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Non-invasive metabolic imaging of brain tumors in the era of precision medicine

Michelle M. Kim, MD¹, Abhijit Parolia, BS², Mark Dunphy, DO³, and Sriram Veneti, MD PhD^{2, #}

¹Department of Radiation Oncology, University of Michigan, MI, 48104

²Departments of Pathology, University of Michigan, MI, 48104

³Molecular Imaging & Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY 10065

Abstract

The genomic revolution in cancer has uncovered a variety of mutations in primary brain tumors. This has created an urgent need to develop non-invasive imaging biomarkers to assess and integrate this genetic information in the clinical management of patients. Metabolic reprogramming is a central hallmark of cancers including brain tumors. Many of the molecular pathways implicated in brain tumors directly reprogram metabolism. This provides the opportunity to devise in vivo metabolism-based imaging modalities for patient stratification, to improve diagnosis, and to monitor treatment response. Metabolic phenomena like the Warburg effect and altered mitochondrial metabolism can be leveraged to image brain tumors using techniques like positron emission tomography (PET) imaging and Magnetic Resonance (MR) metabolic imaging. Moreover, genetic alterations such as isocitrate dehydrogenase mutations produced unique metabolic signatures that can be detected using MR spectroscopy. There is a growing need to translate our understanding of the molecular aspects of brain tumors to in vivo imaging in patients. Metabolism-based imaging provides a unique platform to achieve this. In this review we examine the molecular basis for metabolic reprogramming in brain tumors and examine current non-invasive metabolic imaging strategies to interrogate them, for the ultimate goal of guiding and improving patient care.

Introduction

Primary brain tumors in children and adults remain one of the most challenging forms of cancer to diagnose and treat. They are broadly classified into glial and non-glial tumors¹. Glial tumors are more common in adults while non-glial tumors such as medulloblastomas are more frequent in children¹. The clinical management of these patients relies heavily on non-invasive imaging. Magnetic resonance imaging (MRI), with or without contrast enhancement remains the current standard of care for initial evaluation. MRI can also guide

[#]Corresponding author. Sriram Veneti, MD PhD, Assistant Professor of Pathology and Neuropathology, University of Michigan Medical School, 3520E MSRB 1, 1150 W. Medical Center Dr., Ann Arbor, MI 48104, Phone: 734-763-0674, sveneti@med.umich.edu.

tissue biopsy to establish diagnosis, permit the assessment of disease progression and evaluate the effectiveness of therapies.

While there have been significant strides in understanding the pathology of primary brain tumors, there remains a wide gap that must be bridged between our understanding of the biology of brain tumors and non-invasive imaging to guide diagnosis, treatment, and follow-up. In the era of personalized medicine we are beginning to appreciate the genetic complexity of primary brain tumors. This information can generate novel therapeutic windows to identify actionable targets and targeted therapies. However, the challenge remains in identifying, stratifying and monitoring patients with advanced imaging, and leveraging the information gathered from next generation sequencing to develop molecular imaging modalities.

The best example of molecular imaging in the clinical management of cancer comes from the field of cancer metabolism. Altered tumor metabolism can be imaged by two principle techniques. The first is PET imaging, which is based on labeling biologic substrates with radionuclides such as ^{11}C or ^{18}F . PET imaging is highly sensitive because of its ability to detect low concentrations of radiolabeled substrates. The most common form of PET imaging in cancer takes advantage of the Warburg effect (the anaerobic metabolism of cancer cells, generating high lactate levels even in the presence of oxygen), and is based on labeling a glucose analogue with ^{18}F (2- ^{18}F fluoro-2-deoxyglucose or ^{18}F FDG). Single-voxel MR spectroscopy (MRS) and multi-voxel MR spectroscopic imaging (MRSI) constitute the other technique that enables detailed detection of cellular metabolic activity by characterizing the chemical and molecular composition of tumor and tumor microenvironment using radiofrequency signals generated by nuclear spins of magnetic resonance active nuclei including ^1H , ^{31}P and ^{13}C .

A fundamental concept emerging in cancer biology is that oncogenes directly reprogram cellular metabolism to enable tumor cells to grow, proliferate and survive^{2, 3}. Many of the brain tumor oncogenes influence specific metabolic pathways including glucose, amino acid and fatty acid metabolism as discussed below. In this article, we evaluate (1) the recent genomic revolution in brain tumor biology, (2) the rewiring of metabolic pathways from genetic alterations, and (3) the translation of metabolic reprogramming to non-invasive tumor imaging in patients.

Glial tumors in adults and children are genomically distinct

The World Health Organization defines two major groups of glial tumors: astrocytic tumors and oligodendroglial tumors. Additionally, histologic criteria are used to define tumor grade: low-grade (grade I and grade II) and high-grade (grade III and grade IV, or glioblastoma multiforme (GBM))¹. Glial tumors in adults and children are morphologically comparable and were thought to have similar biology. However, next generation sequencing studies strikingly reveal that gliomas in adults and children are genetically different. In adults, more than 90% of GBM show genetic alterations that converge on the PI3K-AKT/mTOR pathway. This includes enhanced activation of receptor tyrosine kinase such as EGFR (~60%), PDGFRA (~10%), FGFR (~3%) and MET (~1%) that signal mainly through the

PI3K AKT/mTOR pathway^{4, 5}. Other genetic alterations in this pathway include PTEN deletion (~40%) and mutations in PI3K (~20%) (Table 1). Therefore the PI3K-AKT/mTOR pathway is one of the primary drivers of adult GBM. In contrast, high-grade gliomas in children are characterized by epigenetic mutations. Histone H3 K27M and G34R/V mutations are noted in 60% of pediatric glioblastomas and H3K27M mutations occur in more than 80% of brain stem gliomas (termed diffuse intrinsic pontine gliomas)⁶⁻⁹ (Table 1).

Similarly, low-grade gliomas in adults and children, although histologically similar, have different genetic drivers. More than 70% of intermediate-grade (grade II and III) gliomas (including astrocytomas and oligodendrogliomas) in adults bear mutations in isocitrate dehydrogenase (IDH) 1/2 (Table 1). IDH mutant gliomas tend to occur in younger adults and are associated with a favorable prognosis relative to their wild-type counterparts¹⁰ (Table 1). IDH 1/2 mutant gliomas that progress to GBM are termed secondary GBM. These IDH 1/2 mutant GBM constitute ~5% of adult GBM and show a significantly favorable prognosis compared to IDH wild-type tumors (Table 1). Low-grade gliomas in children and young adults such as pilocytic astrocytomas show constitutive activation of BRAF. Oncogenic fusion of the kinase domain of BRAF with KIAA1549 is seen in 30–70% of pilocytic astrocytomas (with varying frequency depending on cortical versus cerebellar tumor location)¹⁰. Likewise, activating *BRAF* point mutations (V600E) are observed in other low-grade pediatric brain tumors like pleomorphic xanthoastrocytomas (70%), gangliogliomas (20%) and at lower frequencies in pilocytic astrocytomas and diffuse astrocytomas¹⁰. Thus, the genetic drivers in childhood and adult gliomas are distinct (Table 1).

Precision medicine: next generation sequencing enables prognostic sub-classification of brain tumors and defines therapeutic targets

Another important insight from these molecular studies is the sub-classification of tumors into distinct groups that can inform clinical management of patients beyond histologic grade. For example, grade IV medulloblastomas (MB), which are typically pediatric tumors can be sub-grouped into four molecular subtypes: SHH, WNT, Group 3 and Group 4¹¹ (Table 1). Of these, WNT tumors constitute ~10% of all cases, have WNT-pathway associated gene expression patterns and bear the best prognosis with a 5-year survival of ~95%. SHH tumors represent ~30% of MB and are characterized by constitutive activation of the SHH pathway and bear an intermediate prognosis with ~75% survival. Group 3 tumors comprising ~25% of cases show alterations in c-MYC and bear the worst prognosis with ~50% survival. Group 4 tumors represent ~35% of cases, demonstrate intermediate prognosis with ~75% survival and are poorly characterized¹¹. Similarly, adult glioblastomas can be sub-grouped into four categories: proneural, mesenchymal, neural and classic. Of these, the proneural subtype is associated with IDH 1/2 mutations and have the best prognosis⁴.

Indeed, next generation sequencing has refined our understanding and approach to caring for adults and children with brain tumors. These studies have opened up novel avenues for the development of targeted therapies. For example, vismodegib, an antagonist of the SHH pathway, is effective in patients with SHH-MB but not in patients with other MB subtypes¹².

Similarly, inhibition of the BRAF V600E mutation with vemurafenib has demonstrated efficacy in childhood brain tumors that bear this mutation^{13–15}. Moreover, pharmacological inhibitors of mutant IDH1 show promise in IDH1 mutant but not in IDH wild-type glioma animal models¹⁶. Thus, integrating the molecular characteristics of these tumors has become integral in the management of brain tumor patients. These molecular features are currently assessed on tissue samples obtained after biopsy or tumor resection. However, this is not always feasible, as some brain tumors such as pontine and brain stem tumors are difficult to biopsy due to surgical challenges associated with tumor location. Further, the direct evaluation of the efficacy of targeted therapies with longitudinal, serial biopsies is not practical. Conventional MRI, the current standard, is inadequate to evaluate molecular alterations in brain tumors. Thus, non-invasive metabolic imaging of brain tumors is now emerging as a means to assess some of these molecular and metabolic alterations.

Glucose metabolism: oncogenic reprogramming and imaging

Glycolysis is the pathway by which six-carbon glucose is metabolized into three-carbon pyruvate (Figure 1). In aerobic conditions, pyruvate can be oxidized to acetyl-coenzyme A, which enters the mitochondrial tricarboxylic acid (TCA) cycle. Brain tumors exhibit the Warburg effect and divert pyruvate away from the mitochondria. Warburg effect is thought to be advantageous to tumor cells for several reasons, such as enhanced production of glycolytic intermediaries to support macromolecular synthesis, generation of reducing equivalents such as NAD⁺, secreted lactate that alters the microenvironment to enable tumor invasion and escape from immune cells, and as an adaptation to lowered oxygen levels in hypoxic environments^{17–20}.

The Warburg effect in brain tumor cells is controlled at several levels, including regulation by the PI3K/AKT/mTOR pathway, BRAF activation and MYC induction. For example, phosphorylated AKT enhances glycolysis by increasing expression of glucose transporters and by activating glycolytic enzymes such as hexokinase-2 (HK2) and phosphofructokinase-1 (PFK-1)^{21–23}. Similarly, Activated mTORC1 alters glucose metabolism and glycolytic gene expression by regulating c-Myc activity in EGFRvIII-driven GBM²⁴. BRAFV600E and MYC can also stimulate the transcription networks related to glycolysis including glucose transporters and glycolytic enzymes^{25, 26, 27}. *TP53*, which is frequently mutated in astrocytic tumors, can also regulate glycolysis by influencing glycolytic enzymes and glucose transporters²⁸ (Figure 1). Thus, imaging glucose metabolism is a very attractive target in brain tumors.

Interestingly, many of the glycolytic enzyme isoforms that are preferentially expressed during brain development in proliferating cells are elevated in brain tumors. For example, HK2 (yielding glucose-6-phosphate from glucose) and pyruvate kinase M2 isoform (PKM2, which converts phosphoenolpyruvate to pyruvate) are two enzyme isoforms that are expressed in the embryonic but not the adult brain^{29–31}. Brain tumors such as GBM and medulloblastomas preferentially express HK2 and PKM2^{31–37}. Gambhir and colleagues reported the generation of a PET imaging probe specific for PKM2 using a class of *N, N*-diarylsulfonamides (DASA) known to promote PKM2 tetramer formation. [¹¹C] labeled

DASA-23 was taken up in orthotopic glioma models and corresponded to tumor-associated PKM2 expression³⁸ (Figure 1).

¹⁸FDG PET imaging was one of the earliest tools used to measure local glucose utilization in the brain. ¹⁸FDG, like glucose, is transported into the cell by glucose transporters and phosphorylated by hexokinase to 2-deoxyglucose-6-phosphate. This intermediate is unable to be further catabolized, and becomes trapped in the cell and is a measure of glucose uptake^{39–41}. However, ¹⁸FDG PET for the imaging of gliomas shows poor tumor-to-background contrast due to the physiologic high levels of glucose uptake in the brain (Figure 3). It also has limited specificity in distinguishing between tumor and non-malignant processes including infection and inflammation⁴². MRS can be used to monitor glucose metabolism in human subjects and glioma animal models using ¹³C-labeled glucose. Because MRS visualizes only paramagnetic atoms, this technique detects only ¹³C rather than the more abundant ¹²C. The conversion of the administered metabolite, such as ¹³C-labeled glucose, into its downstream products can be measured by simultaneously measuring the disappearance of ¹³C-glucose and the appearance of ¹³C into metabolic products such as ¹³C-labeled lactate or pyruvate. Using this technique, glycolysis can be evaluated in ex vivo tumor specimens from animal models and from GBM patients^{43, 44}. Intriguingly, mice implanted orthotopically with GBM cells derived directly from patients and infused with ¹³C-labeled glucose showed entry of glucose carbons into the TCA cycle with lower generation of lactate than expected⁴⁴.

However, ¹³C is difficult to image by MRS due to its low natural abundance (approximately 1%) and unfavorable gyromagnetic ratio, both of which result in low signal to noise ratios⁴⁵. To overcome these limitations, ¹³C-enriched probes can be “hyperpolarized” by exposure to microwaves at extremely low temperatures prior to tracer administration, using a technique known as dynamic nuclear polarization. This alters the Boltzmann distribution of ¹³C and can increase sensitivity by more than 10,000-fold⁴⁶. Because ¹³C-labeled probes remain hyperpolarized for a very short period of time, the probe must be infused immediately into the subject for MRS detection. The conversion of hyperpolarized [1-¹³C] pyruvate to [1-¹³C] lactate (Figure 1) as a result of rapid exchanges between the probe and a large tumor lactate pool arising from the Warburg effect is the most extensively characterized metabolic process, including the first human cancer study⁴⁷. In gliomas, hyperpolarized ¹³C MRS studies have been conducted in animal models. For example, the generation of [1-¹³C] lactate from [1-¹³C] pyruvate was detected in xenografts in rats, but not normal brain. Enhanced sensitivity in hyperpolarized MRS holds significant promise in evaluating glycolysis and other metabolic changes in human glioma patients. Moreover, high-field 7T MRI technique has now expanded the capability of MRS, as well as techniques utilizing chemical exchange saturation transfer (CEST) effect, ²³Na and ³¹P spectroscopy^{48, 49}. Compared to 3T field strengths in which the resonances of glutamate undergo strong coupling and overlap with glutamine and gamma-aminobutyric acid (GABA) peaks, localized ¹H MRS at 7T can be used to reproducibly measure cortical GABA and glutamate concentrations⁵⁰. Moreover, using ³¹P MRS the rate of ATP synthesis in the human brain can be quantified, and extra- versus intracellular pH differentiated⁵¹. Finally, the spectrum of metabolic studies may be further expanded by spectroscopic techniques with enhanced physiological and functional information based on CEST contrast, in which amide and

hydroxyl protons from different amino acids, proteins and other molecules have been used to image glucose accumulation in tumor models (glucoCEST), to detect early tumor response in glioblastoma^{52–54}. Increasingly, combined PET/MRI systems may enable a multiparametric approach to non-invasively characterize brain tumors⁴⁹.

(D)-2-Hydroxyglutarate: IDH1 mutant oncometabolite and MRS imaging

IDH enzymes generate α -ketoglutarate (α -KG) from isocitrate, and resultantly generate reducing equivalents. There are three cellular isoforms: IDH1, 2 and 3. IDH1 is present in the cytosol, while IDH2 and IDH3 are mitochondrial. Mutations in *IDH1* and *IDH2* are heterozygous and missense. IDH1 mutations are the most common in gliomas (more than 90%) and involve the catalytic site arginine at position 132, which is mutated to histidine (R132H), while *IDH2* mutations are rare in gliomas⁵⁵. IDH mutations result in the production of the metabolite (D)-2-hydroxyglutarate ((D)-2HG) (Figure 2). (D)-2HG transforms immortalized human astrocytes, and one of its mechanisms of oncogenesis is related to its structural similarity to α -KG^{56–59}. α -KG serves as a critical cofactor for dioxygenase enzymes that regulate various cellular functions like histone and DNA demethylation. (D)-2HG can inhibit the function of many of these enzymes resulting in both DNA hypermethylation at CpG islands called G-CIMP (glioma-CpG island methylator phenotype) and histone hypermethylation^{60–63}.

As (D)-2HG is produced in IDH 1/2 mutant gliomas but not in wild-type gliomas, the non-invasive detection of (D)-2HG could serve as a biomarker for the diagnosis, treatment and surveillance of these tumors. Detection and quantification of (D)-2HG using in vivo MRS has been demonstrated in IDH1 mutant gliomas^{64–66}. One of the challenges of detecting (D)-2HG is its proximity to glutamine/glutamate and NAA resonance peaks⁶⁷. This requires optimizing MRS using techniques such as two-dimensional correlation spectroscopy or J-difference spectroscopy to enable the differentiation of overlapping metabolites^{64, 65}. Using these techniques, (D)-2HG can be detected in millimolar ranges (1.7–8.9 mM) in IDH1/2 mutant but not in wild-type gliomas. Further, the detection of (D)-2HG in vivo correlates with better prognosis, mirroring previously reported next generation sequencing data^{55, 68, 69}. However, while the detection of (D)-2HG may be sensitive in the assessment of IDH1/2 mutations, the specificity may depend on the size and cellularity of the tumor. A recent study suggests that the sensitivity may be as low as 8% for small tumors (defined as <3.4 mL volume) in contrast to 91% sensitivity for larger tumors (> 8 mL in volume)⁷⁰. The enzymatic function of mutant IDH 1/2 to catalyze the conversion of α -KG to (D)-2HG, detectable in vivo, may be harnessed using hyperpolarized ¹³C MRS⁷¹. For example, the conversion of α -KG labeled with ¹³C at the 1st carbon position (1-¹³C) α -KG to [1-¹³C] (D)-2HG (Figure 2) can be detected in rats bearing IDH1 mutant but not IDH1 wild-type GBM xenografts⁷¹. While these observations are yet to be translated into the clinic, as the only imaging modality specific to IDH mutations, in vivo MRS (with or without hyperpolarization) represents an exciting foray into the use of a pharmacodynamic biomarker.

Metabolic reprogramming and imaging amino acid metabolism

Many amino acids including glutamine, glutamate, methionine, aspartate and tyrosine demonstrate altered metabolism in brain tumors. The mechanisms used by brain tumor oncogenes to reprogram amino acid metabolism are just beginning to emerge.

Glutamate

Glutamate and glutamine form vital metabolic connections between neurons and glia. Glutamine is metabolized to glutamate in neurons. Glutamate is an excitatory amino transmitter and is released at synaptic terminals. After synaptic transmission, glutamate is taken up by astrocytes and is metabolized to glutamine, which is then recycled back to neurons for the synthesis of glutamate. Consequently, both glutamate and glutamine are abundant metabolites in the brain. Since there is significant similarity between the molecular structures of both of these amino acids, they give rise to similar MRS spectra and are usually collectively evaluated. Many primary brain tumors including gliomas, meningiomas and medulloblastomas demonstrate altered levels of both these amino acids^{72–75}. Additionally, tumor cells exchange glutamate for cysteine via the cysteine/glutamate antiporter termed system Xc(–). PET imaging of glutamate exchange via system Xc(–) can be achieved using (4S)-4-(3-¹⁸F-fluoropropyl)-L-glutamate (FSPG)^{76, 77} (Figure 2). The Xc(–) antiporter is expressed in GBM and correlates with tumor invasion and poor outcome^{78, 79}. Thus PET imaging of glutamate uptake may be potentially useful in brain tumors.

Glutamine

Glutamine is the most abundant amino acid in the plasma and many cancers including brain tumors show altered glutamine metabolism. Glutamine is metabolized to glutamate by the enzyme glutaminase, which in turn is metabolized to ammonia and α -KG by the enzyme glutamate dehydrogenase. α -KG thus generated can then enter the TCA cycle and serves as a crucial contributor to anaplerosis and energy production^{80–82} (Figure 2). In brain tumors, MYC, p53 and the PI3K-AKT/mTOR pathways can regulate glutamine metabolism (Figure 2). Amplification or activation of MYC is noted in group 3 and group 4 MB and also in histone H3G34R/V mutant pediatric glioblastomas (Table 1). MYC regulates glutamine metabolism by increasing expression of the glutamine transporter ASCT2 and the enzyme glutaminase^{83–86}. Along similar lines, activation of mTOR stimulates glutamine metabolism by increasing the activity of the enzyme glutamate dehydrogenase⁸⁷. However, orthotopic GBM mouse models infused with ¹³C-labeled glutamine exhibit high tumor glutamine uptake but do not demonstrate glutamine metabolism in the TCA cycle⁴⁴. Thus while glioma cells show enhanced glutamine uptake, how exactly glutamine is metabolized in tumor cells in vivo needs further elucidation.

Non-invasive in vivo measurement of glutamine uptake can be achieved in human glioma patients using radiolabelled 4-¹⁸F-(2S,4R)-fluoroglutamine (¹⁸F-FGln) (Figures 2 and 3). ¹⁸F-FGln uptake is increased in gliomas compared to normal brain enabling clear tumor to background delineation⁸⁸. Significant reduction in ¹⁸F-FGln uptake was seen following chemo-radiation, which correlated with reduced tumor cell burden. Tumor uptake in gliomas can depend on the integrity of the blood-brain barrier. Experiments in animal models and a

small cohort of human subjects shows that uptake of ^{18}F -FGln may not directly depend on disruption of the blood-brain barrier, but need further characterization in a larger patient cohorts⁸⁸. Further, in human subjects, ^{18}F -FGln uptake distinguished patients with progressive disease from stable patients with minimal to no ^{18}F -FGln PET avidity (Figure 4), in contrast to ^{18}F -FDG PET or conventional MRI, making this metabolic imaging modality a potentially valuable clinical tool in the management of patients with glioma

Methionine

Diverse biosynthetic processes, cellular regulatory and maintenance pathways derive their substrates from carbon units donated from specific amino acids, termed one-carbon metabolism⁸⁹. A key component of this biosynthetic processes is methionine (radiolabelled ^{11}C -methionine, (Figure 5)). Its sodium-independent transmembrane uptake across L-type amino acid carriers is increased in malignant cells including gliomas (Figure 5). Methionine can be used for protein synthesis as well as other cellular processes including synthesis of S-adenosylmethionine (SAM) which acts as a methyl donor for many reactions including DNA and histone methylation⁹⁰. Therefore its uptake is a measure of transport and not a pure marker of protein synthesis⁹¹. Transport does not depend on, but may be enhanced by breakdown of the blood brain barrier^{92, 93}. ^{11}C -methionine is one of the best-studied amino acids in primary brain tumors by PET imaging (Figure 5), although the short half-life of ^{11}C (20 minutes) limits the widespread availability of this modality to centers with an on-site cyclotron⁹⁴

Aspartate

Via ^1H MRS, characteristic chemical shifts are seen in gliomas, including a decrease in *N*-acetylaspartate (NAA). NAA is an abundant metabolite in the normal brain and is synthesized mainly in neuronal mitochondria from aspartate and acetyl-CoA⁹⁵. Its exact function in the brain remains controversial. Because of its high abundance in the brain (second only to glutamate) and easy detection on MRS, NAA levels are extensively used as an indicator for neuronal damage for various CNS pathologies including reduced levels in brain tumors (Figure 6)^{96, 97}. This detectable decrease may be due to glioma cells lacking the biosynthetic enzyme for NAA and a reduction in the number of normal neuronal cells due to the invasive nature of many brain tumors^{98, 99}.

Other amino acids

Multiple other radiolabeled amino acid analogs have been studied in primary gliomas. *O*-(2- ^{18}F -fluoroethyl)-L-tyrosine (FET) uptake primarily measures amino acid transport rate as it is neither incorporated into proteins nor metabolized within the cell¹⁰⁰. It has been widely studied in brain tumors and licensed in many countries a radiopharmaceutical agent for the diagnosis of human brain tumors. 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine (^{18}F -FDOPA) uptake is also a reflection of transport, but is additionally the substrate of aromatic amino acid decarboxylase. High levels of physiologic uptake are present in the basal ganglia, making interpretation of tumors located in this region difficult¹⁰⁰. L-[1- ^{11}C]-leucine uptake most directly reflects protein synthesis, although is also affected by alterations in the amino acid transport system in the brain. Other amino acid related metabolites that are often detected by ^1H MRS in brain tumors are taurine an organic acid derived from the amino acid

cysteine and creatine a nitrogenous organic acid derived from the amino acids glycine and arginine. While not direct measure of amino acid metabolism, these metabolites are used to clinically evaluate brain tumors as discussed later.

Brain tumor oncogenes reprogram fatty acid metabolism

Cancer cells can engage in both de novo fatty acid synthesis and enhanced fatty acid oxidation. Synthesized fatty acids can serve as precursors for the generation of many biomolecules including phospholipids, sphingolipids, prostaglandin and cholesterol esters. Choline is an essential nutrient that is required for synthesis of phospholipids and the neurotransmitter acetylcholine. Choline levels are increased in cancer cells and are thought to reflect increased cell membrane turnover. Using ^1H and ^{31}P MRS, the increase in choline-containing metabolites can be non-invasively detected in vivo in brain tumors¹⁰¹ (Figure 6).

Oncogenes such as EGFR can control fatty acid synthesis through the activation of the PI3K-AKT pathway by stabilizing enzymes such as sterol regulatory element-binding protein-1 (SREBP-1) that regulate lipogenesis¹⁰² (Figure 2). Moreover, PI3K-AKT activation in gliomas results in elevated levels of acetyl-CoA, which is a central precursor for fatty acid synthesis, by enabling the incorporation of carbons from acetyl-CoA into growing fatty acid chains^{103–105}. Acetyl-CoA can be derived from pyruvate and can also be synthesized from acetate by the enzyme Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2)^{106, 107}. GBMs show increased expression of ACSS2, which results in increased acetyl-CoA pools that could be used both for oxidation within the TCA cycle and for lipid synthesis (Figure 2). MRS studies using ^{13}C -labeled acetate suggest mitochondrial oxidation of acetate-derived acetyl-CoA in orthotopic brain tumor models and a human GBM patient¹⁰⁸. In small clinical studies, ^{11}C labeled acetate PET imaging has been found to have a sensitivity of 90% in detecting low and high-grade gliomas¹⁰⁹.

Tumor metabolism and advanced imaging of cellular proliferation, hypoxia, and angiogenesis

Additional key components of tumorigenesis driven by alterations in tumor cell energy metabolism may be directly assessed with molecular imaging. Altered tumor metabolism supports rapid cellular proliferation. Compared to normal proliferating cells, tumor cells have increased levels of thymidine kinase (TK-1). Radiolabeled nucleoside analogues such as 3'-deoxy-3'[(18F)-fluorothymidine (^{18}F -FLT) are transported into cells, phosphorylated by TK-1, and trapped intracellularly at an increased rate compared to normal cells due to increased tumor levels of TK-1^{110–112}. This process is dependent on breakdown of the blood-brain-barrier (BBB) since transport across the intact BBB is slow, and is therefore not as useful in non-enhancing primary brain tumors with intact BBB (e.g. low-grade glioma); it may also be limited in distinguishing moderately proliferative tumors driven by thymidine salvage from highly proliferative tumors relying on de novo thymidine synthesis^{113–115}.

Hypoxia is a critical feature of rapidly growing tumors, which develop adaptive responses through angiogenesis, enhanced glucose metabolism and optimized mitochondrial respiration that confers a survival advantage to hypoxic tumor cells. An important prognostic

factor for resistance to antineoplastic treatments including systemic therapy and radiotherapy, hypoxia may be imaged with a number of PET tracers, of which ^{18}F -fluoromisonodazole (^{18}F -FMISO) is the most well-studied¹¹⁶, providing spatial delineation of hypoxia in brain tumors independent of BBB disruption and tumor perfusion¹¹⁷.

A closely related phenomenon, angiogenesis, is a hallmark of tumor growth that contributes to a hostile tumor microenvironment with low oxygen tensions and high interstitial fluid pressure that selects for a more malignant tumor phenotype¹¹⁸. A target structure for molecular imaging, $\alpha_v\beta_3$ -integrin receptor, is highly expressed on activated endothelial cells during angiogenesis. Various ligands based on the tripeptide RGD (Arg-Gly-Asp), which binds with high affinity to the $\alpha_v\beta_3$ -integrin receptor, have been developed for PET¹¹⁹. The glycosylated cyclic pentapeptide ^{18}F -galacto-RGD has been successfully applied to patients with malignant gliomas, with high uptake in regions of rapid proliferation and tumor infiltration in contrast to normal brain¹²⁰.

Integrating metabolic imaging with clinical care in brain tumor patients

We have thus far examined how different genetic alterations in primary brain tumors reprogram metabolism and how some of these pathways can be translated into non-invasive imaging in preclinical animal models and patients. We now examine the potential for metabolic imaging to be assimilated into routine clinical care.

Tumor delineation for local therapy

Metabolic imaging of glioma may enable greater accuracy in biopsy and resection planning, and for radiotherapy target delineation to define the extent of tumor infiltration compared to conventional imaging modalities such as T1 gadolinium enhanced or T2/FLAIR MRI, and to identify aggressive tumor components at risk for recurrence¹²¹. The use of amino acid PET has been shown to better identify the most biologically aggressive components of heterogeneous low and high-grade glioma, which dictate subsequent therapy and also reduces the risk of an incomplete resection, particularly near eloquent regions^{122–125}. The use of multiple imaging modalities including multi-voxel ^1H MRS, diffusion and perfusion MR imaging may also help distinguish between heterogeneous regions of dense tumor, edema with admixed tumor and non-infiltrated edema¹²⁶. Amino acid PET-based tumor volumes have been shown to extend beyond contrast-enhancing volume on conventional MRI by 2–3.5 cm for different tracers, and identifies tumor extent within non-specific regions of T2/FLAIR abnormality (Figure 5)^{127–129}.

Prognostication

^{18}F -FET PET time-activity curves demonstrate correlation between tumor progression and survival outcomes^{40, 41, 130–132}. The volume of uptake on ^{18}F -FET and ^{11}C -MET PET prior to chemoradiation has been shown to be highly prognostic for outcome^{133, 134}. ^1H MRS has also been evaluated in the adult and pediatric brain tumor populations to predict survival outcomes. Multiple studies have shown worse outcome with elevated choline/NAA ratio pre-treatment or prior to adjuvant chemoradiation^{135, 136}. As IDH 1/2 mutant gliomas have

better prognosis compared to IDH wild-type tumors, evaluating (D)-2HG levels could also serve as a prognostic indicator^{68, 137}.

Assessing treatment response

A variety of metabolic changes may be observed following cytotoxic, radiation, and anti-angiogenic therapies in both the tumor and tumor microenvironment, detected by MRS. A decrease in choline/water ratio in low-grade glioma treated with temozolomide parallels a reduction in tumor volume^{138, 139}. Serial MRS imaging of patients undergoing adjuvant radiation treatment for malignant glioma reveal a decline in mean tumor choline/NAA ratio, and early changes during treatment of lactate/NAA and choline/creatine are predictive of outcome¹⁴⁰. Using ³¹P/¹H MRS, increased hypoxia and impaired oxidative metabolism may be seen in patients with recurrent GBM treated with bevacizumab¹⁴¹. Following treatment with cediranib, a direct metabolic effect and anti-tumoral response to anti-angiogenic treatment is seen with serial MRS, demonstrating a significant increase in NAA/choline¹⁴². The metabolism of hyperpolarized [1-¹³C] pyruvate to lactate and the expression and activity of glycolytic enzymes may provide early evidence of response to temozolomide, which precedes changes in tumor growth¹⁴³. This method may also be used to detect the effect of PI3K signaling inhibition and potential drug target modulation¹⁴⁴.

Studies incorporating serial ¹⁸F-FET and ¹¹C-MET PET imaging demonstrate that a reduction of amino acid uptake during the course of therapy is a sign of tumor response correlating with clinical outcome, and more informative than T1-gadolinium enhanced MRI^{132, 145}. Early changes in choline/NAA ratio as well as lactate/NAA even during adjuvant radiation for malignant glioma has been shown to be prognostic of outcome, as were changes from baseline to post-treatment¹⁴⁰. Intriguingly, results from a subset of patients who received multiple MRS scans while undergoing active treatment suggested that a drop in (D)-2HG levels is associated with a treatment response^{70, 137}. As (D)-2HG levels are related to tumor size, applying this technique as a biomarker for treatment response or as a marker for early progression will require additional study⁷⁰.

Treatment resistance/ tumor progression versus treatment effect

The emergence of treatment resistance and tumor recurrence is a major cause of morbidity and mortality in high-grade brain tumors. Metabolic changes that occur during emergence of treatment resistance are less understood. Both glucose and amino acid metabolism undergo reprogramming during the emergence of treatment resistance^{87, 146, 147}. Recurrent GBMs are hypermutated and harbor many new driver mutations in the AKT/mTOR pathway¹⁴⁷. Since the AKT/mTOR pathway directly rewires glucose and amino acid metabolism⁸⁷, it would follow that both glucose and amino acid metabolism would undergo metabolic reprogramming in recurrent GBM. Along these lines, glutamine metabolism is enhanced in preclinical glioma models of treatment resistance¹⁴⁸.

A significant clinical challenge in the non-invasive detection of tumor recurrence in patients is due to pseudoprogression. Pseudoprogression is defined as treatment-related changes that mimic tumor recurrence on conventional MRI. Altered metabolism seen in tumor recurrence may be leveraged to differentiate relapse from pseudoprogression. Metabolic imaging with

amino acid PET has been shown to help distinguish the alteration in blood-brain-barrier and contrast enhancement observed after chemoradiation, which are seen in pseudoprogression, from true progression^{149–153}. Both static and dynamic ¹⁸F-FET PET parameters differentiate glioma progression or recurrence with greater accuracy than conventional MRI¹⁵⁴. In addition ¹¹C-MET, and to a lesser extent, ¹⁸F-FDOPA PET have been shown with high sensitivity and specificity to distinguish tumor recurrence compared to conventional MRI, and to influence provider management in 41–50% of cases^{94, 110, 155}. ¹H MRS has also been applied to differentiate between tumor recurrence and radiation necrosis in the adult and pediatric populations. Increased choline signal (choline/creatine or choline/NAA ratios) suggest tumor recurrence, while reduced choline levels, and possibly elevated lipid and lactate signals, suggest radiation necrosis (Figure 6)^{156–158}. Although MRS may not reliably distinguish these phenomena in instances of mixed viable tumor and radiation necrosis, it is often more informative than conventional MRI and may provide early information on tumor metabolism prior to morphologic or volumetric changes seen on conventional MRI^{159, 160}.

Molecular subgrouping

Another potential application for metabolic imaging is in the non-invasive evaluation of molecular and prognostic tumor subgroups. Imaging of (D)-2HG is a prime example, as IDH 1/2 mutations are characteristic of proneural secondary GBMs (Table 1). Similarly, MRS is able to differentiate SHH-MB from group 3/4 MB. Specifically, SHH-MB show high levels of choline and lipid but low creatine and taurine levels^{161, 162}. In contrast, group 3/4-MB show higher taurine but lower levels of lipids and creatine¹⁶². How SHH signaling or oncogenes in group 3/4-MB mediate these metabolic phenotypes is not known. Activation of MYC in group 3 MB is associated with a poor prognosis. As discussed above, MYC reprograms Gln metabolism, which could potentially serve, in addition to glutamate levels, as a biomarker for more aggressive disease. In line with this, glutamate levels in MB is a prognostic biomarker⁷⁵.

Conclusions

As we make significant strides in understanding the molecular basis of brain tumors, further work is needed to develop non-invasive tools for evaluating these alterations and integrating them into daily clinical practice. Altered cancer metabolism offers a unique window to integrate genomic information with advanced imaging, and the field has rapidly advanced with novel techniques that have been successfully implemented in preclinical models and patients. However, additional work is needed to standardize these metabolic imaging techniques for routine clinical use. In combination with other functional imaging modalities, these techniques may prove complementary to conventional MRI in characterizing tumor biology and metabolism for patient management. Future studies based on these oncogenic-driven metabolic pathways may enhance diagnosis, prognostication, treatment and surveillance, and ultimately improve outcome in patients with brain malignancies.

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Key Points

- Brain tumors in adults and children although morphologically similar, exhibit different genomic alterations, both across and within histological subtypes that impact prognosis and treatment response.
- Many of these genomic alterations reprogram cellular metabolism including glucose, amino acid and lipid metabolism.
- Altered brain tumor metabolism can be used to image patients and could serve as means to non-invasively reflect genomic alterations in brain tumor patients to guide patient care.

Figure 1. Oncogenic reprogramming and imaging of glycolysis in brain tumors

Bold red arrows depict common oncogenic pathways in brain tumors such as the PI3K-AKT pathway, mTOR and MYC activation, and alterations in p53, which impact various aspects of glycolysis. The two main glycolytic substrates that may be labeled for imaging are glucose and pyruvate, indicated by yellow circles. Glucose analogues can be used for PET imaging (^{18}F -FDG) or for MRS (^{13}C -labelled glucose). MRS may be used to detect the metabolism of hyperpolarized ^{13}C -pyruvate to ^{13}C -lactate. The pyruvate kinase M2 isoform may be imaged by PET using ^{11}C DASA-23.

Figure 2. Oncogenic reprogramming and imaging of TCA-related, fatty acid and amino acid metabolic pathways

Common oncogenic proteins in brain tumors like the PI3K-AKT pathway, MYC activation, alterations in p53 and mutations in isocitrate dehydrogenase 1 (IDH1) directly or indirectly influence TCA cycle-related, fatty acid or amino acid metabolism (depicted by bold red arrows). The oncometabolite D-2-hydroxyglutarate produced by the mutant IDH1 can be detected by MRS. MRS can also be used to detect the metabolism of hyperpolarized ^{13}C - α -ketoglutarate to ^{13}C -D-2-hydroxyglutarate. Acetate may be labeled with ^{11}C for PET imaging or with ^{13}C for MRS. Amino acids such as glutamine and methionine may be labeled with ^{18}F or ^{11}C for PET imaging.

Figure 3. PET imaging with ^{18}F -labeled Glucose (FDG) in a patient with a glioblastoma
(A) T1 gadolinium-enhanced brain MRI showing nodular enhancing disease in the right temporal lobe, anteriorly (red arrow). (B) MRI/FDG-PET fusion in a patient with GBM. FDG PET shows corresponding hotspots with the tumor (red arrow). Note high background uptake within the normal brain.

Figure 4. PET imaging with ^{18}F -labeled Glutamine in a patient with a low-grade glioma with malignant transformation to high-grade glioma
(A) T1 gadolinium-enhanced brain MRI of a patient with a history of a WHO grade II low-grade glioma diagnosed 2 years prior, now with malignant transformation identified by a new focus of enhancement (red arrow). (B) ^{18}F -FGln PET shows uptake within the corresponding area of contrast-enhancement 90 minutes post tracer-injection. Subsequent surgical resection confirmed high-grade transformation.

Figure 5. PET imaging using ^{11}C -labeled Methionine in a patient with GBM

Post-operative, pre-radiotherapy ^{11}C -methionine (structure in A) PET scan in a patient with GBM demonstrates uptake inferior to the surgical cavity (B), in contrast to the T1-gadolinium enhanced MRI (C), which does not demonstrate any residual enhancing abnormality in the corresponding area (red contour). Six months after treatment, enhancing tumor recurrence is noted in the area initially identified by ^{11}C -methionine PET (D).

Figure 6.

A patient with bifrontal GBM treated with concurrent chemoradiation, with progression soon after completion of treatment. The patient was treated with several lines of systemic therapy with subsequent appearance of additional enhancing lesions 22 months after diagnosis. ^1H MRS imaging was obtained to evaluate for progression versus treatment effect. Evaluation of the left frontal lesion was consistent with disease progression, with

Cho/NAA ratio 2.35 (**A**) and 1.88 (**B**), in contrast to the metabolic composition of the normal brain with Cho/NAA ratio 0.51 (**C**). Courtesy of Yue Cao, Ph.D.

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Cancer type	Subgroup	Frequently altered genetic loci	Frequency of subtype	Typical patient age at diagnosis	Common localization	Typical outcome
	WNT-activated	<i>CTNNB1</i> , <i>TP53</i> , <i>DDX3X</i> , monosomy 6	10% of medulloblastomas	Childhood (7–17 years)	Cerebellum	~95% 5-year survival rate
	Group 3	<i>MYC</i> , <i>GFI1/1B</i> , isodiscentric 17q	25% of medulloblastomas	Infancy, childhood (<17 years)	Cerebellum	~50% 5-year survival
	Group 4	<i>MYNC</i> , <i>CDK6</i> , <i>KDM6A</i> , <i>SNCAIP</i> , isodiscentric 17q	35% of medulloblastomas	Childhood (7–17 years)	Cerebellum	~75% 5-year survival

Tumour classification, subgrouping, and clinical information was derived from the 2016 update of the *WHO Classification of Tumours of the Central Nervous System* and Central Brain Tumour Registry of the United States 1.177.178. GBM, glioblastoma multiforme; G-CIMP, glioma CpG-island methylator phenotype; NA, not applicable/available; RTK, receptor tyrosine kinase; SHH, Sonic Hedgehog.