Stalling the Engine of Resistance: Targeting Cancer Metabolism to Overcome Therapeutic Resistance

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Abstract

Cancer cells are markedly different from normal cells with regards to how their metabolic pathways are used to fuel cellular growth and survival. Two basic metabolites that exemplify these differences through increased uptake and altered metabolic usage are glucose and glutamine. These molecules can be catabolized to manufacture many of the building blocks required for active cell growth and proliferation. The alterations in the metabolic pathways necessary to sustain this growth have been linked to therapeutic resistance, a trait that is correlated with poor patient outcomes. By targeting the metabolic pathways that import, catabolize, and synthesize essential cellular components, drug-resistant cancer cells can often be resensitized to anticancer treatments. The specificity and efficacy of agents directed at the unique aspects of cancer metabolism are expected to be high; and may, when in used in combination with more traditional therapeutics, present a pathway to surmount resistance within tumors that no longer respond to current forms of treatment. *Cancer Res; 73(9); 2709–17. ©2013 AACR.*

Introduction

One of the distinguishing features of cancer is an escape from the typical regulatory constraints that prevent rapid and uncontrolled cellular division. Many cellular modifications occur within the bioenergetic and metabolic pathways, driven by the energetic needs of a dividing cell. One of the earliest examples of altered metabolism was shown in Otto Warburg's seminal work, wherein Warburg observed that cancerous tissues use oxygen-independent methods for breaking down glucose (1, 2). While the Warburg effect is not yet fully understood, it seems to consistently arise in a wide variety of cancers with diverse genetic backgrounds.

For cells integrated into the vasculature, nutrients are continually available and cancer cells absorb these nutrients at a much higher rate than normal cells (3–5). Thus, the metabolic changes exhibited in cancer are a result of factors beyond pure energy production and instead work to support unconstrained cellular growth by generating the cellular resources that a rapidly dividing cell requires (6, 7). Nucleotide triphosphates and amino acids are necessary building blocks for genome replication and protein synthesis that occur as cells grow. Furthermore, growth and division both require expansion of the cellular, nuclear, and mitochondrial membranes, which necessitates increased fatty acid synthesis to support the production of the lipid bilayers. In addition to basic building blocks, other components necessary to fuel cellular growth (ATP and NADPH) or protect the growing cell (NADH and NAD^+) are regulated through components of the aerobic glycolysis machinery and must have their levels carefully managed to ensure that the basic building blocks can be efficiently converted into new biomass (8).

Glucose and glutamine can be broken down into the raw materials necessary to drive tumor growth (6, 9). The metabolic shift and increased glucose catabolism observed in cancer cells results in increased production of the biosynthetic precursors consumed as a cell grows. With upregulated glucose import, a fraction of the glucose taken in will be used in biosynthesis pathways upstream of pyruvate or be converted to pyruvate and enter the TCA cycle to provide precursors for fatty acid and amino acid synthesis, whereas all remaining glucose is converted to lactate and exported from the cell (4). Glutamine catabolism follows a similar pattern: Glutamine uptake is enhanced, and a portion of the glutamine is catabolized to maintain cellular levels of basic biosynthetic precursors, but the majority of cellular glutamine is converted into lactate or alanine (4, 10, 11). In contrast with the catabolism of glucose, conversion of glutamine to lactate passes through the TCA cycle, which aids in the maintenance of the pool of mitochondrial carbons and NADPH. The remaining glutamine provides carbon and nitrogen sources for amino acid synthesis and contributes nitrogen in purine and pyrimidine base synthesis (11). The uptake and breakdown of glucose and glutamine represent the central pathway for fueling tumor growth and methods that target these pathways can have significant effects on cellular growth and viability.

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Although many aspects of tumor metabolism rely on the conserved metabolic pathways commonly used by rapidly proliferating cells, evidence indicates that there are facets of tumor metabolism that differ from nontumorigenic proliferating cells. Work investigating the M2 isoform of pyruvate kinase (PKM2) indicates that in cells with low pyruvate kinase activity, as it is in those expressing the PKM2 isoform, pyruvate can be formed from PEP through PGAM1 phosphorylation (12). This alternative pathway allows for a decoupling of ATP production from glucose metabolism, providing a way to prevent the allosteric inhibition of glycolysis pathway enzymes that occurs at high concentrations of ATP while still generating the downstream biomolecules necessary for cellular growth (12). Comparison of the gene expression profiles for oncogenic foci and induced pluripotent stem cells (iPSC) shows that whereas many pathways are modulated in a similar fashion, such as the upregulation of monosaccharide metabolic genes or downregulation of differentiation related genes, there are still distinct differences (13). The oncogenic foci upregulated a large variety of metabolic clusters—such as carbohydrate metabolism, sphingolipid metabolism, membrane lipid metabolism, and organophosphate metabolism—in addition to cellular stress and damage pathways, whereas the expression profile of the iPSC activated pluriopotency-related gene families (13). Exploiting the cancer-specific upregulation of stress pathways has already been shown to be an effective strategy for the development of highly selective anticancer treatments (14). Piperlongumine triggers cell death in cancerous cells but not in rapidly or slowly proliferating normal cells; murine tumor xenografts treated with piperlongumine displayed drastic response with no observed toxicity in normal mice (14). Similar specificity may be achievable through treatments targeting the dysregulated aspects of cancer metabolism.

Work linking dysregulated metabolism to drug resistance indicates that resistance may arise in part because altered metabolism can produce elevated ATP and NADPH levels (15, 16). Common mechanisms for generating chemoresistance are energy intensive and include enhanced DNA repair, misregulation of growth factor signaling, increased drug efflux, higher expression of antiapoptotic genes, or survival signaling pathways (17). Chemotherapies exert cytotoxic effects in part by inducing oxidative damage (18, 19), whereas increased glucose consumption gives rise to abundant NADPH, which contributes to therapeutic resistance (20, 21). The ability of deregulated metabolic pathways to protect cancer cells makes them attractive targets for improving chemotherapeutics (Supplementary Table S1).

Targeting the Resource Absorption Machinery to Potentiate Therapeutics

Cancer cells depend on their altered metabolism to generate the necessary resources to fuel their growth, and the synthesis of these building blocks is dependent on the catabolism of glucose and glutamine. The uptake of glucose and glutamine is often increased through the upregulation of transporters, such as the GLUT family glucose transporters or the ASCT2 amino acid transporter. These are commonly targeted in an attempt to disrupt the dysregulated metabolism observed in cancer cells.

Glucose transport

The GLUT family proteins facilitate the uptake of extracellular glucose, and are often upregulated in cancer. Directly targeting these transporters is one way to attack tumor growth. In nude mice xenografts and cell culture, A549 lung cancer cells display lower GLUT1 expression and glucose uptake when treated with the irreversible GLUT1 inhibitor WZB117, resulting in an inhibition of growth that is synergistic with both cisplatin and paclitaxel (22). Exogenous ATP rescued cellular growth, indicating that the decrease in GLUT1 expression slowed tumor growth by limiting available ATP (22). *In vitro* WZB117 shows selectivity for cancer cells, whereas studies in animal models show relatively high efficacy and low toxicity, but treatment also induces transient hyperglycemia and a slight decrease in weight resulting from a loss of fat (22). Renal cell carcinomas lacking functional von Hippel–Lindau (*VHL*) tumor suppressor genes have been shown to be selectively targeted by an inhibitor of GLUT1, STF-31, whereas no effect has been observed on glycolysis in cells expressing the wild-type *VHL* gene (23). *In vivo*, STF-31–based inhibition of GLUT1 was able to impede glucose uptake and kill tumor cells with no toxicity for noncancerous cells (23). Although inhibition of glucose transporters varies in efficacy based on the tumor type when the strategy is used alone, it is effective when coupled with other drugs as part of a combinatorial strategy. The glucose transporters are critical for maintenance of multiple myeloma cells, but studies have shown that inhibition of glucose transporters can increase sensitivity to other chemotherapeutics. This can be observed in how the off-target inhibition of the GLUT4 transporter by the HIV protease inhibitor ritonavir increases doxorubicin sensitivity in multiple myeloma cell lines (24). Combinatorial treatment has also been an effective way to overcome chemoresistance. Hypoxia-inducible factor-1α (HIF-1α) enhances the expression of GLUT1 in hypoxic environments, a condition that frequently occurs in tumors. Hypoxia is well known to contribute to resistance to chemotherapeutics, yet inhibition of GLUT1 via phloretin overcomes this hypoxia-induced resistance when used in combination with daunorubicin (25). Whereas phloretin is a competitive inhibitor for glucose transporters, low concentrations have been shown to be effective on hypoxic cells—a property that could enhance the selectivity of this treatment (25). With data indicating that GLUT3 is upregulated in temozolomide-resistant cells, overcoming chemoresistance by targeting glucose transport coupled with treatment with standard chemotherapeutic agents may be an effective strategy against drug-resistant tumors (26).

Glutamine transport

Like glucose transport, upregulation of glutamine transporters is commonly observed in cancer cells (11). For many cancers, disruption of the constant uptake of glutamine can lead to outcomes more drastic than expected for pure amino acid starvation (27–30). In hepatocellular carcinoma, silencing of the glutamine transporter ASCT2 by inducible antisense

RNA results in cellular death within 48 hours (31). The importance of glutamine transporters for cellular survival is further shown by the effect of selective estrogen receptor modulators (SERM), such as tamoxifen and raloxifene, on ER$^-$ cell lines and cell lines derived from estrogen-insensitive tissues (32). Both tamoxifen and raloxifene can inhibit the glutamine transporter ASCT2 and lower cellular uptake of glutamine, resulting in growth inhibition and apoptosis in cell lines that are estrogen insensitive (32). Finally, inhibition of the SLC6A14 amino acid transporter by α-methyl-DL-tryptophan (α-MT) induces phenotypes associated with amino acid starvation, such as mTOR inhibition and activation of autophagy, but when coupled with an inhibitor of autophagy, the combined treatment triggers apoptosis (33). Although α-MT is only effective in the subset of cells expressing the SLC6A14 transporter, which is not expressed in all cancer types, it is highly selective for malignant cells, as SLC6A14 seems not to be expressed in nonmalignant cells (33). Both glucose and glutamine transporters play a key role in providing cancerous cells with resources, and inhibiting them results in slower cell growth or cellular death, even in cells that have been shown to be refractory to other chemotherapeutic treatments.

Targeting the Metabolic Machinery to Potentiate Therapeutics

Targeting the resource import machinery that fuels dysregulated metabolism can be an effective strategy for cancer therapeutics. Once the basic resources have entered the cell, a wide variety of components within the biosynthetic cellular machinery are required to synthesize the biologic precursors that support continued cellular division. Later in this review we discuss selected elements within the biosynthetic pathways that have shown promise in sensitizing chemoresistant cells.

Glycolysis

Hexokinase catalyzes the first step in the catabolism of glucose, a key step in the glycolytic pathway. Two small-molecule inhibitors, 2-deoxy-D-glucose (2-DG) and 3-bromopyruvate (3-BP), target hexokinase and to disrupt the early steps of glycolysis and have shown promise as chemotherapeutic agents.

2-DG is a glucose analogue that cannot be fully processed by the glycolytic enzymes, resulting in an inhibition of glycolysis after it is phosphorylated by hexokinase. We have shown that 2-DG can effectively induce apoptosis in alveolar rhabdomyosarcoma, whereas hypoxic tumor cells are known to be sensitive to 2-DG treatment (34–36). The use of 2-DG as a solo agent is limited because of the high concentration necessary to compete with glycolytic pathway products, but it has been effective as part of a combinatorial treatment regimen. The chemotherapeutic agents doxorubicin and paclitaxel significantly slowed tumor growth and prolonged survival of mice with osteosarcoma and non–small cell lung xenografts, respectively, when mice were cotreated with 2-DG (36). We have also shown that trastuzumab-resistant breast cancer cells can be resensitized to trastuzumab through the addition of 2-DG (37). Finally, Bcl-2 family antagonists are only effective in certain cell varieties, but highly resistant leukemias are sensitized and undergo rapid apoptosis when Bcl-2 antagonist treatment is preceded by glycolysis inhibitor 2-DG (38).

A second small-molecule glycolysis inhibitor that has shown promise as a chemotherapeutic agent is the pyruvic acid derivative 3-BP, which also targets hexokinase. Supplying extra ATP exogenously can induce chemoresistance in colon cancer cells, whereas ATP-depleting factors such as 3-BP have been shown to help induce sensitivity to cell lines selected for resistance to chemotherapeutic agents such as oxaliplatin and 5-fluorouracil (16). Studies show that ATP-binding cassette (ABC) transporter-based resistance to daunorubicin or mitoxantrone is also highly dependent on cellular ATP levels (39). Daunorubicin or mitoxantrone treatment *in vitro* (human myeloma, myelogenous leukemia, and liver carcinoma cell lines) or *in vivo* (murine xenografts) showed suppressed resistance, increased cytotoxicity, and slowed subcutaneous tumor growth when coupled with 3-BP (39). Studies in animal models have shown a lack of *in vivo* toxicity and an inability to cross the blood brain–barrier, but as a competitive inhibitor, the concentrations necessary for therapeutic effect as a solo agent may be prohibitive. The success of glycolysis inhibitors such as 2-DG and 3-BP predicts that other inhibitors targeting components in these pathways will also have a high likelihood to produce drug-sensitizing effects.

PKM2 is preferentially expressed in many cancers and favors glycolysis (12, 40). Inhibitors of PKM2 have shown highly selective antitumor activity in animal and human xenografts tumor models (41–45). Recent work also shows that reducing PKM2 activity via CD44 knockdown results in lower cellular glutathione levels, decreased glucose uptake, lactate production, and ATP production while increasing reactive oxygen species (ROS) levels and also enhancing cisplatin sensitivity (20). As decreased activity of PKM2 helps overcome hypoxia-induced drug resistance, small-molecule compounds that modify PKM2 activity—such as TLN-232 (inhibitor) and 2-Oxo-N-aryl-1,2,3,4-tetrahydroquinoline-6-sulfonamides (activator)—may also be effective in lowering resistance to current chemotherapeutic treatments (41, 46). The TLN-232 inhibitor has exhibited high selectivity even at low doses for cancer cells *in vitro* and in *in vivo* animal models, and although TLN-232 treatment does trigger a transient weight loss, it is well tolerated with no toxicity observed even at high doses (41, 46).

Glutamine catabolism

Glutaminase catalyzes the first step in the catabolism of glutamine, hydrolyzing it into glutamate and ammonia. Inhibition of glutaminase can deprive the cell of biosynthetic precursors needed for rapid growth, evidenced by the reduction of *in vitro* growth of glioblastoma cells containing an isocitrate dehydrogenase 1 mutation common to many gliomas and acute myelogenous leukemias observed when glutaminase activity was reduced through siRNA or BPTES treatment (30). Glutamine analogues often cause *in vivo* toxicity, lack specificity, or are generally ineffective, whereas inhibitors of glutaminase—such as BPTES—provide an opportunity to realize the benefits of glutamine deprivation in a way that minimizes the clinical downsides (30). The small-molecule inhibitor 968 prevents Rho GTPase-mediated cellular transformation by

inhibiting glutaminase, an essential component in Rho GTPase-mediated transformation, yet elicited no effect on the growth or morphology of normal cells (47). In addition to blocking cellular transformation, 968 also showed the ability to inhibit the *in vivo* growth of lymphoma murine xenografts (47). Glutaminolysis is also integrated into the amino acid biosynthesis pathways by activating mTORC1 signaling and fueling cellular growth, which also could induce mTORC1-mediated resistance to common chemotherapeutic agents such as cisplatin in malignant AFP-producing gastric carcinomas (48, 49). Inhibition of mTORC1 with the dual phosphoinositide 3-kinase (PI3K)/mTOR inhibitor NVP-BEZ235 can resensitize Jurkat cells with induced vincristine resistance, clearly showing that reducing mTORC1 activity can lead to therapeutic sensitivity in resistant cells (50). NVP-BEZ235 exhibits minimal effects on normal cells *in vitro* but shows good oral bioavailability and low toxicity *in vivo* (50). Inhibiting glutaminolysis is predicted to have a similar sensitizing effect, through the reduction of mTOR signaling and depletion of the cellular pool of available resources. Glutamine is a critical resource for dysregulated cellular growth, and inhibition of glutamine breakdown by targeting glutaminase merits further exploration as an antitumorigenic and therapeutic potentiating strategy. The important role of mTOR and PI3K pathways in cancer has been covered exhaustively elsewhere (51–63).

Lactate production and export

Lactate dehydrogenase (LDH) is a key glycolytic enzyme, as it converts pyruvate into lactate and provides a pathway for nonoxidative disposal of the byproducts of glycolysis. Lactic acid is a significant byproduct of cancer cell metabolism and is often exported from the cell to remove excess carbon and maintain cellular NADPH stores (4). Inhibition of MCT1-based lactate export through treatment with α-cyano-4-OH-cinnamate (CHC) or lonidamine causes the tumor microenvironment to decrease in pH, with significant levels of cellular death occurring as the pH reaches 6.5, the typical microenvironmental tumor pH (64–66). CHC treatment has been shown to effectively slow the tumor growth rate in murine models of lung adenocarcinoma and colorectal adenocarcinoma xenografts, whereas Lewis lung carcinoma tumor-bearing mice treated with CHC showed greatly increased sensitivity to a single 6 Gy dose of radiation (65, 66). Mild side effects have been observed in patients after lonidamine treatment, with approximately half displaying myalgia; similarly, animal models indicate that the negative side effects of lonidamine are less likely to occur when it is given orally rather than intravenously. The LDH-A isoform has been shown to be upregulated in response to the overexpression of oncogenes such as *HER2* and *MYCN* (64, 67). Targeting the conversion of pyruvate to lactate has also been shown to be a productive anticancer strategy. Glycolytic cell types have shown susceptibility to FX11-based LDH-A inhibition, exemplified by inhibition of tumor growth formation in P198 pancreatic xenografts, p493 β-lymphoma xenografts, and pancreatic LZ10.7 cells. Inhibition of LDH-A via siRNA or FX11 treatment results in increased mitochondrial function, evidenced by higher oxygen consumption and ROS generation, as well as an increase in necrosis and cellular death.

When FX11 was combined with FK866, a nicotinamide phosphoribosyltransferase inhibitor, tumors underwent regression, whereas FK866 or FX11 alone merely slowed tumor growth (68, 69). Although solubility may require further derivatization of FX11, animals undergoing FX11 treatment did not lose weight or exhibit any symptoms of toxicity (68, 69). In addition, we have shown that the inhibition of LDH-A, either through siRNA or oxamate treatment, can overcome resistance to both paclitaxel and trastuzumab (37, 70).

Citric acid cycle

Metformin is a complex I inhibitor for the mitochondrial respiratory chain that is best known for its use as a treatment of diabetes. A study of the incidence rate of cancer within diabetics linked metformin use to lower incidence rates of cancer and better survival for diabetic patients who developed pancreatic cancer (71–74). In addition to the initial studies linking metformin to better clinical outcomes for diabetic patients with pancreatic cancer, newer work has investigated the ability of metformin to address therapeutic resistance in a variety of cancer types.

Cisplatin-resistant ovarian cancer cell lines showed a synergistic response to treatment with metformin and phenethyl isothiocyanate (PEITC), resulting in slower cancer cell growth and induction of cell death for ovarian cancer cells (75). Similarly, pancreatic cancer ductal adenocarcinoma cell lines (SUIT-2 and MIAPaCa-2) exhibiting varying degrees of gemcitabine resistance have been used to test the efficacy of gemcitabine treatment in combination with metformin or metformin and R1507 [a humanized anti–insulin-like growth factor-IR (IGF-IR) monoclonal antibody]. The combination of gemcitabine with metformin or metformin and R1507 induced greater inhibition of cellular proliferation and more apoptosis than solo treatment, whereas gemcitabine treatment alone increased the expression of genes indicative of chemoresistance, such as survivin and XIAP (76). Metformin has also been tested with respect to trastuzumab-resistant HER2-amplified breast cancers (77). Selectively targeting more chemoresistant cell populations, such as cancer stem cells (CSC), may provide a strategy to resensitize a tumor to chemotherapeutic compounds. Metformin has been reported to preferentially target CSC-like cells and is significantly more effective in $CD44^+/CD24^-$/low JIMT-1 cells, a cell line derived from a pleural metastasis of a patient resistant to trastuzumab, compared with non-the $CD44^+/CD24^-$/low JIMT-1 cell population, *in vitro* (77). Similarly, xenografts of JIMT1 were resistant to trastuzumab treatment, as no reduction in tumor growth was observed over a 7-week course of treatment. However, when treated with metformin alone or trastuzumab in combination with metformin, tumor volumes were reduced by 2- or 4-fold respectively, indicating that metformin treatment can help overcome trastuzumab resistance (77).

Pyruvate dehydrogenase kinase (PDK) phosphorylates and inhibits pyruvate dehydrogenase, preventing the formation and entry of acetyl-CoA into the citric acid cycle. Increased expression or activity of PDK isoforms may play a role in the metabolic shift away from mitochondrial oxidation and contributes to drug resistance, as siRNA-targeting PDK restores

mitochondrial oxidation in cancerous, but not normal, cells (78, 79). The small-molecule dichloroacetate (DCA) also inhibits PDK-triggering apoptosis in cancerous cells but requires pharmacologically prohibitive concentrations to be effective, likely due to the decrease in expression of the cellular transporter responsible for DCA uptake in cancer cells (78, 80). Combination therapy with other agents, such as omeprazole or temozolomide, has shown to be more effective than solo treatments (81, 82). This shows that targeting components related to the citric acid cycle can be an effective strategy in the design of new therapeutics.

Fatty acid synthesis

ATP citrate lyase (ACLY) catalyzes the ATP-dependant conversion of citrate to acetyl-CoA and oxaloacetate, a key step in fatty acid biosynthesis. As expected, treatment with the ACLY inhibitor SB-204990 reduced cellular acetyl-CoA concentrations (83). In A549 xenografts, ACLY inhibition is cytostatic and induces differentiation, whereas for pancreatic xenografts SB-204990 treatment resulted in significant growth inhibition. ACLY inhibition results in more severe effects for more glycolytic cells, as ACLY inhibition hinders glucose-dependant lipid synthesis, and this is expected to make the effects of compounds that inhibit ACLY favor tumor cells over nonglycolytic and vegetative cells, as the latter are less dependant on ACLY activity (83). SB-204990 is orally bioavailable and shows no toxicity in animal models, but may have low *in vivo* stability (83).

Synthesis of the fatty acids used for lipogenesis requires precursors derived from the citric acid cycle, such as acetyl-CoA or malonyl-CoA. These precursors are then used by fatty acid synthase (FASN) enzyme complex to produce components necessary for lipogenesis, such as palmitate. FASN is upregulated in many cancers and correlates with poor patient outcomes, such as metastasis. FASN knockdown xenografts had smaller, slower-growing tumors with lower tumorigenic potential and less metastasis relative to FASN-expressing xenografts (84). FASN inhibitors, such as G28UCM, were able to effectively reduce the size of established xenografts by 20% to 90%. This decrease in size was accompanied by increased apoptotic cell death and decreased HER2 phosphorylation (85). Most FASN inhibitors (e.g., cerulenin, C75, EGCG) are unstable or impotent, or have significant side effects (anorexia and weight loss) *in vivo*, yet G28UCM-treated animals displayed no anorexia or weight loss, whereas G28UCM retained the ability to inhibit FASN activity and reduce tumor size (85). *In vitro*, G28UCM showed synergistic interactions with trastuzumab, lapatinib, erlotinib, and gefitinib; whereas trastuzumab (AU565TR) or lapatinib (AU565LR)–resistant cells retained FASN expression and sensitivity—providing an alternative method for overcoming drug resistance (85).

Conclusions

Earlier we have provided examples of compounds that can effectively resensitize cancer cells to therapeutics to which they had shown resistance. The focus of this article is on metabolic inhibitors that target either signaling transduction networks or key metabolic enzymes that are commonly dysregulated in cancer (Fig. 1). Although both strategies can be effective, directly targeting signal transduction networks often results in compensation through other closely related pathways, whereas the mechanisms allowing a cell to compensate for loss or inhibition of a rate-limiting or pathway-initiating enzymes in the essential metabolic pathways are more limited (86).

Metabolic pathway components, such as those involved in glucose usage and amino acid biosynthesis, are likely to be good targets. Inhibition of PFKFB3 represses phosphofructokinase 1 (PFK1) by reducing fructose 2,6 bisphosphate (F2,6BP) synthesis. This leads to a decreased glycolytic characteristics evidenced by lower glucose uptake and less production of lactate, ATP, NAD^+, and NADH (87). 3-(3-Pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) is a small-molecule inhibitor of PFKFB3 that has shown selectivity for transformed cells *in vitro* and suppresses growth of Lewis lung carcinoma, MDA-MB-231 breast adenocarcinoma, and HL-60 promyelocytic leukemia xenografts (87). Given the observed effects on tumor growth in a variety of cancers as well as the metabolic changes 3PO treatment induces, PFK1 inhibition may produce chemosensitization in a similar manner to what happens when other glycolytic enzymes are inhibited.

Recent work also shows that for some forms of breast cancer, a key component of the serine biosynthesis pathway, phosphoglycerate dehydrogenase (PHGDH), is often amplified in cancer resulting in increased activity of the serine biosynthesis pathway (88). Knockdown of PHGDH in breast cancer cell lines exhibiting increased PHGDH expression reduces α-ketoglutarate (α-KG) levels, inhibits proliferation, and induces cellular death (88). Because increased PHGDH is observed in approximately 70% of ER^- breast cancers, it is reasonable to expect that treatments disrupting PHGDH function and enzymes related to serine biosynthesis will present an attractive strategy for overcoming resistance to chemotherapeutics (88, 89). Similarly, cellular stress pathways have been shown to be upregulated in cancerous cells (13). New research linking cellular stress to metabolism indicates that components within the ROS and heat shock response pathways might also be targets capable of producing highly selective synergistic responses with current chemotherapeutic agents (13, 14, 67, 90, 91).

The link between therapeutic sensitivity and dysregulated cancer cell metabolism is quickly being dissected in a variety of studies about a diverse array of cancers and therapeutic agents. It is becoming clear that this may provide a strategy for surmounting the drug resistance that endangers so many patients with cancer. We have described a variety of metabolic aspects ranging from resource uptake to breakdown or biosynthesis that can contribute to or be targeted to overcome therapeutic resistance to an assortment of agents. Although no unifying mechanism is apparent to show how inhibition of metabolic pathways can result in resensitization to chemotherapeutics, common themes do occur. When cancer cell metabolism is disrupted, the presumed resource shortfalls are
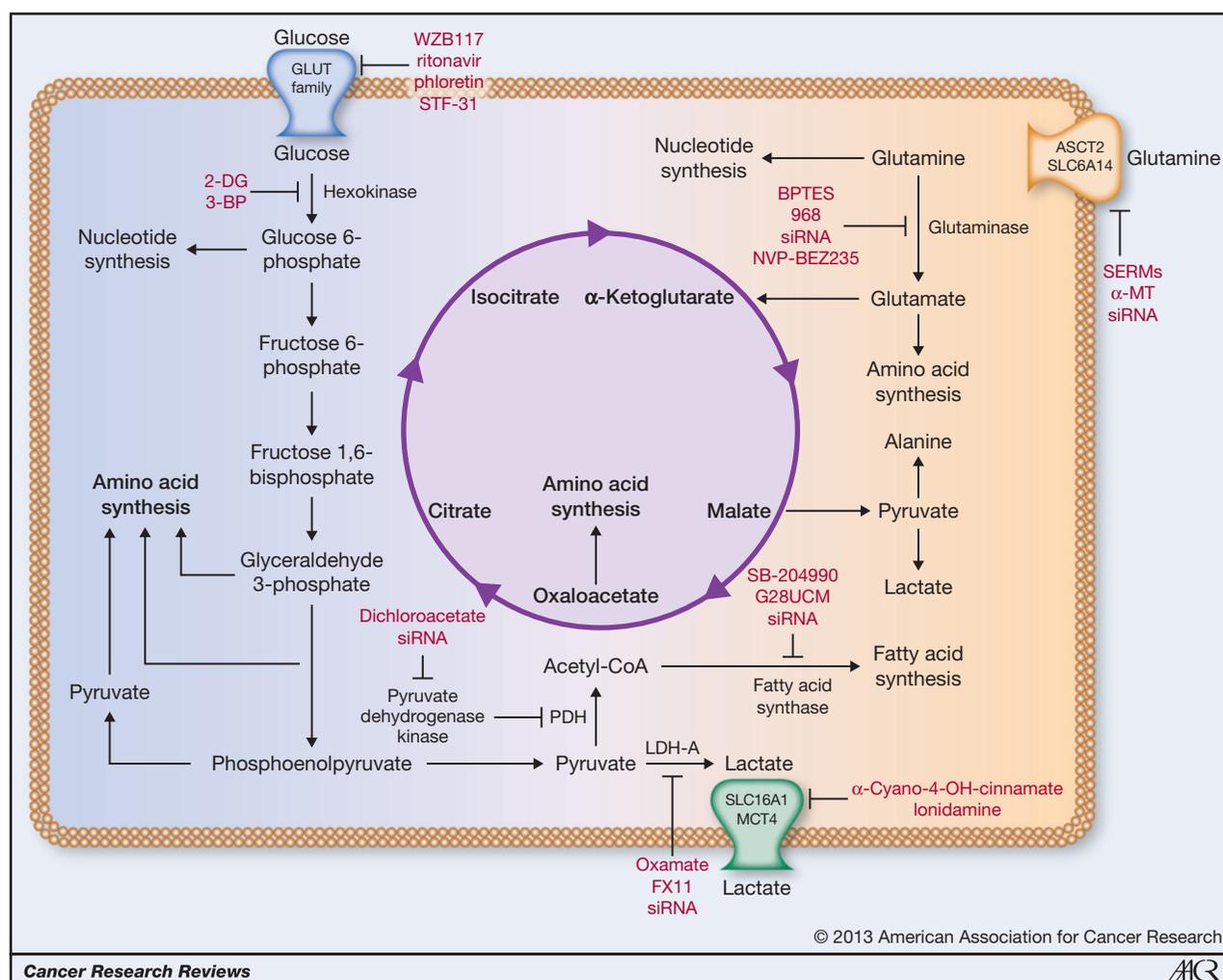
Figure 1. A wide range of metabolic components supports the cancerous phenotype. Glucose and glutamine are metabolized into critical intermediates necessary for cellular growth, such as amino acids, nucleotides, and fatty acids. The metabolic inhibitors discussed in this review are shown in red near their target of inhibition. Disruption of these metabolic networks can reduce drug resistance and render cancer cells more susceptible to current therapeutic regimens.

often not fatal. Many of the metabolic inhibitors or gene knockdowns produced inhibitory effects on the cellular growth rate but do not induce cellular death. Rapid cellular growth seems to have a protective function, possibly due to the fact that rapidly dividing cells have access to sufficient resources to enact energy-intensive therapeutic resistance pathways on demand (15, 16). The extra resources available may allow for the synthesis and operation of drug efflux pumps and antiapoptotic genes such as surviving, and inhibition of the dysregulated metabolism often reduces ATP and other metabolic levels which may prevent efficient activation of resistance pathways (15, 76). Genomic instability frequently observed in cancers also ensures that a population of growing cells is more likely to have the genetic diversity to adapt to the selective pressures induced by chemotherapeutic treatments (92–95). By curtailing or preventing continued cellular growth, metabolic disruption might limit the ability of the tumor to adapt to the

chemotherapeutic regimen. Finally, in many cases the disruption caused by inhibiting glycolytic metabolism results in increased cellular stress (often in the form of higher levels of ROS) or decreased protective response (such as NADPH levels), which may predispose cells toward apoptosis or limit the ability of the tumor to address further chemotherapeutic insult (14, 20, 68, 69). Many survival pathways have both cytoprotective and cytotoxic functions, and the increase in cellular stress induced by metabolic inhibition may precondition the stress response pathways toward apoptotic outcomes (14). As evidenced by the diverse array of cancers discussed earlier, this method of attacking therapeutic resistance in cancer is demonstratively effective in a wide variety of cancer types and merits continued investigation.

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No potential conflicts of interest were disclosed.

Authors' Contributions

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