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The Role of Metabolic Plasticity in Blood and Brain Stem Cell Pathophysiology

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Abstract

Our understanding of intratumoral heterogeneity in cancer continues to evolve, with current models incorporating single cell signatures to explore cell-cell interactions and differentiation state. The transition between stem and differentiation states in non-neoplastic cells requires metabolic plasticity, and this plasticity is increasingly recognized to play a central role in cancer biology. The insights from hematopoietic and neural stem cell differentiation pathways were used to identify cancer stem cells in leukemia and gliomas. Similarly, defining metabolic heterogeneity and fuel switching signals in non-neoplastic stem cells may also give important insights into the corresponding molecular mechanisms controlling metabolic plasticity in cancer. These advances are important, because metabolic adaptation to anti-cancer therapeutics is rooted in this inherent metabolic plasticity and is a therapeutic challenge to be overcome.

Introduction

The initiation and progression of cancer requires the dysregulation of normal physiologic cell signals, metabolism, and biological processes, particularly those that are involved in human development. Human developmental and metabolic programs have evolved to respond to environmental changes. Cancer cells have accelerated this adaptability to respond to changing requirements for tumor growth, metastasis, and therapeutic resistance. Cancer cells select for the best adapted metabolic and growth programs encoded by mutations allowing the fittest cells to adjust and survive in their changing microenvironments. Because biological fitness reflects energy investment in progeny, it is not surprising that metabolic plasticity is one of the key hallmarks of cancer (1).

The metabolic plasticity of cancer indicates the ability of and need for cancer cells to adapt to intrinsic and extrinsic pressures to survive. To achieve this goal, cancer cells take

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advantage of the complete set of existing metabolic pathways, utilizing those most beneficial in the current environmental conditions to promote and maintain their growth. This notion of metabolic adaptation in cancer is enshrined in the Warburg hypothesis, which has evolved over the last few decades of research (2). An important feature of the aerobic glycolysis characteristic of the Warburg effect is that it is not simply about producing energy; intermediates used for the synthesis of biomolecules are also generated by glucose-dependent pathways including the pentose phosphate pathway. These building blocks are required for rapid cell growth, providing a fundamental benefit for aerobic glycolysis in tumor cells. To obtain the additional glucose required to fuel these pathways, cancer cells upregulate glucose transporters (GLUTs), including the ubiquitously expressed GLUT1 and the more selectively expressed GLUT3. The metabolic differences in glucose utilization between normal and tumor tissue are exploited clinically for the detection of primary tumors and metastasis, monitoring response to therapy, and detecting recurrent neoplasms by using the glucose analog 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) in conjunction with positron emission tomography (PET).

A number of excellent articles describe the importance of metabolic plasticity in a broad range of cancers (3-6). From these and other studies, we now understand that cancer cells are metabolically heterogeneous and metabolic adaptation to the changing environments a cancer cell experiences through its lifetime requires an intrinsic plasticity. However, metabolic plasticity, particularly partitioning between glycolysis and mitochondrial oxidative phosphorylation and fuel selection, is not unique to tumor cells. For example, macrophage phenotypes exhibit plasticity between glycolysis and oxidative phosphorylation as they adapt to the different stages of inflammation (7,8). Similarly, T-cells adopt an aerobic glycolysis program as they become activated (9,10). During development, metabolic plasticity is critical for the regulation of cell fate, as shown by the activation of glycolysis during induced pluripotent stem cell reprogramming (11-13) which is partially characterized by teratoma formation. These data suggest that understanding mechanisms of metabolic plasticity in non-neoplastic cells may inform metabolic plasticity in cancers.

Stem cells can self-renew to regenerate themselves or differentiate into defined lineages during development and for tissue maintenance, including after injury. Hematopoietic stem cells differentiate into well-characterized hematopoietic lineages yielding distinct cell populations with unique marker profiles (including erythrocytes, granulocytes, lymphocytes, monocytes, and thrombocytes). Similarly, neural stem cells differentiate into brain lineages (neurons, astrocytes, and oligodendrocytes) with stem cell and differentiation states that can be distinguished based on distinct markers. Building on these hierarchies, cancer cells with characteristics similar to stem cells were identified, first in leukemias (14) and subsequently in solid tumors, including gliomas (15,16). These cancer stem cells, or tumor initiating cells, were identified partly on the basis of the expression of cell surface stem cell markers, which permitted segregation of subsets of tumor cells via flow cytometry. For example, leukemia stem cells were $\text{CD34}^{\text{hi}}\text{CD38}^{-}$ similar to hematopoietic stem cells, and glioblastoma stem cells were CD133^{+} similar to neural stem cells (14-16). In comparison with non-stem (marker-negative) cancer cells, which typically constitute the majority of the cancer, cancer stem cells isolated from the same patient had enhanced ability to propagate the disease in immunocompromised mice. Cancer stem cells underwent self-renewal or differentiation into

lineages bearing the same genetic mutations as in the original cancer. The functional similarities between cancer stem cells and non-neoplastic stem cells were partially attributed to the utilization of common stem cell signaling pathways that are activated/elevated in cancer stem cells when compared to non-stem cancer cells. Increasing evidence suggests similarities in metabolism and metabolic plasticity between normal and neoplastic stem cells that also contribute to common phenotypes. As the cancer stem cell hypothesis states that a subset of cancer cells exhibits similarities to non-neoplastic stem cells, it does not directly address the cell of origin for a cancer (17). However, multiple studies demonstrate that the acquisition of mutations by hematopoietic stem cells or neural stem cells leads to blood or brain tumors (14,18-23). These data indicate the importance of the perturbation of developmental programs for the initiation and maintenance of cancers. They also suggest that cancer cell metabolic plasticity is another instance of cancer cell acquisition or reactivation of existing developmental programs to promote cancer growth.

In both normal and neoplastic stem cells, it is now becoming clear that metabolic plasticity is important for self-renewal and differentiation programs, linking bioenergetics to cell proliferation and cell state (13,24-28). We highlight here similarities in metabolic reprogramming in stem cells and cancer to understand how developmental cellular bioenergetics contributes to tumor initiation and growth. We will focus on examples of pathways regulating metabolic plasticity in hematopoietic and neural stem cells and their potential relationships to cancers of the blood and brain. We will highlight two important pathways, one regulating glycolysis and one regulating fatty acid oxidation, which impact normal and neoplastic blood and brain cell fate to exemplify how stem cell metabolic plasticity may inform cancer. We additionally provide examples of therapeutic interventions at both the preclinical and clinical stage. These studies on understanding metabolic pathways in cancer and their impacts on metabolic plasticity may inform new metabolotherapies.

Glycolytic Metabolism in Non-neoplastic and Neoplastic Blood and Brain Stem Cells Regulated by Oxygen Dependent Plasticity and HIFs

Hypoxia, or low oxygen tension, is known to promote glycolysis through stabilization of hypoxia inducible transcription factor 1 α and 2 α (HIF1 α and HIF2 α), which can transcriptionally upregulate multiple members of the glycolysis pathway and facilitate increased GLUT-dependent glucose uptake (Figure 1A). While HIF1 α and HIF2 α have many overlapping target genes, there are unique targets including the HIF2 α -dependent, stem cell transcription factor Oct4 (29). The importance of modeling hypoxia, and *in vivo* microenvironments in general, is still relatively underappreciated considering that the majority of experiments continue to be performed at atmospheric oxygen tensions (21% O₂), estimated to be 17-20% O₂ with 5% CO₂ supplementation in standard cell culture incubators in buffered, high glucose media. Physiological oxygen tensions in the brain and bone marrow are approximately 3-7%, with some regions less than 1.5% O₂ (30), and even short-term exposure to atmospheric oxygen had deleterious effects on hematopoietic stem cell self-renewal and engraftment (31). In solid tumors, including gliomas, some tissue portions approach anoxia. However, fluctuations in oxygen tension can quickly occur due to blood vessel formation during angiogenesis or rapid tumor growth, contributing to the

requirement for metabolic plasticity as the cancer cell inhabits these changing tumor microenvironments.

As our understanding of the impact of physiological levels of oxygen tension has improved, a number of similarities between normal and neoplastic stem cell biology have been uncovered. Many of these findings have been recently reviewed (32-35); therefore, we provided here a summary of the commonalities between hematopoietic and neural stem cell responses to changes in oxygen tension that inform stem cell fate and metabolism. In both hematopoietic stem cells and neural stem cells, hypoxia facilitated growth and survival (36-38) via a glycolytic shift (39,40). During reprogramming, induced pluripotent stem cells also undergo a glycolytic shift that is HIF1 α and HIF2 α dependent (41,42). While both HIF1 α and HIF2 α were important for hematopoietic stem cell maintenance in hypoxia, HIF2 α was also critical for hematopoietic stem cell colony forming ability in normoxia where loss of HIF1 α had no effect (43).

Similar results have been reported with leukemia and glioma stem cells as culture in hypoxia promoted growth, stem cell percentages and/or marker expression, and therapeutic resistance (44,45). In glioma stem cells both HIF1 α and HIF2 α were important for glioma stem cell maintenance, but HIF2 α was expressed at higher oxygen tensions than HIF1 α and was particularly elevated in the glioma stem cell fraction (46). In leukemia, a majority of the research has focused on HIF1 α as it was associated with poorer disease prognosis and maintenance of leukemia stem cells (47), whereas HIF2 α was not. However, HIF2 α has been shown to protect both hematopoietic and leukemia stem cells from apoptosis in response to endoplasmic reticulum stress (43). As such, an area of increasing interest for cancer therapy has been the development of HIF inhibitors (48). HIF1 α inhibitors may have promise for leukemia treatment as HIF1 α targeting inhibits leukemia stem cell (49), but not hematopoietic stem cell (50), self-renewal. HIF2 α inhibitors have been of particular interest for the treatment of glioma (51) with two HIF2 α inhibitors, PT2385 and PT2977, in clinical trial for glioma after successful preclinical development (52-54). These data suggest distinct roles for HIF1 α and HIF2 α that still need to be further delineated while affirming a critical role for hypoxia/HIF in the regulation of normal and neoplastic hematopoietic and neural stem cell maintenance and metabolism.

Integrating Mitochondrial Respiration, ROS, and HIF Regulation of Glycolysis: FOXO3 Importance in Non-neoplastic and Neoplastic Stem Cells of the Blood and Brain

While it is common to consider distinct shifts in metabolism (i.e. glycolysis or oxidative phosphorylation), there is considerable interplay between metabolic states and gradients of metabolic functions that regulate cell fate. As an example, we highlight roles of the Forkhead box O3 (FOXO3) transcription factor in developmental programs and metabolism in the blood and brain. FOXO3 is a transcription factor that is inhibited by growth factor mediated, AKT phosphorylation-induced translocation from the nucleus, but oxidative and nutrient stress increase FOXO3 mediated-transcription (55-57). Thus, environment mediated

shifts in FOXO3 activity may explain why FOXO family members are generally considered to be tumor suppressors even though some data indicate a pro-tumorigenic role for FOXO3.

FOXO3 is a critical regulator of stem cell maintenance that is linked to metabolism (Figure 1B). Studies using cells cultured from FOXO3 knockout mice revealed roles in both hematopoietic stem cell and neural stem cell self-renewal and differentiation (58-63). Loss of FOXO3 in hematopoietic and neural stem cells decreased stem cell characteristics and resulted in lineage shifts, with gene signatures associated with changes in HIF targets (58-63). Interestingly, metabolic profiling of FOXO3 knockout cells demonstrated reduced glycolysis, glutaminolysis, and utilization of the pentose phosphate pathway along with elevations in reactive oxygen species (ROS) (64,65). Multiple studies suggest FOXO3 is critical for reducing levels of hypoxia-induced ROS and HIF-1 stabilization/activity, although FOXO3 may maintain mitochondrial metabolic function independent of regulation of redox homeostasis (66). These data provide a strong rationale for investigating the role of FOXO3 in neoplastic stem cells of the brain and blood as they link mitochondria and ROS to HIF and glycolysis.

Similar to hematopoietic stem cells, FOXO3 was critical to maintain the long-term malignant potential of leukemia stem cells (67) as nuclear FOXO3 was elevated in the leukemia stem cell population (68). However, consequences of FOXO3 manipulation in glioma stem cells have been mixed. FOXO3 targeting in gliomas decreased glucose uptake (69) and increased ROS (Figure 1B), and FOXO3 was elevated in chemotherapy (temozolomide) resistant glioblastoma cells (70) that have reduced ROS in association with changes in oxidative phosphorylation (71,72). FOXO3 was important for glioma stem cell maintenance post-irradiation (73), but other results indicated that elevated FOXO3 levels or activity increased glioma stem cell differentiation (74). These differences may be explained by evidence that FOXO3 effects are p53 dependent in gliomas (73), but the signaling pathways downstream of FOXO3 or its transcriptional targets may also mediate context dependent phenotypes that are likely to complicate treatment strategies.

The data summarized here present an intriguing case in which one protein is able to coordinate multiple responses to integrate metabolic signals and provide evidence that two cancers have co-opted this to promote growth and survival. These studies provide links between FOXO3 and both stem cell states and metabolic shifts in brain and blood cancers, while also demonstrating crosstalk between pathways that are important for regulating metabolic plasticity.

Adaptive metabolism in Hematopoietic, Neural, and Neoplastic Stem Cells

Fuel switching is an important aspect of metabolic plasticity and is also a feature of cancer stem cells. Several studies demonstrate that fatty acid oxidation is important for both stem and cancer cell growth (Figure 1C) (75). For example, neural progenitor cell oxygen consumption was maintained when cells were cultured without glucose and mitochondrial function was fatty acid dependent, with linoleic acid promoting oxidative phosphorylation (76). One pathway found to be critical for the regulation of hematopoietic stem cell self-renewal through a lipid metabolism dependent mechanism involves promyelocytic leukemia

protein (PML). This protein is important for the formation of nuclear bodies that regulate cell growth, survival, and genomic stability. Loss of PML in hematopoietic and neural stem cells resulted in increased proliferation and loss of quiescence followed by exhaustion (77-80) or decreased neurogenesis (81). Effects of loss of PML in hematopoietic stem cells were associated with decreased peroxisome proliferator-activated receptor γ (PPAR γ) (78), which regulates fatty acid oxidation due, in part, to transcriptional upregulation of carnitine palmitoyltransferase 1 (CPT1). CPT1 transports fatty acids into the mitochondria for fatty acid oxidation (Figure 1C) (82,83). Changes in CPT1 expression and fatty acid utilization to generate energy promote the survival of thymocytes in mice with a hematopoietic cell oxidative phosphorylation defect (84), directly linking metabolic shifts to cell survival in hematopoietic progenitor subsets. Elevation of CPT1 and fatty acid oxidation was also important for neural stem cell quiescence and cell fate as loss of CPT1A decreased neural stem cell percentages in vivo (85,86). These data suggested a link between stem cell maintenance and lipid metabolism, which was confirmed when the CPT1 and fatty acid oxidation inhibitor etomoxir was determined to decrease neural stem cells (76,86) and promote hematopoietic stem cell exhaustion (82).

Regulation of the fatty acid oxidation pathway by a PML/CPT1 cascade is also suggested to be important in cancer, particularly in the cancer stem cell fraction. Leukemia stem cells were found to reside in an adipose tissue niche where the breakdown of lipids could facilitate fatty acid oxidation (87). Indeed, addition of fatty acids increased glioma cell proliferation (88) and oxygen consumption (89). PML targeting in leukemia stem cells or glioma stem cells reduced tumor initiating capacity in animal models (77,90), and degradation of PML mediated sensitivity to several chemo- and small molecule inhibitor therapies (90-92). While conflicting data suggested that PML is lower in glioblastoma cells (93,94) and could be elevated to increase cell death (95), CPT1 was elevated (96), supporting the notion that fatty acid oxidation is important for glioma growth. Together, the data suggest that cancer stem cells can reside in a lipid-rich niche and readily utilize fatty acids as a fuel source.

The utilization of fatty acid oxidation can be suppressed when glucose is available, but some cancers downregulate pathways that suppress fatty acid oxidation. With the loss of suppression, fatty acid oxidation can be active in cancers even if glucose is available. For example, levels of prolyl hydroxylase 3 (PHD3), which reduces fatty acid oxidation and promotes fatty acid synthesis when nutrients are high, are decreased in acute myeloid leukemia and a subset of gliomas (97,98). PHD3 hydroxylates the proline residues of the rate limiting enzyme for fatty acid synthesis, acetyl-coA carboxylase 2 (ACACB or ACC2), which results in increased conversion of acetyl-CoA to malonyl-CoA. Malonyl-CoA is important for fatty acid synthesis, but can also repress the activity of CPT1, decreasing transport of fatty acids into the mitochondria (99). Loss of PHD3 increased the growth of glioma cells, including in hypoxia, and PHD3 is a hypoxia response gene (98,100) that may repress glycolysis under hypoxia (101). These data suggest the possibility that PHD3 could mediate hypoxia dependent fatty acid oxidation suppression and that both glycolysis and fatty acid oxidation can be activated in hypoxia when PDH3 is lost, further promoting metabolic plasticity and fuel switching in cancers. Furthermore, elevation of fatty acid binding proteins by hypoxia in glioma cells can increase fatty acid uptake and formation of

lipid droplets that can be used for energy generation upon reoxygenation (102). These data indicate an alternative method for metabolic shifts toward fatty acid oxidation that could be targeted for patient treatments, either by direct inhibition of fatty acid uptake or inhibition of hypoxia signaling.

In addition to providing leukemic stem cells with byproducts for fatty acid oxidation, adipocytes release glutamine into the microenvironment. Glutamine is able to support cellular metabolism as a carbon source and aiding in redox homeostasis and has been reviewed as an important metabolic factor in both leukemias and gliomas previously (103-106). Glutamine protects leukemia cells from L-asparaginase, a first-line therapy for acute lymphoblastic leukemia (107). However, leukemia cell lines exhibit varying responses to glutamine withdraw conditions, indicating heterogeneity in metabolic programs and suggesting that glutaminase inhibition may be a viable therapeutic option for a subset of leukemias (108,109). Glutamine also plays an important role in cell fate determination for hematopoietic stem cells. Erythropoiesis is reliant on glutamine with differentiating cells consuming more glutamine and showing decreased levels of glycolysis (110); however, when glutamine metabolism is inhibited, the cells instead develop toward a myelocytic lineage (111,112). In neural stem cells, glutamine is able to enhance survival following perinatal hypoxia in the subventricular zone (113), and multiple studies indicate elevated glutamine utilization in gliomas with the ^{18}F -labeled amino acids [^{18}F]fluciclovine (FDA approved for detection and localization of biochemically recurrent prostate cancer) and (2*S*,4*R*)-4-[^{18}F]fluoroglutamine (4-FGln) being tested as PET imaging agents for glioma detection and characterization (114). Together, the data strongly indicate that similarities in metabolic developmental programs and cell signaling, particularly with regards to fuel switching required for transitioning cell state, can be used to understand the underlying mechanisms of cancer cell pathways and identify potential vulnerabilities for therapeutic targeting.

Cancer cell metabolism as a diagnostic tool and therapeutic target

Non-invasive monitoring of cancer progression and therapeutic response is a major benefit of cancer imaging. Many current cancer imaging techniques, as well as those under development, were based on determinations of fundamental differences in metabolism between cancer and non-cancer cells and/or solid tumors. For example, the glycolytic shift and increased uptake of glucose in gliomas and other solid tumors provided the basis for the use of the glucose analog FDG for PET imaging. However, the relatively high consumption of glucose by the normal brain as well as the elevated levels of FDG in regions of inflammation are substantial limitations of this approach (115). Studies suggest that aerobic glycolysis can be estimated in gliomas using [^{18}F]FDG in combination with [^{15}O]oxygen, but larger studies are needed to establish the utility and clinical significance of this approach (116-118).

The leading PET imaging agents for glioma target system L amino acid transport, allowing them to cross the blood-brain barrier and accumulate preferentially in glioma cells due to upregulation of specific transporter proteins (particularly LAT1/*SLCA5*) (115,119,120). This class of PET tracers, including L-[^{11}C]methionine (MET), 3,4-dihydroxy-6-[^{18}F]fluoro-L-

phenylalanine (FDOPA), and *O*-(2-[¹⁸F]fluoro)-L-tyrosine (FET), is becoming standard of care in some countries and is entering international society guidelines for glioma imaging (121,122). The PET tracer [¹⁸F]FDOPA is currently under review by the Food and Drug Administration (FDA) in the United States (US) for congenital hyperinsulinism, which may make this agent more widely available for other applications including neuro-oncology in the US.

Other PET tracers have been investigated for glioma imaging include amino acids targeting glutamine transport and metabolism such as 4-[¹⁸F]FGln and [¹⁸F]fluciclovine as mentioned above (114,123-127). At the time of publication of this manuscript, [¹⁸F]fluciclovine has been submitted for approval to the FDA for a new indication in glioma. Other tracers that have been investigated in glioma include the thymidine analogue 2'-deoxy-2'-[¹⁸F]fluorothymidine (FLT) for proliferation imaging, 1-[¹⁸F]fluoranyl-3-(2-nitroimidazol-1-yl)propan-2-ol (FMISO) for hypoxia imaging (128-132), [¹¹C]choline targeting membrane synthesis (133-135), and [¹¹C]acetate targeting oxidative phosphorylation and fatty acid synthesis (136,137). There has been less application of metabolic PET tracers for leukemias, although [¹⁸F]FDG and [¹⁸F]FLT are the PET tracers that have been most studied in leukemias. [¹⁸F]FDG can play a role in detecting extramedullary sites of leukemia (138-140), and recent studies suggest that [¹⁸F]FLT-PET can serve as an early indicator of response to therapy in acute myelogenous leukemia (141,142).

Another approach for measuring tumor metabolism in both clinical and research settings uses the inherent nuclear spin properties of endogenous stable nuclides including protons, carbon atoms, and phosphorous atoms using single-voxel magnetic resonance (MR) spectroscopy (MRS) or multi-voxel magnetic resonance spectroscopic imaging (MRSI) (143). The inherent low signal in MR can be overcome using hyperpolarization techniques to generate short-lived small molecules with orders of magnitude greater signal than conventional MR. Hyperpolarized MRS using ¹³C has been utilized to evaluate the conversion of pyruvate to lactate as well as the production of bicarbonate to determine glioma metabolism and growth (144,145). Intriguingly, MRS can also be used to detect 2-hydroxyglutarate, the novel metabolite resulting from isocitrate dehydrogenase mutations, which are found in gliomas and leukemias (143). These data demonstrate that cancer imaging could provide information about tumor genetics without biopsy. Monitoring immediate changes in metabolism post-treatment may also be used to rapidly determine therapy responders and non-responders, permitting personalized medicine approaches in real time.

Beyond tumor imaging, understanding the metabolic alterations of cancer could provide opportunities for therapeutic intervention. Direct inhibition of glucose uptake and utilization is one commonly pursued approach, with a number of groups developing inhibitors to components of the glycolysis pathway, including via targeting GLUTs. Some GLUT inhibitors have shown promise *in vitro* for targeting a wide range of solid tumors, including gliomas, with limited toxicities observed *in vitro* (146-149). However, GLUTs are widely expressed with GLUT1 at the blood brain barrier and GLUT3 important for neurons, complicating treatment options for brain tumors. Nevertheless, there is hope that in

combining GLUT inhibitors and the ketogenic diet, another way to decrease glucose availability to the tumor while providing ketones for an alternative fuel, could ameliorate potential side effects (150-152). While the ketogenic diet was originally developed to treat epilepsy, it has been of interest for cancer therapy (152-158), with multiple trials currently listed on clinicaltrials.gov as recruiting patients. Unfortunately, it is difficult for patients to maintain the ketogenic diet and success has been limited (152-158), but this relatively simple intervention will permit evaluation of impacts when used in combination with current standard of care.

Glucose metabolism can also be inhibited by the non-metabolizable analog of glucose, 2-deoxy glucose (2-DG). 2-DG can reduce glucose uptake and tumor growth in animal models, but is not-specifically imported by tumor cells (159). However, one clinical trial indicated 2-DG was well tolerated in patients with glioma (160). A recent study showed that the ketogenic diet was able to increase the maximum tolerated dose of 2-DG and reduce its side effects in non-tumor bearing mice (161). 2-DG has also been reported to reduce leukemia cell viability at low doses (162), and in combination with the pentose phosphate pathway inhibitor dehydroepiandrosterone was effective at lower doses (163). 2-DG, however, has not been fully explored due to concerns regarding toxicities (159,164). These data lead to the potential of combining metabolic therapies at lower doses to potentiate possible toxicities as a potential therapeutic option for glioma in particular.

Dichloroacetate is a clinically utilized inhibitor of glycolysis via targeting of pyruvate dehydrogenase, but it is also controversial as it is an environmental toxin with the potential to induce liver toxicities and neoplasia (165-167). However, as dichloroacetate is blood brain barrier penetrant, many studies have tested its efficacy against gliomas, with significant antitumor effects shown, depending on the dosage and schedule (168,169). Two completed clinical trials demonstrated that dichloroacetate was safe, and Michelakis and colleagues indicated dichloroacetate may provide a therapeutic benefit for some patients with glioma (170,171). In leukemia, dichloroacetate was mainly studied in the context of B-chronic lymphocytic leukemia where it decreased viability of p53 wildtype cells and also synergized with the p53 activator, Nutlin-3 (172-174). Dichloroacetate was also reported to work in concert with metformin, another agent that targets metabolism as described below, to induce B-chronic lymphocytic leukemia cell death (175). Again, these data suggest that combinations of metabolic therapies have the potential to target both glioma and leukemia.

Metformin is more commonly known as an anti-diabetic therapy, however, it has become of interest as a cancer therapeutic because it targets mitochondrial metabolism. There are over 250 clinical trials currently active or complete. In both glioma and leukemia, metformin has shown anti-cancer efficacy alone and in combination with chemotherapies (176-179) (Supplemental Table 1). Metformin or its more potent analog phenformin have been reported to activate adenosine monophosphate-activated protein kinase (AMPK), leading to glioma or leukemia cell death (180,181), but the clinical benefit is not yet clear and development of lactic acidosis is a risk. Additional preclinical studies have investigated the combination of metformin and arsenic trioxide in glioma and observed a decrease in proliferation and elevated autophagy and apoptosis (182). Both of these agents lead to the dysregulation of mitochondrial metabolism and may have potential benefits in various combinations. Arsenic

trioxide and its various derivatives have shown much promise *in vitro* with dramatic reductions in tumor growth through inhibition of hexokinase 2 or activation of AMPK (183-185). *In vivo* studies have been inconclusive as subcutaneous studies showed tumor regression (184), but intracranial studies indicated that insufficient drug was able to cross the blood brain barrier to promote survival (186). Nonetheless, over 75 studies have investigated arsenic trioxide compounds for the treatment of glioma or leukemia in the clinic. Unfortunately, one of the most efficacious compounds *in vitro*, 4-(N-(S-penicillaminylacetyl)amino) phenylarsonous acid, did not increase progression free survival time in a clinical trial, although it was shown to be safe (187). Overall, many new approaches to targeting glucose and mitochondrial metabolism are beginning to be investigated in the clinic, and the results of these ongoing studies will be of much interest as they are reported.

On the basis of the utilization of fatty acids in cancers, including the therapy resistant cancer stem cells, inhibition of fatty acid oxidation with etomoxir has been explored as a potential therapeutic strategy. Etomoxir treatment decreased the percentage of leukemia stem cells, sensitized them to apoptosis (188,189) and even resensitized tyrosine kinase inhibitor ibrutinib resistant cells by targeting the metabolic shift to fatty acid oxidation in those cells (190). However, it is important to note that, in addition to inhibiting CPT1 as mentioned above, etomoxir also inhibits diglyceride acyltransferase (regulating triacylglycerol production and retinoid signaling) and has the ability to inhibit coenzyme-A at high concentrations (191). In human glioblastoma, including glioma stem cells, etomoxir decreased cell proliferation in multiple assays (88,192) and improved survival of orthotopic tumor bearing mice with etomoxir delivered via osmotic pumps (192). Alternative methods to target fatty acid oxidation with the lipid avocatin B (193), perhexiline (194), or ST1326 (195) also increased leukemia cell death. Linking these growth inhibitory data to cellular bioenergetics, adenosine triphosphate (ATP) levels, and oxygen consumption rates in both glioblastoma and leukemia cells were decreased with etomoxir treatment (88,189,192). While these data suggest the potential of targeting of fatty acid oxidation as an anti-glioma therapy, hepatotoxicity and variability in glioma stem cell responses to etomoxir/fatty acid oxidation inhibitors due, in part to metabolic heterogeneity and plasticity will complicate patient treatments. Metabolic profiling of glioma stem cell lines indicated a subset with elevated lipid signaling as well as cells with increased lipid droplet formation after treatment with the ATP synthase inhibitor oligomycin. However, these cells did not all respond similarly to etomoxir treatment. Cells either increased or decreased number in response to etomoxir (196) indicating that more research will be needed to fully understand the context dependent signaling at play, likely due to further metabolic plasticity.

In addition, direct targeting of fatty acid synthesis via pharmacologic or genetic targeting of ACC1/2 has also been shown to decrease the growth of glioblastoma cells in association with reduced ATP production (197). However, long-term treatment of cells with an ACC1/2 inhibitor resulted in increased extracellular acidification in some glioblastoma cells, suggesting the potential for shifts toward glycolysis to compensate for loss of fatty acid synthesis (197). In addition, statins, also known as 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, showed efficacy *in vitro* via inhibiting cholesterol production in glioma and leukemia, leading to decreased proliferation and increased apoptosis (198-202).

Statins are particularly attractive as they have a long clinical history, limited toxicities, and may reduce graft-vs-host disease in patients with acute myeloid leukemia, although this was not seen across all leukemia subtypes (203). A combination of idarubicin and cytarabine with pravastatin was shown to both promote regression or have no benefit, indicating that further studies are warranted to investigate the benefit of using such a widely available drug as an adjuvant therapy (204,205) as well as the possibility that other combinations may prove more beneficial (Supplemental Table 1). While *in vitro* studies were encouraging (206), clinical evidence for the benefit of statins against gliomas is lacking, although there are a number of ongoing trials further investigating their role (207-210) (Supplemental Table 1). When considered more broadly, the data suggest there must be additional investigations to determine the best strategies for the application of metabolic inhibitors for anti-cancer therapies.

Conclusions

We summarize evidence that pathways common between normal and neoplastic stem cells, which regulate cell fate and survival mediate changes in metabolism, need to be more closely considered for developing novel therapeutics (Figure 2A). The data suggest that the metabolic plasticity intrinsic to cancer biology is itself a metabolic target. Given the inherent plasticity of the cancer cell, this will likely require a strategy that develops a multi-pronged approach to prevent the evolutionary adaptations for cell survival from thriving in cancer cells (Figure 2B). In limited studies where strategies to target both glycolysis and fatty acid oxidation have been tested, some benefits of the combinations have been demonstrated. Additional studies have indicated that combinatorial therapies may provide for a lower effective dose and thereby limit toxicities in non-malignant tissues that do not rely on multiple highly functioning metabolic pathways. Thus, there may be benefits from combinatorial metabolism targeting approaches that have not yet been identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

2-DG	2-deoxy-D-glucose
ACC	acetyl-coA carboxylase
AMPK	adenosine monophosphate-activated protein kinase
ATP	adenosine triphosphate
CPT1	carnitine palmitoyltransferase 1

FDG	2-deoxy-2-[¹⁸ F]fluoro-D-glucose
FDOPA	3,4-dihydroxy-6-[¹⁸ F]fluoro-L-phenylalanine
FLT	2'-deoxy-2'-[¹⁸ F]fluorothymidine
GLUT	glucose transporter
HIF	hypoxia inducible transcription factor
MR	magnetic resonance
MRS	MR spectroscopy
PET	positron emission tomography
PHD3	prolyl hydroxylase 3
PML	promyelocytic leukemia protein
PPARγ	peroxisome proliferator-activated receptor γ
ROS	reactive oxygen species

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Figure 1. Pathways for Fuel Switching in Normal and Neoplastic Brain and Bone Stem Cells.

(A) Low oxygen tension is a physiologic environment in the brain and bone marrow impacting glycolytic metabolism with hypoxia stabilization of HIFs leading to increased expression of genes regulating glycolysis and stem cell maintenance. While tissue culture is typically performed under atmospheric oxygen (21% O_2), lower oxygen levels (1.5-7% O_2) are common in the normal brain and bone marrow with nearly anoxic conditions in portions of solid tumors. All enzymes and/or genes shown in green are induced by hypoxia/HIF with the impact of increasing glycolysis and decreasing oxidative phosphorylation. (B) Perturbation of FOXO3 levels in normal and neoplastic neural (and hematopoietic) stem cells demonstrates a role in the regulation of self-renewal, ROS, and glycolysis due in part to regulation of HIF stability or activity. (C) Normal hematopoietic and neural stem cell signaling indicate the importance of PPAR γ transcriptional regulation of CPT1 for fatty acid oxidation. Results in leukemia and brain tumors confirm the importance of fatty acid oxidation as a mechanism for energy production, particularly when glucose levels are low.

Figure 2. Summary of Metabolic Plasticity in the Context of Stem Cell State and Pathobiology and Potential Therapeutic Interventions.

(A) Tumor environments, importantly oxygen tension as well as nutrient availability, potentially impact cellular metabolism which is critical for cell state transitions. Cancer cell activation of developmental programs permits metabolic plasticity critical for adaptations necessary for cell survival. (B) Multiple strategies and specific inhibitors are available to target glycolysis, oxidative phosphorylation, and fatty acid oxidation in cancer cells, but specificity to the tumor is likely to be a concern. By preventing alternative fuel sources

and/or maintenance of a quiescent population, combinatorial approaches may sensitize tumor cells to chemo- and radiotherapy.

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