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Targeting Glucose Metabolism in Patients With Cancer

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Abstract

Nearly a century ago, Otto Warburg made the astute observation that the metabolic properties of cancer cells differ markedly from those of normal cells. Several decades passed before the concept of exploiting cancer cell metabolism came into clinical practice with the advent of chemotherapy, the underlying principle of which is to target rapidly dividing cells by interfering with critical processes that are all, on some level, driven by cell metabolism. Although chemotherapy can be quite effective, success rates are highly variable and the adverse effects associated with treatment often outweigh the benefits due to the fact that chemotherapy is indiscriminately cytotoxic against all rapidly dividing cells, cancerous or healthy. During the past several years, a more intricate understanding of cancer cell metabolism has permitted the development of targeted therapies that aim to specifically target cancer cells and spare healthy tissue by exploiting the altered metabolism of cancer cells. The identification of new metabolic targets and the subsequent development of small-molecule inhibitors of metabolic enzymes have demonstrated the utility and promise of targeting cancer cell metabolism as an anticancer strategy. This review summarizes recent advances in the identification and characterization of several metabolic enzymes as emerging anticancer targets.

Keywords

the Warburg effect; cancer metabolism; metabolic enzymes; small-molecule inhibitors; anticancer targets

INTRODUCTION

The recent resurgence of interest in tumor metabolism, a concept pioneered by German physiologist Otto Warburg nearly a century ago, has led to several discoveries concerning specific alterations to cellular metabolism in cancer cells, some of which are requisite for malignant transformation.^{1,2} In a phenomenon later designated the “Warburg effect,” Warburg observed that cancer cells produce energy primarily by glycolysis in the cytosol rather than by oxidative phosphorylation in mitochondria as in most normal cells. Although normal cells switch to glycolysis for energy production in the absence of oxygen, cancer

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cells use glycolysis even when oxygen is present (aerobic glycolysis). Leukemia cells, for example, are highly glycolytic despite residing in the bloodstream, in which oxygen is plentiful. Warburg hypothesized that this altered metabolism arose from mitochondrial defects that inhibited their ability to effectively oxidize glucose carbon to carbon dioxide.³

Despite his prescient observations regarding the distinctiveness of tumor metabolism and the suggestion that such alterations could represent targetable vulnerabilities in cancer cells, nearly 80 years passed before Warburg's hypothesis was revisited. Although recent discoveries have served to reinforce many of his initial postulations, the notion that the metabolic properties of cancer cells are a result of damaged mitochondria has since been refuted. Instead, it has been found that these alterations are in fact a result of oncogene-driven metabolic reprogramming required to support cancer cell proliferation and survival. This helps to illuminate why cancer cells would "choose" glycolysis, a relatively inefficient mode of energy production, over the much more efficient oxidative phosphorylation: glycolysis is quicker, and readily provides energy in the form of adenosine triphosphate (ATP) required by rapidly proliferating cancer cells.^{4,5}

In addition to the expeditious production of energy, aerobic glycolysis also facilitates rapid cell division by providing metabolic intermediates that can be shunted into divaricating pathways, in which they serve as precursors for the anabolic biosynthesis of macromolecules. These include nucleotides, amino acids, and fatty acids, respectively, to produce RNA/ DNA, proteins, and lipids, which are necessary for rapid cell division.³⁻⁵ Moreover, glycolytic intermediates can also be diverted into pathways that produce reduced nicotinamide adenine dinucleotide phosphate (NADPH), which not only fuels macromolecular biosynthesis of lipids but also functions as an antioxidant to quench the reactive oxygen species produced during rapid proliferation of cancer cells, which is imperative for the maintenance of cellular redox homeostasis.

Traditional Approaches to Targeting Cancer Cell Metabolism

The concept of exploiting cancer cell metabolism is one that has been in practice for nearly 50 years, since the advent of chemotherapy. The rapid proliferation that characterizes cancer cells is fueled in part by metabolic processes that serve to provide the cell what it requires to grow and divide. The enduring principle of chemotherapy has been to target rapidly dividing cells by interfering with these critical processes that are all, on some level, driven by cell metabolism.

The first use of chemotherapeutic drugs to treat cancer came in the mid-20th century, with the application of nitrogen mustards to treat patients with advanced lymphoma. During World War I, mustard gas was used as a chemical warfare agent by the Imperial German Army. Among the many powerful physiological effects of mustard gas, those afflicted experienced potent hematopoietic suppression, particularly in the leukocyte compartment. It was later reasoned that similar compounds may be useful in treating hematopoietic malignancies that display an overproduction of white blood cells. Indeed, patients with lymphoma who are treated with nitrogen mustards displayed a marked reduction in their

white blood cell count and experienced a transitory remission period.⁶ This opened the door for the development of chemotherapeutic drugs to treat cancer over the next several decades.

The majority of chemotherapeutic drugs can be divided into 5 major classes, all of which function to inhibit cell division: alkylating agents, anthracyclines, plant alkaloids, topoisomerase inhibitors, and antimetabolites. Antimetabolite drugs were among the first effective chemotherapeutic agents to be discovered, and provide the most direct evidence to support the usefulness of disrupting cancer cell metabolism as a treatment strategy. Just as the name suggests, antimetabolites inhibit the use of a metabolite needed for normal cellular metabolic functions. These compounds often masquerade as the metabolite with which they interfere.⁷

Methotrexate

In 1947, after the discovery that the administration of folic acid conjugates could promote leukemia cell proliferation in patients, Farber and his colleagues found that aminopterin, a chemical analog of folic acid, was effective in treating children with acute lymphoblastic leukemia (ALL). To the best of our knowledge, aminopterin was the first antimetabolite used in cancer treatment, and the first drug shown to induce remission in patients with ALL. Methotrexate soon replaced aminopterin as a chemotherapeutic agent, and is still used in treatment regimens for many cancers.⁸

Although unknown at the time of their first clinical use, the molecular mechanism of folate analogues was later elucidated. Methotrexate competitively inhibits dihydrofolate reductase, an enzyme essential to tetrahydrofolate synthesis, by catalyzing the conversion of dihydrofolate to active tetrahydrofolate. Folic acid is needed for the de novo synthesis of thymidine, which in turn is required for DNA synthesis.⁷

5-Fluorouracil

The chemotherapeutic agent 5-fluorouracil (5-FU) has been in clinical use for 40 years, and is used to treat a variety of malignancies including cancers of the colon, rectum, and head and neck. 5-FU primarily functions as an inhibitor of thymidylate synthase, an enzyme that converts deoxyuridine monophosphate (dUMP) into thymidine monophosphate (dTMP). dTMP is subsequently phosphorylated to form thymidine triphosphate for use in DNA replication. The depletion of dTMP by 5-FU thus prevents DNA replication and ultimately results in cell death.⁷

L-asparaginase

The use of the enzyme L-asparaginase to treat patients with ALL represents a fairly rudimentary example of how the distinctive metabolism of cancer cells has been exploited for therapy. In contrast to normal hematopoietic cells, ALL cells are unable to synthesize the nonessential amino acid asparagine and thus depend on circulating asparagine. L-asparaginase catalyzes the conversion of asparagine to aspartic acid, thereby depriving the leukemic cell of the circulating asparagine it requires to survive, leading to cell death.^{9,10} However, its systemic administration may lead to severe side effects, including pancreatitis, hepatic dysfunction, nephrotoxicity, and central nervous system dysfunction.¹¹

Although chemotherapeutic agents can be quite effective, success rates are highly variable. Moreover, the adverse effects associated with chemotherapy often outweigh the benefits. Current regimens can be highly aggressive and are associated with extremely adverse side effects that severely affect quality of life. Because chemotherapeutic agents are indiscriminately cytotoxic, they prove to be equally detrimental to all rapidly proliferating cells, whether healthy or cancerous. Common side effects of chemotherapy result from the damage incurred by rapidly proliferating healthy cells, including alopecia due to effects on hair follicles, myelosuppression due to effects on bone marrow cells, and nausea/vomiting due to effects on the gastric mucosa. Life-threatening side effects include vital organ toxicity and secondary neoplasms.

A New Era of Targeting Cancer Cell Metabolism

The past decade has seen tremendous advances in the understanding of cancer cell metabolism, as well as a more developed appreciation for its complexity. The molecular characterization of metabolic differences between cancer cells and normal cells has provoked exploration of the therapeutic opportunities these differences might provide. Drug development in this vein has sought to exploit metabolic vulnerabilities in cancer cells, with the aim of developing molecularly targeted therapies against cancer cell-specific metabolic alterations. The past several years has witnessed validation of metabolic enzymes as emerging anticancer targets, such as ATP citrate lyase,¹² lactate de-hydrogenase,¹³ pyruvate dehydrogenase kinase,^{14–16} and glutaminase.¹⁷ Below we will focus on several new targets including pyruvate kinase M2 (PKM2), phosphoglycerate mutase 1 (PGAM1), and isocitrate dehydrogenase (IDH) 1/2 in cancer cell metabolism (Fig. 1).

PKM2

PK is a glycolytic enzyme that catalyzes the conversion of phosphoenolpyruvate into pyruvate while concurrently producing ATP. The M1 isoform of PK (PKM1) is expressed in most adult tissues, whereas the M2 isoform (PKM2), an alternatively spliced variant of M1, is expressed during embryonic development.¹⁸ More recently, it has been shown that cancer cells also express PKM2,^{18–20} and that PKM2 plays a key role in promoting the Warburg effect in tumor cells.¹⁸

PKM2 can adopt 2 possible conformations: an inactive dimer and an active tetramer. Recent studies have shown that oncogenic tyrosine kinase fibroblast growth factor receptor kinase 1 phosphorylates PKM2 at tyrosine 105 to inhibit the formation of active tetrameric PKM2, thereby promoting the formation of the inactive dimer.²¹ Moreover, PKM2 has been shown to be acetylated on lysine 305 in response to high intracellular glucose levels. Acetylation at K305 decreases PKM2 enzyme activity and promotes its lysosomal-dependent degradation via chaperone-mediated autophagy.²² Together, these results suggest that negative regulation of PKM2 activity is advantageous to cancer cells. When PKM2 is less active, glycolytic flux is decreased. This in turn allows cancer cells to accumulate building blocks and precursors produced in the upper glycolytic process above PKM2, and shunt intermediates into divericating biosynthetic pathways including the pentose phosphate pathway and the serine biosynthesis pathway, which support cancer proliferation.

This notion prompted the development of several small-molecule PKM2 activators (Table 1). Because PKM2 is expressed in cancer cells and not normal adult tissue, selectively targeting PKM2 should have minimal adverse effects on healthy cells, making it a promising anticancer target. Current PKM2 activators, including TEPP-46, DASA-58, and ML-265, have all been shown to promote constitutive activity of PKM2, mimicking the enzymatic activity of PKM1. Increased PKM2 activity consequently results in decreased cell proliferation under hypoxia and attenuated tumor growth in mice, likely due to decreased anabolic biosynthesis.^{23,24} To the best of our knowledge, the extent of off-target toxicity induced by PKM2 activators has yet to be fully elucidated, and further studies are warranted to better understand the potential toxicity of PKM2 activators at the whole-organism level.

It is important to note that PKM2 has recently been shown to have nonmetabolic functions implicit in tumor-igenesis as well. In particular, various studies have demonstrated a nuclear role for PKM2 in which it serves to directly regulate transcription of genes encoding tumor-promoting factors including Oct-4,²⁵ hypoxia-inducible factor 1- α (HIF-1 α),²⁶ and β -catenin.²⁷ The nonglyco-lytic functions of PKM2 must therefore be accounted for as well during the continued development of small-molecule PKM2 activators and inhibitors.

PGAM1

PGAM1 catalyzes the conversion of 3-phosphoglycerate (3PG) to 2-phosphoglycerate (2PG) during glycolysis. PGAM1 is uniquely positioned at the branching point between glycolysis and anabolic biosynthesis, making it an attractive anticancer target. In many cancers, including hepatocellular carcinoma, colorectal cancer,^{28,29} and leukemia,³⁰ PGAM1 activity is increased compared with normal tissues. Moreover, PGAM1 gene expression is believed to be upregulated due to loss of *TP53* in cancer cells, because *TP53* negatively regulates the PGAM1 level.^{31–33} PGAM1 has been shown to regulate distal metabolic pathways by controlling the metabolite levels of its substrate 3PG and product 2PG, which exert regulatory functions on key metabolic enzymes including 6-phosphogluconate dehydrogenase in the oxidative pentose phosphate pathway and 3-phosphoglycerate dehydrogenase in the serine biosynthesis pathway, respectively.³⁰ Thus, the inhibition of PGAM1 not only affects glycolytic flux in cancer cells but also compromises biosynthetic pathways.

There currently exist 2 small-molecule inhibitors of PGAM1, MJE3 and PGMI-004A (Table 1). MJE3 was found to inhibit proliferation of MDA-MB-231 breast cancer cells, and was subsequently shown to target PGAM1 through in situ proteome reactivity profiling. MJE3 inhibits PGAM1 exclusively in intact cells, suggesting that the drug may be modified to its active form in cells.³⁴ This presents a set of limitations with regard to determining inhibitor specificity. The small-molecule PGAM1 inhibitor PGMI-004A was identified through coupled PGAM1 and enolase assays, using a pure in vitro system to overcome the limitations associated with MJE3. PGMI-004A was shown to inhibit proliferation of diverse cancer and leukemia cell lines, as well as primary leukemia cells from patients, without demonstrating any significant toxicity to normal proliferating cells or peripheral blood and bone marrow cells isolated from healthy patients. Moreover, PGMI-004A was shown to be effective in attenuating tumor growth in mice with minimal off-target toxicity at the whole-

organism level.³⁰ Together, these results suggest that targeting PGAM1 is a promising anticancer strategy that may produce minimal adverse side effects in humans. However, to the best of our knowledge, the effect of PGAM1 inhibition on normal, metabolically active, postmitotic tissue such as the heart, brain, and skeletal muscle remains to be determined, and represents a potentially sizeable obstacle to be overcome before anti-PGAM1 therapy can be used in humans.

IDH

IDH catalyzes the oxidative decarboxylation of isocitrate, producing α -ketoglutarate in the citric acid cycle. Both IDH1 and IDH2 produce NADPH, in which the former is localized to the cytosol and the latter to the mitochondria. Unlike PKM2 and PGAM1, IDH1 and IDH2 have both been identified as mutated in human cancer. Large-scale sequencing studies have revealed that 60% to 90% of patients with secondary gliomas and 12% to 18% of patients with acute myeloid leukemia (AML) have heterozygous mutations in IDH1 or IDH2.^{35,36} Mutations affecting IDH1 and IDH2 confer neomorphic activity to the enzyme, wherein isocitrate is converted to 2-hydroxyglutarate (2-HG) instead of α -ketoglutarate. It has been reported that 2-HG increased 100-fold in patients with gliomas and AML with IDH mutations, suggesting it could serve as a clinical biomarker.^{37,38} Subsequent studies have identified 2-HG as an onco-metabolite, capable of competitively inhibiting α -ketoglutarate-dependent dioxygenases, including histone and DNA demethylases, leading to genome-wide hypermethylation and ultimately a block in cellular differentiation.^{39–42}

The identification of IDH mutations and glioma and AML followed by the discovery of 2-HG as an onco-metabolite quickly prompted the development of IDH mutant inhibitors (Table 1). Currently, 2 IDH mutant inhibitors have been developed: AGI-5198, which selectively inhibits IDH1-R132H,⁴³ and AGI-6780, which selectively inhibits IDH2-R140Q.⁴⁴ Both inhibitors promote cellular differentiation and impair IDH mutant but not IDH wild-type cancer cell proliferation in vitro and in vivo (AGI-5198 in glioma cells and AGI-6780 in leukemia cells).

Future Directions and Remaining Obstacles

In addition to identifying new targets for monotherapy, combination therapies targeting complementary metabolic pathways may result in the enhanced or synergistic inhibition of cancer cell viability. For example, cancer cells rely primarily on glycolysis for ATP production, but inhibiting glycolysis would in theory drive cells toward oxidative phosphorylation as an ATP source. Targeting both glycolysis and oxidative phosphorylation would likely lead to the severe depletion of intracellular ATP levels and, consequently, cell death. This concept has been explored in a prostate cancer model using the glycolytic inhibitor 2-deoxyglucose and the oxidative phosphorylation inhibitor metformin. It was shown that prostate cancer cells displayed significant sensitivity to this combination, whereas normal prostate cells were only moderately affected.⁴⁵

An alternative strategy involves the combined inhibition of distinct biosynthetic pathways. In cancer cells, glucose and glutamine serve as primary carbon sources for ATP production and biosynthesis.⁴⁶ Glutamine has recently been shown to be crucial for de novo lipogenesis

in cells under hypoxia. Normally, precursors for fatty acid synthesis are generated from glucose-derived pyruvate through the oxygen-dependent tricarboxylic acid cycle. However, proliferating cells undergoing aerobic glycolysis and those grown under hypoxic conditions use reductive carboxylation of glutamine-derived α -ketoglutarate to synthesize lipid precursors, with the latter relying almost exclusively on this pathway for de novo lipogenesis.⁴⁷ Inhibition of this pathway would thus disrupt de novo lipid biosynthesis in hypoxic tumor cells. Therefore, combined inhibition of the reductive glutamine pathway together with inhibitors of glycolytic flux would block at least 2 different biosynthetic pathways from 2 different carbon sources, which may in turn lead to enhanced or synergistic inhibition of cancer cell viability, particularly under hypoxia.

The major outstanding concern associated with targeting cancer cell metabolism lies in the fact that all cells use the same life-sustaining metabolic networks, and the disruption of any of these metabolic processes has the potential to adversely affect cancer cells and normal cells alike. The majority of metabolic enzymes implicated in the pathogenesis of cancer are not mutated, and are expressed both in transformed cells and normal cells throughout the body. This presents a considerable set of challenges with regard to achieving specificity in targeting cancer cells versus normal cells. However, the altered metabolism in cancer cells does provide a window for therapeutic intervention. Although most metabolic enzymes are not mutated in cancer, there is increasing evidence to suggest that many are aberrantly regulated by oncogenes, which can in turn create addictions to specific metabolic pathways.¹⁰ Dissecting how oncogenes drive metabolic enzyme activity will certainly provide insight into potential therapeutic strategies that exploit the altered metabolism in cancer cells. For example, several metabolic enzymes have been shown to be regulated by posttranslational modifications in cancer cells but not normal cells. Oncogenic tyrosine kinase signaling has been well documented to regulate the activity and function of several metabolic enzymes, including PKM2,²¹ lactate dehydrogenase-A,⁴⁸ pyruvate dehydrogenase kinase 1,⁴⁹ and PGAM1.⁵⁰ This has provided a great deal of insight into how oncogene addiction can in turn regulate cellular metabolism, thereby providing an important distinction between metabolic regulation in cancer cells versus normal cells.

Drug combinations also represent an important avenue to be explored with regard to targeting cancer cells and sparing normal cells. Metabolic reprogramming in cancer cells renders them more reliant on certain metabolic pathways, and thus potentially more sensitive to metabolic inhibitors compared with normal cells. Drug combinations would likely permit reduced drug doses, which may limit the effect metabolic enzyme inhibitors would have on normal, metabolically active cells.

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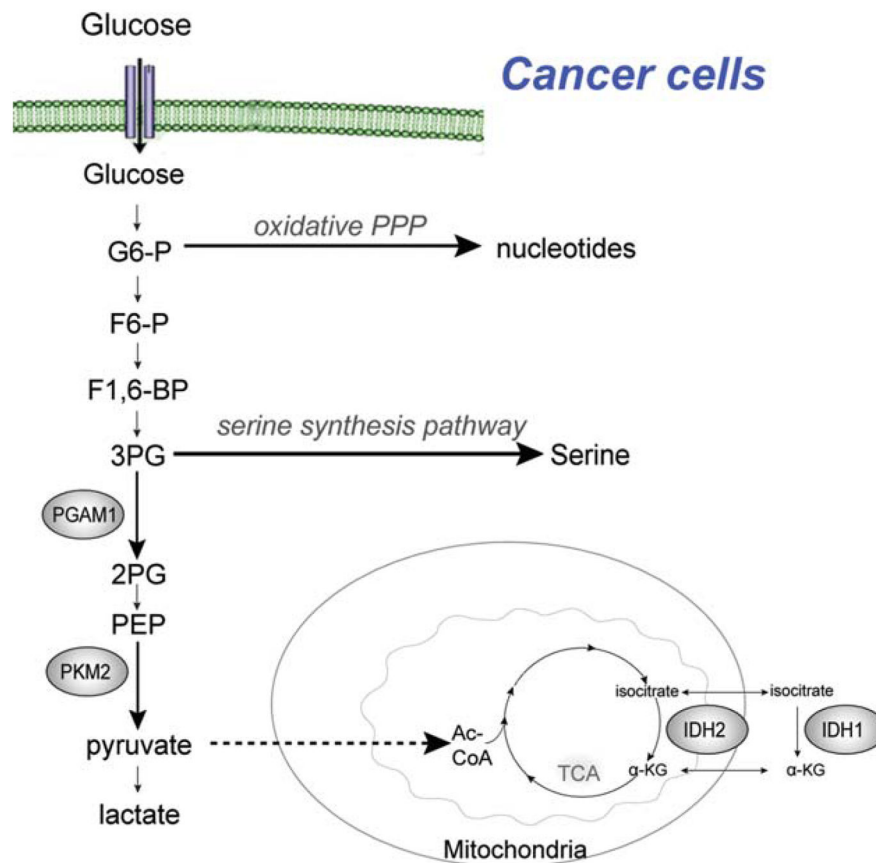


Figure 1.

New targets in cancer cell metabolism are shown. The glycolytic enzymes pyruvate kinase M2 (PKM2) and phosphoglycerate mutase 1 (PGAM1) as well as the tricarboxylic acid (TCA) cycle enzyme isocitrate dehydrogenase (IDH) 1/2 have been recently identified as new and promising targets for cancer therapy. PKM2 catalyzes the conversion of phosphoenolpyruvate (PEP) into pyruvate while concurrently producing adenosine triphosphate, and has been shown to play a key role in promoting the Warburg effect in tumor cells. PGAM1 catalyzes the conversion of 3-phosphoglycerate (3PG) to 2-phosphoglycerate (2PG), and is uniquely positioned at the branching point between glycolysis and anabolic biosynthesis, making it an attractive anticancer target. PGAM1 activity is increased in many cancers, and its gene expression is believed to be upregulated due to loss of *TP53* in cancer cells, because *TP53* negatively regulates the PGAM1 level. IDH catalyzes the oxidative decarboxylation of isocitrate, producing α -ketoglutarate (α -KG) in the citric acid cycle. Both IDH1 and IDH2 produce nicotinamide adenine di-nucleotide phosphate (NADPH), and both have been identified as being mutated in human cancers, namely glioma and acute myeloid leukemia. G6-P indicates glucose 6-phosphate; PPP, pentose phosphate pathway; F6-P, fructose 6-phosphate; F1,6-BP, fructose 1,6-bisphosphate; Ac-CoA, acetyl coenzyme A.

TABLE 1

Targeting Metabolic Enzymes for Cancer Therapy

Target	Agent(s)	Development Stage	Drug Development Platform(s)
PKM2	TEPP-46	Preclinical (cell line and animal data)	H1299 lung cancer cells
	DASA-58	Preclinical (cell line data only)	H1299 lung cancer cells
	ML-265	Preclinical (cell line and animal data)	H1299 and A549 lung cancer cells
PGAM1	MJE3	Preclinical (cell line data only)	MDA-MB-231 breast cancer cells
	PGMI-004A	Preclinical (cell line and animal data)	Diverse leukemia and solid tumor cells
IDH1	AGI-5198	Preclinical (cell line and animal data)	R132H-positive glioma cells
IDH2	AGI-6780	Preclinical (cell line and animal data)	R140Q-positive AML cells

Abbreviations: AML, acute myeloid leukemia; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2, PGAM1, phosphoglycerate mutase 1, PKM2, pyruvate kinase M2.