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Targeting the Warburg Effect in Hematological Malignancies: from PET to Therapy

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Abstract

Purpose of Review—To highlight key studies providing rationale for and utility in targeting glycolysis for the treatment of hematological malignancies.

Recent Findings—Several therapeutic strategies are capitalizing on the diagnostic utility of FDG-PET that relies on increased glycolysis and glucose utilization in tumor cells. While aerobic glycolysis was initially proposed by Warburg to be due to mitochondrial impairment, recent studies have shown a preferential switch to glycolysis in tumor cells with functional mitochondria. Increased glucose consumption can be advantageous for a tumor cell through stimulation of cellular biosynthetic, energetic, and pro-survival pathways. We now have a greater appreciation for the utilization of glucose in specific metabolic pathways that in some aspects can be complemented with other nutrients such as glutamine. Targeting glucose consumption for the treatment of hematological malignancies seems to be a promising field that will require characterization of tumor cell specific targets to inhibit glucose uptake and/or glycolysis. It is imperative to further our understanding of the tumor cell metabolome to target cellular bioenergetics in the treatment of cancer.

Summary—Targeting the glycolytic pathway for the treatment of hematological malignancies has sufficient rationale given the utility of FDG-PET in diagnostic imaging. Further research is required in developing tumor cell specific therapeutics.

Keywords

Glucose; hematologic malignancies; glycolysis

Introduction

Hematological malignancies account for approximately ten percent of diagnosed cancers (1). These cancers of lymphoid and myeloid origin, while having diverse genomic profiles, demonstrate deregulation of core molecular and biochemical pathways. In the nineties, alkylating agents, antimetabolites, anthracyclines, topoisomerase inhibitors, anti-microtubule drugs and steroids formed the spectrum of available therapeutics. The emergence of newer

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targeted therapeutics like imatinib, bortezomib, and rituximab coupled with advances in autologous stem cell transplantation have tremendously increased the average lifespan of patients living with these diseases. What continues to be a caveat in the treatment of all cancers is the development of resistance and the emergence of a more aggressive cancer. Therefore, the discovery of novel approaches targeting pathways that become increasingly important during disease progression is necessary.

The Warburg Effect

Nearly 80 years, ago Otto Warburg made the seminal observation that tumor cells consume surprisingly high amounts of glucose and use the less efficient glycolytic pathway (as depicted in Figure 1) to generate adenosine triphosphate (ATP) even in the presence of oxygen (2). Normal cells preferentially use the mitochondrial tricarboxylic acid (TCA) cycle for the oxidative degradation of glucose and generation of ATP, resorting to glycolysis only under conditions of oxygen deprivation such as under muscle fatigue. In the mid 1800s, Louis Pasteur studied yeast fermentation processes and demonstrated the ability of oxygen to inhibit glycolysis, facilitating mitochondrial oxidative degradation of glucose (3). While Warburg believed the preferential use of glycolysis even in the presence of oxygen by tumor cells was due to defects in the mitochondrial respiratory pathways required for oxidation of glucose, recent studies have shown that tumor cells do contain functional mitochondria (4) yet still produce excessive lactate, suggesting that the enhanced glycolytic flux may confer a growth advantage.

In support of this notion, interference with lactate dehydrogenase activity (the enzyme responsible for conversion of lactate to pyruvate) in tumor cells forces a reversion to glucose catabolism via oxidative phosphorylation and results in reduced tumorigenicity (4). Forcing tumor cells to revert to the use of oxidative metabolism by overexpression of mitochondrial frataxin, a protein regulating mitochondrial iron transport and respiration (5), or with chemical inhibitors like dichloroacetate, also reduces tumor growth in mouse xenograft studies (6). Recently, requisite events preceding the switch from oxidative phosphorylation (OXPHOS) to aerobic glycolysis in neoplastic cells have been shown to involve expression of the embryonic form of pyruvate kinase, which appears to be required for tumor formation. This isoform is uniquely regulated by tyrosine kinase activity and is thought to divert glucose to anabolic processes, thus facilitating tumor growth (7). Several studies have demonstrated the role of mitochondrial uncoupling proteins in limiting catabolism of pyruvate in the TCA cycle and increasing fatty acid oxidation thereby promoting the Warburg effect (8,9). Progressive oncogenic transformation by serial transduction of a set of viral oncogenes in an *in vitro* cell line model of tumorigenesis was also found to correlate with a progressive switch to glycolysis and increasing sensitivity to glycolytic pathway inhibitors (10). Several mechanisms have now been shown to contribute to the Warburg effect i.e. mitochondrial defects, adaptation of the cancer cells to hypoxic microenvironments, oncogenic signals and abnormal expression of metabolic enzymes (11). The intimate association between transcriptional control of glycolytic genes and the activity of classical oncogenes and tumor suppressors, including myc, p53, N and K Ras and Hif1α further underscores the prevalence of de-regulated cellular metabolism in cancer cells (12). These observations have stimulated a renewed interest in strategies that target metabolism and cellular bioenergetics unique to cancer cells.

Benefits of enhanced glycolysis

A high glycolytic rate and enhanced glucose uptake can provide several benefits to a proliferating tumor cell. Although OXPHOS generates more ATP per molecule of glucose, glycolysis can provide ATP at a higher rate provided glucose supply is unlimited (13,14). In addition glucose can provide intermediates such as ribose sugar for nucleotide synthesis and

NADPH used in the reductive biosynthesis of lipids and fats through the oxidative pentose phosphate pathway. In tumor cells much of the carbon that enters the TCA cycle is extruded as citrate resulting in a truncated TCA cycle that is used for synthesis of lipids and fatty acids (15). Glucose can contribute to maintaining mitochondrial integrity by promoting the association of hexokinase II with the mitochondria, thereby preventing the release of cytochrome C (16,17) as well as by regulating various effectors of cell death i.e. regulation of pro-survival Mcl-1 (18), pro-apoptotic BAD (19), and pro-apoptotic Bax (20). Lactate, the by-product of glycolysis, is thought to promote tumor invasion and metastasis via degradation of extracellular matrices (21). In summary, glucose plays a critical role in sustaining tumor cell growth, thus providing a rationale for the development of therapeutic strategies to preferentially kill cancer cells by targeting glycolysis.

Hematopoietic malignancies and glucose utilization

While most of our knowledge on deregulated tumor cell metabolism comes from solid tumors, large-scale gene-expression analyses reveal the selective upregulation of genes encoding constituents of the glycolytic pathway in hematopoietic malignancies (22). Acute lymphoblastic leukemia cells demonstrate upregulation of genes facilitating glycolysis such as GLUT 1, GLUT4 and monocarboxylic acid transporter SLC16A2 (23). A study on the molecular pathogenesis of chronic myelogenous leukemia showed that transformation of normal hematopoietic cells with the BCR-ABL oncogene results in increased glucose metabolism and intracellular ROS levels, which is likely mediated through AKT/mTOR signaling (24). In certain leukemia cell lines, it has been demonstrated that co-culture with mesenchymal stem cells induces the expression of uncoupling protein 2 which further exacerbates the glycolytic phenotype of these cells (25). Probably the most crucial evidence pointing towards the preferential utilization of glycolysis and excessive glucose consumption in hematopoietic malignancies lies in the successful imaging of these tumors through ^{18}fluoro-deoxyglucose positron emission tomography (FDG-PET) (26,27). While proliferating primary lymphocytes also utilize the glycolytic pathway to convert 90% of glucose derived carbon to lactate (28,29), their tumor cell counterparts consume higher amounts of glucose for the very same reasons outlined above. PET has primarily been used in the detection and diagnostic staging of Hodgkin's disease, aggressive non-Hodgkin's lymphomas and in multiple myeloma (26,30)

Irrespective of whether altered metabolism and increased glucose consumption in hematopoietic malignancies are a cause or consequence of the disease, the fundamental role of glucose in maintaining energy homeostasis and apoptotic resistance provides sufficient rationale to explore inhibition of glucose utilization as a treatment strategy for these cancers.

Targeting Glycolysis in the Clinic

The wealth of compelling data pointing to glycolytic inhibition as a viable therapeutic strategy in cancer combined with the relevance of the "Warburg effect" to myriad forms of malignancy have led to the development of numerous compounds targeting this critical growth-related pathway. In addition to the ability to increase tumor cell sensitivity to a variety of traditional chemotherapeutics, interference with glucose metabolism has also recently been shown to induce a cytoprotective effect in nonmalignant tissue (31). Achieving both these benefits through the inclusion of anti-glycolytic agents in combinatorial drug regimens could result in a significant widening of the therapeutic window associated with traditional chemotherapeutics. Despite existing evidence for the glucose avidity of certain hematological malignancies, nearly all glycolysis-targeted therapies have been tested exclusively in solid tumors (32). Therefore, the following overview of the clinical development of three of the most prominent glycolytic inhibitors (as depicted in Figure 1) will focus on the successes and failures

in this class of neoplasms with the understanding that expansion to the treatment of hematopoietic malignancies remains plausible, if not promising.

Lonidamine

Lonidamine, 1-(2,4-dichlorobenzyl)-1-H-indazole-3-carboxylic acid, is a glycolysis-targeting compound which has exited clinical trials and gained approval in Europe for the treatment of various solid tumors. Lonidamine acts as an inhibitor of hexokinase and exhibits selectivity for the mitochondria-bound form of the enzyme, which appears to play a prominent role in increasing glycolytic flux in both proliferating normal and neoplastic cells (33,34). Binding of hexokinase to the outer mitochondrial membrane enhances the activity of the enzyme by modifying its interaction with a necessary substrate in two ways: first, by ensuring a constant source of ATP generated by the electron transport chain, and second, by increasing the affinity of hexokinase for the ATP molecule (35). Three clinical trials have recently come to completion utilizing lonidamine in combination with other chemotherapeutics, with the authors of these studies reporting varying degrees of success. In a phase II clinical trial evaluating the administration of both lonidamine and diazepam to patients with recurrent glioblastoma multiforme, 50% of patients exhibited disease stabilization following treatment including one case in which progression did not occur for 12 months (36). Authors of a phase II study designed to examine the efficacy of paclitaxel, cisplatin, and lonidamine co-administration to patients with advanced ovarian cancer observed an 80% overall response rate, including 40% complete responses and 40% partial responses (37). However, this trial was designed as a single-arm, uncontrolled study making the contribution of lonidamine to the overall success difficult to ascertain. A larger phase III study completed in previously untreated breast cancer patients revealed a 9% increase in overall response rate in patients receiving epirubicin plus lonidamine in comparison with epriubicin alone which bordered on reaching statistical significance (38). In comparing toxicity results between these three studies, all reported the occurrence of myalgia and the phase III study effectively linked this occurrence to the addition of lonidamine to the therapeutic regimen.

2-Deoxy-D-glucose

The most widely employed compound to investigate glycolytic inhibition in *in vitro* studies, 2-deoxy-D-glucose (2DG) has exhibited broad activity in tumor cell lines as a single agent and in combination with other chemotherapeutics (24,39). This anti-metabolite with nearly complete structural identity to glucose is taken up into cells via glucose transporters and subsequently phosphorylated by hexokinase. However, as this molecule is not a recognizable substrate for the next enzyme in the glycolytic pathway, phosphoglucose isomerase, phosphorylated 2DG accumulates to high levels in the cytosol and inhibits hexokinase activity. Unlike lonidamine, this drug does not appear to display selectivity for different hexokinase isoforms and derives its selectivity (however minimal) for tumors simply through increased glucose consumption rates. According to the NIH website clinicaltrials.gov, there are currently three clinical trials utilizing this drug which are ongoing or have recently reached completion. Authors of a phase I trial conducted by Threshold Pharmaceuticals employing 2DG in combination with docetaxel in patients with advanced solid tumors observed disease stabilization in 6 of 18 evaluable patients and one partial response (40). However, grade 3 hyperglycemia limited dose escalation above 88 mg/kg in certain patients. This observation is particularly concerning given previous animal studies in which much higher dosages of 500–2000 mg/kg were required to achieve tumor growth inhibition in xenograft tumors in immuno-compromised mice (41). This compound has also been shown to stimulate Akt phosphorylation *in vitro* and antagonize the anti-tumor activity of a radio-immunotherapeutic *in vivo*, effects which further degrade the therapeutic value of 2DG (42,43). It was recently announced that Threshold Pharmaceuticals is no longer pursuing clinical development of this compound.

Dichloroacetate

An alternative strategy to blocking flux through the glycolytic pathway by directly targeting individual constituent enzymes consists of forcing the entry of pyruvate into the mitochondria for oxidative catabolism in the TCA cycle, thus antagonizing rapid conversion to lactate in the cytosol. Pyruvate dehydrogenase is a mitochondrial enzyme which converts pyruvate to acetyl CoA. The activity of this enzyme is negatively regulated by pyruvate dehydrogenase kinase (PDK), the expression of which is cooperatively induced by HIF1α and c-myc (44). Dichloroacetate (DCA) is a small molecule inhibitor of PDK which can effectively induce a metabolic switch from aerobic glycolysis to glucose oxidation, decreasing mitochondrial hyperpolarization and rendering tumor cells more sensitive to apoptosis induction (6). This compound has previously been used in the clinic for the treatment of lactic acidosis and exhibits an appealing toxicity profile when dosed chronically, making it an ideal candidate for cancer treatment (45). Currently, a phase I trial in Canada is accepting patients with recurrent or metastatic solid tumors.

Future Directions for Anti-Glycolytic Therapies

While many compounds targeting glycolysis have generated much enthusiasm due to *in vitro* potency, widespread successes have not yet been realized in *in vivo* settings. A recurring theme in clinical trials investigating compounds within this class of drugs is the high prevalence of dose-limiting toxicities, presumably due to on-target effects in nonmalignant tissue. Therefore, it appears that a significant hurdle that must be overcome in targeting tumor cell metabolism is increasing the selectivity of these pharmaceuticals for malignant tissue versus normal. The fact that lonidamine displays an inherent selectivity for tumor (or at least actively proliferating) cells seems to at least partially account for its success in the clinical arena. Identification of tumor-specific metabolic alterations should provide a therapeutic window wide enough to substantially inhibit glucose utilization by malignant cells without impairing the metabolism of normal cells. The monocarboxylate transporters, which function to export cytoplasmic lactate, have generated interest recently as potential targets due to their relatively selective upregulation in a variety of tumors (46,47). Additionally, our lab has shown that the purine nucleoside analogue 8-amino-adenosine (8-NH2-Ado) is capable of interfering with glucose transporter (GLUT) localization to the plasma membrane in myeloma cells, representing yet another level at which tumor selectivity may be achieved (Submitted paper: Shanmugam M, McBrayer S et al. unpublished data). With current drug development efforts aimed at improving selectivity, glycolysis inhibition as a strategy for cancer treatment may experience a broader utility in the future.

In addition to identifying tumor-specific glycolytic targets, it will also be imperative to identify new means of capitalizing on the metabolic stress induced by this therapeutic approach. A critical cellular process that is initiated to counteract metabolic stress and could provide resistance to glycolysis inhibition *in vivo* is autophagy. Sequestration of intracellular organelles and their subsequent breakdown through the autophagic pathway provides metabolic substrates such as amino acids which can be used as a reserve fuel source for tumor cells (48,49). We have demonstrated in our studies that myeloma cells can resist apoptosis following 8-NH2-Ado-induced glucose deprivation through induction of autophagy (Submitted paper: Shanmugam M, McBrayer S et al. unpublished data). Consistent with this observation, co-treatment of cells with inhibitors of this pathway results in a synergistic apoptotic response. Therefore, evaluating the relationship between various glycolytic inhibitors and autophagy inhibitors could produce marked increases in therapeutic efficacy due to the potentiation of cytostatic effects and conversion to cytotoxic outcomes.

Conclusions

While considering targeting the glycolytic pathway in the treatment of cancer one must take into account compensatory contributions of other cellular metabolites. This is particularly important given the fact that specific TCA cycle intermediates generated by glucose metabolism can also be generated by glutaminolysis. Therapeutics targeting the glycolytic pathway have been shown to synergize with specific therapeutics (41). Further characterization of other classes of drugs that may synergize with the inhibition of glycolysis will aid in enhancing sensitivity to current therapeutics. Targeting the very basis for clinical imaging of cancer (i.e. glucose uptake) can provide new therapeutic options that may be less prone to the development of resistance.

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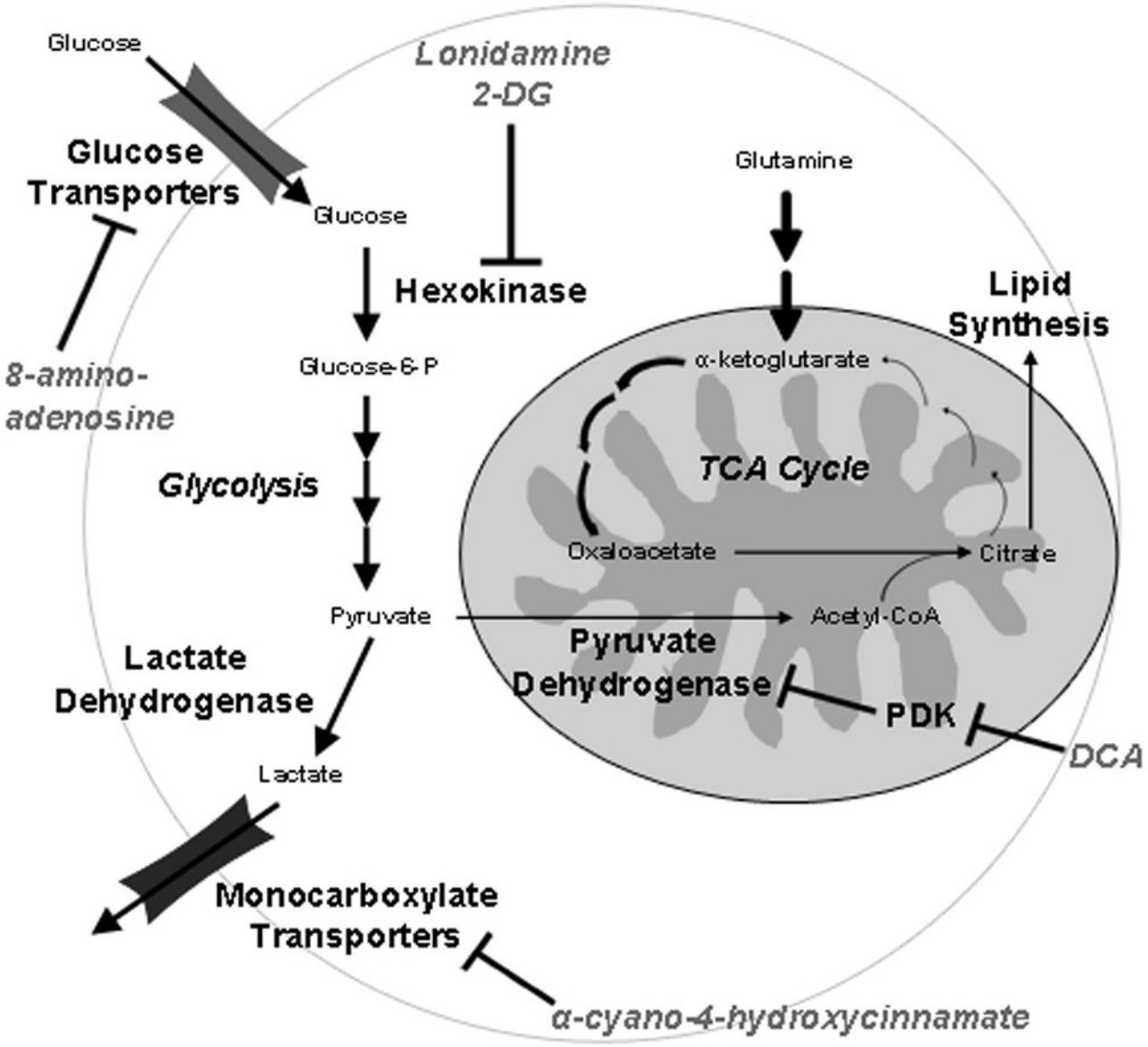

Figure 1. Metabolic alterations promoting tumor cell aerobic glycolysis and associated therapeutic targets

Tumor cells increase glucose consumption through enhanced expression and activity of glucose transporters and hexokinase. Hexokinase carries out the initial phosphorylation of glucose, which is required to retain glucose molecules within the cell. In normal cells, glucose is converted to pyruvate in a series of reactions in the cytosol. Pyruvate, the end product of these reactions, enters the mitochondria and is converted to acetyl-CoA, which is used in the tricarboxylic acid cycle (TCA) cycle to drive ATP synthesis via oxidative phosphorylation. In tumor cells, glucose-derived pyruvate is preferentially converted to lactate in the cytosol and subsequently extruded from the cell through monocarboxylate transporters. Pyruvate molecules which do enter the mitochondria in this context are used largely to fuel a truncated TCA cycle wherein citrate is siphoned out of the mitochondria to stimulate fatty acid biosynthesis. Glutamine can then be used to replenish subsequent metabolites in the TCA cycle through conversion to α-ketoglutarate. Specific enzyme targets for lonidamine, 2-

deoxyglucose (2-DG), 8-amino-adenosine, dichloroacetate (DCA), and α-cyano-4-hydroxycinnamate are indicated. Bold arrows indicate enhanced activity in tumor cells.