosphate (NADPH), that can be used by ROS scavenging pathways, connecting the increased glucose consumption and upregulation redox metabolic pathways seen in many cancers.\textsuperscript{24}

Despite the evidence of the importance of alterations in both glycolysis and redox metabolism to cancer initiation and progression, no current standard-of-care therapies specifically target these metabolic pathways, and clinical investigations have been limited. There are accumulating preclinical data that targeting hydroperoxide metabolism at both the glutathione and thioredoxin pathways increases ROS and is toxic to cancer cells, and that targeting glycolysis in addition to these pathways further increases redox stress and toxicity.\textsuperscript{18,22,24} Therapies that increase oxidative stress may be particularly valuable as a means to sensitize cancers to radiation. Damage from radiation therapy is classically thought to be mediated by ROS created by ionizing radiation, and upregulation of ROS scavenging pathways may therefore help cancers mitigate damage from radiation.\textsuperscript{25} Inhibiting both glycolysis and hydroperoxide metabolism has therefore also been proposed as a potential radiosensitization strategy.\textsuperscript{23,26} Here we aim to review the preclinical and clinical data on therapies targeting glycolysis and the glutathione and thioredoxin pathways, either alone or in combination, with particular focus on how these therapies might improve radiation response.

Targeting Glycolysis

There are a number of potential therapeutic targets within the early steps of glucose uptake and metabolism (Fig. 1). Furthest upstream, the GLUT family of transporters can be targeted for anticancer effect,\textsuperscript{27} and some cancers express unique GLUT isoforms.\textsuperscript{28} WZB117 is an inhibitor of GLUT1 that has been shown to inhibit cancer growth and cause cell-cycle arrest, senescence, and death in vitro and in vivo through a mechanism that appears to be dependent on ATP, and it has also been shown to decrease the tumor-initiating capacity of cancer stem cells derived from a number of different cancers.\textsuperscript{29,30} The protease inhibitor ritonavir, approved for the treatment of HIV, has an off-target inhibitory effect on the GLUT4 transporter, and has been proposed as a therapy for multiple myeloma, which is dependent upon expression of the GLUT4 transporter.\textsuperscript{31}

Hexokinase, which phosphorylates glucose after it has entered the cell, is another potential upstream target in glucose metabolism. A number of drugs have been evaluated in the preclinical and clinical setting as hexokinase inhibitors, including 2-deoxyglucose (2-DG), and lonidamine.\textsuperscript{32,33} Lonidamide has been evaluated in clinical trials, but widespread clinical utility of lonidamide has been limited by significant hepatic and pancreatic toxicities.\textsuperscript{34} As with [F-18] FDG, 2-DG is taken up by GLUT transporters and phosphorylated by hexokinase, at which point it becomes trapped within cells and is not metabolized any further. Excess accumulation of 2-DG leads to cell cycle inhibition and ultimately cell death in a variety of preclinical cancer models.\textsuperscript{27,35,36} There is also evidence that increased oxidative stress in cancer cells relative to normal cells mediates selective toxicity of 2-DG for cancers.\textsuperscript{36}

Much of the preclinical and clinical work studying 2-DG has been in glioblastoma multiforme (GBM). 2-DG selectively inhibits proliferation of GBM cell lines relative to normal human astrocytes.\textsuperscript{37} Use of 2-DG has also been shown to inhibit cancer growth and carcinogenesis in noncentral nervous system cancers (eg, mammary cancers).\textsuperscript{38} However, 2-DG alone may not act as an effective anticancer therapeutic. For example, although glucose deprivation has been shown to induce apoptosis through a ROS dependent mechanism in GBM derived cell lines but not normal human astrocytes, treatment with 2-DG actually prevents apoptosis through depletion of ATP.\textsuperscript{39} Controversy remains over the precise mechanism of 2-DG toxicity when this drug is administered a monotherapy.\textsuperscript{33,40} Hypoxia and activation of the hypoxia-inducible-factor-1 transcription factor have been linked to 2-DG monotherapy resistance,\textsuperscript{41} and some studies have demonstrated activation of prosurvival pathways in cancer cells after 2-DG treatment, leading some investigators to propose 2-DG combination therapies rather than 2-DG monotherapy as the most appropriate strategy.\textsuperscript{42,43}

Numerous combination therapies, utilizing 2-DG in addition to another metabolic agent, a chemotherapeutic drug, or radiation therapy, have, however, proven to be effective strategies. For example, the combination of 2-DG and the oxidative phosphorylation inhibitor oligomycin has been shown to synergistically suppress growth and mobility in GBM cell lines, and the combination of 2-DG and inhibition of NADPH oxidase 4 likewise inhibits proliferation and angiogenesis in GBM cells.\textsuperscript{35,44} In addition, 2-DG has been shown to enhance the efficacy of systemic and chemotherapeutic agents, such as cisplatin, topoisomerase, and trastuzumab, in vivo and in vitro,\textsuperscript{27,45-47} and the combination of 2-DG and docetaxel has been evaluated in a phase I trial in patients with advanced solid tumors with tolerable and reversible side effects including hyperglycemia and QTc prolongation.\textsuperscript{48} Most germane to this review, 2-DG has been shown to increase the efficacy of radiation therapy in a number GBM and other cancer cell lines, with evidence supporting that this is due to disruptions in thiol metabolism.\textsuperscript{49-52}

The enhanced response to radiation seen in GBM cell lines has formed the basis for a number of clinical trials combining 2-DG with radiation therapy. The published trials have for the most part been small phase I/II trials evaluating the safety and tolerability of administering 2-DG prior to radiation therapy using escalating doses of 2-DG, and have used large fractions of RT (5 Gy) delivered once a week 20-30 minutes after 2-DG administration. These trials have reported that such a regimen is tolerated, with acute side
effects of restlessness, nausea, and vomiting, and without any apparent significant long-term toxicities. There are currently no open randomized controlled clinical trials evaluating the efficacy of 2-DG as an anticancer agent alone or in combination with radiation or chemotherapy. Limiting factors include unacceptable side effects at high doses used to limit glucose metabolism in cancer cells, and limited efficacy for glycolysis inhibition when lower doses of 2-DG monotherapy are used.

Finally, although separate from glycolysis, the pentose phosphate pathway represents another potential target for anticancer therapy (Fig. 1). The pentose phosphate pathway is one of the primary sources of cellular NADPH, which provides electrons for ROS scavengers like glutathione and thioredoxin. For example, 6-aminonicotinamide is an inhibitor of glucose-6-phosphate dehydrogenase that has shown anticancer activity in vitro, either alone or in high doses with radiation, but that also has significant side effects. Other strategies for inhibiting glucose-6-phosphate dehydrogenase have also been investigated, for example using dehydroepiandrosterone in combination with 2-DG. Whether the pentose phosphate pathway can effectively be targeted for anticancer therapy in humans remains an open question.

Targeting Glutathione Metabolism

As outlined above, glutathione has been identified as an important factor in carcinogenesis, and as one of the most abundant antioxidant molecules in cells it plays a key role in maintaining redox balance, particularly in cancer cells. One of the most widely used strategies to target glutathione metabolism is the drug buthionine sulfoximine (BSO), which inhibits γ-glutamylcysteine synthase, the enzyme responsible for the first step in the synthesis of glutathione. A number of preclinical studies have demonstrated that BSO can be used to sensitize cancer cells to a number of therapies including arsenic, cisplatin, mephalan, and radiation. Some of these studies have demonstrated that BSO also sensitizes cancer cells to therapies that are not conventionally thought of as inducing ROS on their own (eg, cisplatin), and that

Figure 1 Potential targets of glucose metabolism for anticancer therapy. Blocking glucose metabolism serves to inhibit both a major energy source for cancer cells, as well as a major source of reducing equivalents (eg, NADPH). The major glucose metabolic pathways, and potential drug strategies to target them are shown. Drugs are shown in bold. Abbreviations: HK, hexokinase; 2-DG, 2-deoxyglucose; LND, lonidamide; G6PD, glucose-6-phosphate dehydrogenase; 6-AN, 6-aminonicotinamide; DHEA, dehydroepiandrosterone; PPP, pentose phosphate pathway; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; 3-BrPA, 3-bromopyruvate; LDHA, lactate dehydrogenase A; TCA cycle, tricarboxylic acid cycle.
glutathione depletion may have an effect on mediating cell death pathways like apoptosis.62

BSO was first studied in clinical trials in combination with melphalan over 20 years ago. These phase I trials in small cohorts of patients with advanced refractory cancers studied different doses and dosing schedules (eg, BSO every 12 hours vs as a continuous infusion), the biologic activity of BSO, namely reduced glutathione levels in the peripheral blood and within tumors, and toxicities associated with its use. These trials found that BSO given in combination with melphalan is fairly well tolerated, with low-grade nausea and vomiting the most common acute toxicity, and a more frequent incidence of severe (grade 4) myelosuppression. They have also reported depletion of glutathione in the peripheral blood of <10% of pretreatment values, and depletion to ≤20% of pretreatment values within tumors.65-67 More recently, the combination of BSO and melphalan has been tested in a pilot study of children with recurrent neuroblastoma, again assessing for tolerability and toxicity, biochemical efficacy, and clinical efficacy.68 This trial showed the combination of these drugs decreased blood mononuclear cell glutathione levels and, an 18% response rate was observed. Grade 3-4 leukopenia and thrombocytopenia in these patients were common, and 2 grade 5 toxicities were reported (acute renal tubular necrosis and diffuse cerebral edema) after the initiation of BSO.

**Targeting Thioredoxin Metabolism**

The other major thiol-based ROS scavenging pathway in mammalian cells is the thioredoxin system. Thioredoxin donates electrons to peroxiredoxins, which then remove hydroperoxide radicals. Thioredoxin is then converted back to its reduced form by thioredoxin reductase, using electrons donated by NADPH. Along with the glutathione system, this is one of the key regulators of intracellular ROS.69

There are a number of drug strategies that have been proposed to inhibit the thioredoxin pathway. These include auranofin, a gold complex initially developed for treating rheumatoid arthritis that acts as a thioredoxin reductase inhibitor, and sulfasalazine, an inhibitor of the XC− cystine transporter also used in rheumatoid arthritis and other inflammatory conditions (Fig. 2).18,23 Auranofin has been shown to inhibit both mitochondrial and cytosolic thioredoxin reductase, resulting in an increase in ROS levels.70 As a result of the increased oxidative stress, auranofin causes endoplasmic reticulum stress and mitochondrial dysfunction, which can be reversed using the thiol antioxidant n-acetylcysteine (NAC), suggesting that this effect is mediated by ROS.71,72

Auranofin has shown activity against a number of cancer types in preclinical studies. This includes diverse disease sites such as chronic lymphocytic and chronic myeloid leukemias, multiple myeloma, osteosarcoma, and gastric cancer.71-75 In each of these cases, the toxicity due to auranofin appears to be mediated by increased ROS, which trigger programmed cell death pathways. Auranofin alone can also act as a radiosensitizer in both normoxic and hypoxic cancer cells, and appears to do so through increased ROS generation, which can be reversed by NAC, as well by inducing mitochondrial dysfunction.76

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**Combined Inhibition of Glucose and Hydroperoxide Metabolism**

As outlined above, inhibition of glutathione alone does not result in significant toxicity to cancer cells. The glutathione...
and thioredoxin pathways are the 2 major thiol ROS scavenging systems in mammalian cells, and selective targeting of 1 pathway often results in increased activity of the other. For example, thioredoxin pathway proteins are overexpressed in cancer cells depleted of glutathione. Therefore, inhibition of both pathways may be needed to induce ROS dependent toxicity, and a number of studies have found that many cancers are sensitive to the simultaneous inhibition of both the glutathione and thioredoxin pathways. Combining glutathione and thioredoxin pathway inhibition has also been shown to sensitize cancer cells, including breast cancer stem cells, to radiation therapy, and to inhibit cancer cell migration and invasion. The toxicity of combined glutathione and thioredoxin pathway inhibition and the resulting sensitization to radiation therapy are mediated by ROS, and reversible using exogenous ROS scavengers like NAC.

Altered glucose metabolism, particularly through the generation of NADPH in the pentose phosphate pathway, provides another means for cancer cells to manage excess oxidative stress. The pyruvate produced by glycolysis may also help mediate ROS scavenging. Furthermore, treatment with 2-DG has been shown to increase levels of superoxide and hydrogen peroxide in cancers. Therefore, the combination of inhibition of glucose metabolism and inhibition of the glutathione and thioredoxin pathways may increase oxidative stress in cancer cells even further (Fig. 3). As all of these pathways are upregulated in many cancer types this approach therefore offers a potential means of selectively targeting one of the more reproducible observations with respect to dysregulated metabolism seen in many cancers. The combination of glycolysis inhibition using 2-DG, pentose phosphate pathway inhibition using dehydroepiandrosterone, and thioredoxin pathway inhibition using auranoﬁn is significantly more toxic than when any one of these pathways is inhibited alone as documented in human breast and prostate cancer cells, and importantly this combination treatment is significantly more toxic to breast cancer cells than normal mammary cells. As such, the dual targeting of glycolysis in combination with redox metabolism holds great promise for cancer therapy.

Our group has recently evaluated the combination of glycolysis, glutathione, and thioredoxin inhibition as a means to radiosensitize cervical cancer cell lines. Increased [F-18]FDG uptake is an established prognostic factor in human cervical cancers, and persistent tumor [F-18]FDG uptake following definitive chemo-radiation therapy portends a poor outcome. These clinical observations suggest that glucose metabolism is a marker for aggressive, radiation-resistant cervical cancers. Cervical cancer may therefore be well suited to a treatment approach using inhibition of glycolysis in combination with inhibition of hydroperoxide metabolism to increase oxidative stress and enhance sensitivity to standard of care radiation therapy. We have demonstrated that combining 2-DG, buthionine sulfoximine, and auranoﬁn results in significant toxicity to a number of cervical cancer cell lines that is mediated by an increase in ROS. Furthermore, treatment with this combination of drugs results in decreased tricarboxylic acid cycle activity, as well as AMPK activation in cell lines sensitive to this drug combination. The mechanism of cell death from this combination

![Figure 3](image-url)

**Figure 3** Simultaneous inhibition of the glycolysis and the glutathione and thioredoxin systems reduces cancer cells' defenses against reactive oxygen species, and can be used as a strategy to sensitize cancer cells to therapies that increase oxidative stress, like radiation therapy. An example inhibitory combination drug strategy using 2-DG, BSO, and AUR is shown. Abbreviations: 2-DG, 2-deoxyglucose; BSO, buthionine sulfoximine; AUR, auranoﬁn; PPP, pentose phosphate pathway; GSR, glutathione reductase; GPX, glutathione peroxidase; TrxR, thioredoxin reductase; PRDX, peroxiredoxin.
treatment appears to be dependent on expression of specific pathways, namely MYC. In MYC transformed cells, this therapy causes a caspase and poly ADP ribose polymerase (PARP) dependent autophagic cell death, whereas non-MYC transformed cells die by an AMPK dependent nonautophagic death. These data also demonstrated that this drug combination was an effective radiosensitization strategy in vivo. This high quality preclinical evidence supports further investigation of this drug combination as an adjunct to radiotherapy in the context of clinical trials for cervical cancer.

Future Directions

An important future direction in this field is selection of the best drug strategy to target aerobic glycolysis in tumors. A number of glycolytic enzymes downstream of hexokinase have been explored as potential cancer therapeutic targets, and are at various stages of preclinical vs clinical development. Small molecule inhibitors of 6-phosphofructo-2-kinase are being developed and have been shown to influence tumor growth in animal models. As the first enzymatic step within glycolysis associated with NADH production, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) represents a unique therapeutic target. Inhibition of GAPDH leads to accumulation of glucotrioses, which, during the course of their metabolism generate methylglyoxal, which is toxic to the cell. Enzymes responsible for the metabolism of methylglyoxal are dependent upon reduced glutathione (GSH). Therefore, in the presence of limited GSH, targeting GAPDH represents an attractive opportunity to not only limit ATP production via glycolysis, but also to enhance intracellular levels of oxidative stress by simultaneously limiting NADH production and generating a toxic metabolite that consumes intracellular GSH.

A number of GAPDH inhibitors have been tested in the preclinical setting. For example, 3-bromopyruvate has been well studied in this role and has entered early phase clinical trials. Recently, Gunda et al demonstrated that pretreatment with 3-bromopyruvate abrogated radiation resistance in MUC1 overexpressing pancreatic cancer models. Pyruvate kinase (PK) catalyzes the near final step of conversion of phosphoenolpyruvate to pyruvate. Early studies showed that knockdown of PKM2 in tumor cells and replacement with the PKM1 isomorph reversed the Warburg effect, and preclinical studies of PKM2 inhibition have demonstrated anticancer effect. Although it is now clear that expression of PKM2 is not cancer-specific, additional study of PKM2 regulation and biology may lead to effective and selective anticancer strategies. It is important to note that PKM2 is an inefficient enzyme, and backflow of glycolytic intermediates can be diverted to the PPP to generate NADPH that can be used to metabolize ROS. PKM2 itself is inhibited directly by ROS, and detailed understanding of this relationship will be important to design rationale drug or radiation combinations with PKM2 inhibitors. Further downstream, inhibitors of lactate dehydrogenase A, such as the pyruvate analog oxamate, have been shown to increase efficacy of systemic agents such as paclitaxel and traztuzumab. Further preclinical studies, particularly in vivo, supporting the use of these drug strategies in the context of radiotherapy should be performed.

A second important future direction is optimization of drug strategies to increase intracellular oxidative stress in cancer cells. In this review, we have focused on dual targeting of glutathione and thioredoxin pathways with BSO and auranozin, the most well studied drugs in each category. Other drug strategies exist to deplete cells of GSH reserves, including inhibitors of cysteine/glutamate transporter XCT (sulfasalazine), inhibitors of glutathione peroxidase, and glutathione disulphide mimetics (NOV-002). It is important to note that glutamine can be converted to glutamate, which is required for GSH synthesis. As such, developing drug strategies that inhibit glutamine metabolism will, by definition, decrease intracellular glutathione levels. A number of drug strategies are being developed to target glutamine metabolism, and detailed study of the effects of these drugs on intracellular levels of oxidative stress will need to be performed. Although it is well accepted that radiation treatment results in increased ROS, the precise source, species and timing of ROS increases after RT exposure are not well known, and may be unique in certain cancer types. Understanding the precise mechanism and timing of ROS fluctuations after RT exposure will be important for the successful timing of administration of ROS inducing agents. Preclinical studies that incorporate variations in dose and schedule for ROS inducing agents in the context of single fraction and multi-fraction radiation schedules should be performed.

Determining the most appropriate biomarker to identify cancers that are uniquely susceptible to inhibition of glycolysis and redox metabolism is also critical. Historically, increased uptake of [F18]FDG-PET by tumors has been used to identify tumors that engage in increased rates of aerobic glycolysis; however, it is important to note that this imaging modality is limited to glucose uptake, and does not directly visualize glucose metabolism. Significant improvement in imaging technology, specifically the development of magnetic resonance imaging with hyperpolarized substrates, will allow for direct visualization of enzymatic steps within glycolysis and other metabolic pathways in tumors (ie, the pyruvate to lactate transition.) Ongoing research efforts in our own group are evaluating novel PET imaging strategies that can be used to noninvasively monitor levels of tumor oxidative stress.

Conclusions

Dysregulated metabolism is a hallmark of cancer cells. Specifically, cancers demonstrate changes in both glucose metabolism and redox metabolism to help them meet high energy and growth requirements in environments with limited resources, and manage excess ROS that result from excess growth and aberrant metabolic pathways. Both glycolysis and thiol-mediated hydroperoxide metabolism represent targetable pathways that are upregulated in many cancer
types, and this work has reviewed the preclinical and clinical literature on the efficacy of such an approach. The available clinical data are restricted to inhibitors of a single pathway (e.g., glycolysis or the glutathione pathway) given in combination with radiation or chemotherapy, and have been limited to early phase trials in small cohorts. The preclinical data reviewed here demonstrate that the combination of glucose and hydroperoxide metabolism is an effective treatment strategy across a number of cancer types, particularly when also combined with radiation or chemotherapy, and far more effective than inhibiting any one single pathway on its own. Ongoing research to identify the most appropriate biomarker for susceptibility to inhibition of glycolysis and redox metabolism, including development of novel imaging strategies, should be performed.

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