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Altered cancer cell metabolism in gliomas with mutant *IDH1* or *IDH2*

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Abstract

Purpose of review—*IDH1/2* mutations occur in up to 70% of low-grade gliomas and secondary glioblastomas. Mutation of these enzymes reduces the wildtype function of the enzyme (conversion of isocitrate to α -ketoglutarate) while conferring a new enzymatic function, the production of D-2-hydroxyglutarate (D-2-HG) from α -ketoglutarate (α -KG). However, it is unclear how these enzymatic changes contribute to tumorigenesis. Here, we discuss the recent studies that demonstrate how *IDH1/2* mutation may alter the metabolism and epigenome of gliomas, how these changes may contribute to tumor formation, and opportunities they might provide for molecular targeting.

Recent findings—Metabolomic studies of *IDH1/2* mutant cells have revealed alterations in glutamine, fatty acid, and citrate synthesis pathways. Additionally, D-2-HG produced by *IDH1/2* mutant cells can competitively inhibit α -KG-dependent enzymes, including histone demethylases and DNA hydroxylases, potentially leading to a distinct epigenetic phenotype. Alterations in metabolism and DNA methylation present possible mechanisms of tumorigenesis.

Summary—Recent attempts to improve outcomes for glioma patients have resulted in incremental gains. Studies of *IDH1/2* mutations have provided mechanistic insights into tumorigenesis and potential avenues for therapeutic intervention. Further study of *IDH1/2* mutations might allow for improved therapeutic strategies.

Keywords

astrocytoma; epigenetics; glioblastoma; glioma; *IDH1*; *IDH2*; metabolism; oligodendroglioma

INTRODUCTION

Gliomas are a collection of nervous system tumors arising from glial cells such as astrocytes and oligodendroglia. The most deadly and aggressive of these gliomas is the grade IV astrocytomas or glioblastoma multiforme (GBM). To better understand the genetic basis of

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Conflicts of interest

G.J.R. is coinventor on *IDH1* related intellectual property owned and managed by Johns Hopkins University in accordance with its conflict of interest policy.

GBM, 22 GBM genomes were sequenced. This study quantified the frequency of previously known mutations (e.g. *TP53*, *EGFRvIII*, and *PI3KCA*) and led to the discovery of acquired mutations in *IDH1*, which were not previously known or associated with cancer [1]. Subsequent studies discovered mutations in *IDH2*, the mitochondrial homolog of *IDH1* [2]. The role of *IDH1/2* mutation in tumorigenesis and tumor maintenance is unclear, but recent findings have implicated altered metabolism, modified epigenetic states, and possible connections between the two as potential tumorigenic mechanisms.

METABOLISM AND CANCER

Associations between metabolism and cancer were first documented in the 1920s by Otto von Warburg, who demonstrated that cancer cells exhibited increased rates of glycolysis and decreased dependence on oxidative phosphorylation, despite the presence of sufficient oxygen [3,4]. Recently, understanding and therapeutically exploiting altered metabolism in cancer cells has received renewed interest. Oncogenes and tumor suppressors (e.g. *MYC*, *p53*, *PI3KCA*, etc.) contribute to the regulation of both tumor and normal cell metabolism [5–7]. However, relatively few mutations in genes encoding metabolic enzymes are known to contribute to oncogenesis. These known mutations include succinate dehydrogenase (*SDH*), fumarate dehydrogenase, and *IDH1/2* [1,6,7]. *SDH* and fumarate dehydrogenase mutations are associated with familial cancer syndromes and lead to enzymatic inactivation with subsequent accumulation of their substrates, succinate and fumarate. Accumulation of these metabolites contributes to tumorigenesis by stabilizing HIF-1 α in the presence of sufficient oxygen through inhibition of prolyl hydroxylase domain 2 (PHD2). PHD2 utilizes O₂ and α -ketoglutarate (α -KG) to hydroxylate HIF-1 α , leading to its degradation. Inhibition of PHD2 in the presence of sufficient oxygen leads to increased HIF-1 α and promotes tumorigenesis through increased glycolysis and angiogenesis [6–10].

IDH1/2 MUTATION FREQUENCY

IDH1 mutations occur in up to 12% of all GBMs [1]. GBMs develop *de novo* (primary) or from lower grade gliomas (secondary). Mutations in *IDH1/2* occur in up to 70% of low-grade gliomas and secondary GBMs [2]. *IDH1* and *IDH2* mutations occur in 16% of acute myelogenous leukemias (AMLs) and up to 33% in AMLs with normal karyotypes [11], 56% of central and periosteal cartilaginous tumors [12], and 40% of gliomatosis cerebri cases [13–15].

The role of *IDH1* or *IDH2* mutation as an indicator of progression and survival is not well established. *IDH1/2* mutation may result in decreased prognosis for AML [16–18] and increased prognosis for both low-grade gliomas (65 months for mutant *IDH1/2* versus 38 months for wildtype) and secondary GBMs (31 months for mutant *IDH1/2* versus 15 months for wildtype) [2]. However, *IDH1/2* mutant tumors may be recognized earlier than *IDH1/2* wildtype tumors, resulting in an apparent, rather than real, association with increased survival.

IDH1 MUTATION AND ENZYMATIC FUNCTION

IDH1 mutations occur at a single amino acid residue, R132 [1,2], whereas *IDH2* mutations occur at two residues, R140 or R172 (the functional equivalent of R132 in *IDH1*) [11]. The most common mutation is the R132H *IDH1* mutation [2]. *IDH1/2* mutations result in two enzymatic changes: decreased wildtype IDH function (oxidative decarboxylation of isocitrate to α -KG with simultaneous reduction of NADP⁺) [19,20,21] and gain of a new enzymatic capability [reduction of α -KG to D-2-hydroxyglutarate (D-2-HG)] with simultaneous oxidation of NADPH [19,20] (Fig. 1). Changes in the active site of mutant *IDH1/2* enzymes prime the enzyme to produce D-2-HG by increasing its affinity for α -KG [19,20] and shifting the conformation of the enzyme to favor an intermediate transition state [22].

IDH1/2 MUTATIONS, D-2-HYDROXYGLUTARATE, AND METABOLIC DISORDERS

D-2-HG accumulation is a biochemical hallmark of *IDH1/2* mutant tumors. Cells expressing wildtype *IDH1/2* have low levels of D-2HG, a byproduct of L-hydroxylysine breakdown, which has no known function within the cell. D-2-HG is removed from the cell through conversion to α -KG by D-2-hydroxyglutarate dehydrogenase. Interestingly, D-2-HG and its stereoisomer L-2-hydroxyglutarate (L-2-HG) accumulate in certain metabolic disorders, D-2 or L-2 hydroxyglutaric aciduria (D-2 or L-2-HGA), respectively [23–26].

L-2-HGA results from inactivation of L-2-hydroxyglutaric dehydrogenase [25], whereas D-2-HGA results from inactivation of D-2-hydroxyglutarate dehydrogenase or *IDH2* mutations [23,25,27,28]. *IDH2* mutations found in D-2-HGA are identical to those documented in gliomas or AML. L-2-HGA patients have been documented to develop gliomas [28–32]; however, no cases of glioma have been documented in D-2-HGA patients, despite D-2-HG accumulation [23,25–27]. This may suggest that increased D-2-HG levels alone are not sufficient to cause tumorigenesis.

IDH1/2 MUTATIONS AND TUMORIGENESIS

IDH1/2 mutations are significant driver mutations in glioma development as evidenced by computational analyses using Cancer-Specific High-Throughput Analysis of Somatic Mutations (CHASM) [33]. Additionally, *IDH1/2* mutations occur first in grade II gliomas and their frequency does not increase with tumor grade, suggesting that these mutations are critical for initial tumor development [2,34]. How *IDH1/2* mutation contributes to the development of cancer is currently under investigation.

Initially, studies suggested that *IDH1/2* mutations contribute to tumorigenesis through stabilization of HIF-1 α , similar to *SDH* and fumarate dehydrogenase mutations. The authors suggested α -KG levels were significantly decreased in *IDH1/2* mutant cells, leading to inactivation of PHD2 and stabilization of HIF-1 α [21]. However, subsequent studies have found that α -KG levels are not significantly altered in *IDH1/2* mutant cells, despite increased cellular demand for D-2-HG production [19,20,35,36,37]. Additionally, studies

in AML and glioma with *IDH1/2* mutations did not detect increased stabilization of HIF-1 α [38,39]. Therefore, although HIF-1 α stabilization could contribute to tumorigenesis, other pathways may play a larger role (Fig. 1).

In cells harboring *IDH1/2* mutations, intracellular D-2-HG levels can reach up to 10mM [19, 20,40]. D-2-HG and α -KG are similar in structure, and recent studies have shown that D-2-HG serves as competitive inhibitor of enzymes that utilize α -KG as a co-factor [38,41]. More than 60 enzymes utilize α -KG as a cofactor [42], and D-2-HG outcompetes α -KG for binding to several classes of histone demethylases, PHD2 and TET 5-methylcytosine hydroxylases [38,41]. Crystallographic studies confirm that D-2-HG fits into binding sites for α -KG in dual-specificity histone demethylase KIAA1718 (KDM7A), factor inhibiting hypoxia-inducible factor (FIH), and jumonji domain containing protein 2A (JMJD2A) [38,41]. High intracellular levels of D-2-HG in *IDH1/2* mutant tumors are likely sufficient for potent enzymatic inhibition [38] and suggest a possible mechanism by which *IDH1/2* mutations contribute to tumorigenesis.

Interestingly, mutant *IDH1/2* cases in AML have a characteristic hypermethylated phenotype which may result from inhibition of TET2 by D-2-HG [43]. TET2 catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine and is mutated in approximately 24% of secondary AMLs. TET2 mutations result in a hypermethylated phenotype similar to that seen in mutant *IDH1/2* AMLs, although the two mutations are mutually exclusive [43]. Differentially methylated genes in *IDH1* mutant gliomas include processes known to contribute to tumor progression as well as several metabolic pathways (Table 1). In gliomas, a hypermethylated phenotype has also been identified, the glioma-CpG island methylator phenotype (G-CIMP) which correlates tightly with *IDH1* mutations. Although 78% of G-CIMP positive tumors possess an *IDH1* mutation, no causative link between *IDH1/2* mutations and this phenotype has been directly studied [35,44].

***IDH1/2* MUTATIONS AND METABOLIC ALTERATIONS**

Transcriptional analysis of aberrantly methylated genes in G-CIMP tumors by Noushmehr *et al.* [44] found significant upregulation in genes involved in metabolic processes including carbohydrate metabolism, oxidative stress response, and nucleic acid synthesis (Table 1). Pathways transcriptionally repressed in G-CIMP tumors include those involved in tumor invasion, extracellular matrix remodeling, retinoic acid signaling, and mesenchymal markers (Table 1) [44]. Although the mechanisms for these changes are not yet known, D-2-HG produced by *IDH1/2* mutations may alter the epigenetic profile and thereby alter the expression of metabolic and other genes that promote tumor formation and growth.

Metabolic changes have been confirmed by metabolomics studies on *IDH1/2* mutant cells [36,37]. Reitman *et al.* [36] identified changes resulting from expression of mutant *IDH1/2* or treatment with D-2-HG (1). Some metabolic alterations were found under both conditions; however, approximately half of the observed changes in *IDH1/2* mutant expressing cells could not be replicated by treatment with exogenous D-2-HG. Most notably, decreases in glutamate levels and metabolites whose synthesis involves glutamate were not

replicated by D-2-HG treatment. Therefore, these changes are a direct result of the enzymatic activity of *IDH1/2* mutant enzymes.

One such metabolic alteration is the reduction of the neuropeptide N-acetyl-aspartyl glutamate (NAAG) and its precursor N-acetylated aspartic acid (NAA) in *IDH1/2* mutant cells and tumors by up to 50-fold [36■]. NAAG is synthesized from NAA and glutamate by NAAG synthase and functions in glutamatergic pathways of the brain [45]. Reitman *et al.* found that even when NAA levels are restored, NAAG levels are not fully restored indicating that the glutamate necessary for generation of NAAG may be shuttled for production of α -KG and subsequently D-2-HG. In either case, the consequences of lowered intracellular NAAG levels on tumor formation and maintenance are unknown and warrant further study.

Mutant *IDH1/2* produce D-2-HG from glutamine-derived α -KG, resulting in increased flux through this pathway [20]. Therefore, cells expressing mutant *IDH1/2* may be more dependent upon this pathway for growth and survival. Interestingly, inhibition of α -KG synthesis from glutamine led to a 15–20% decrease in growth for cells expressing mutant *IDH1* [37■■]. To further characterize this growth inhibition, metabolite levels were evaluated following treatment with BPTES, a small molecule inhibitor of glutamine, the first enzyme in the synthesis of α -KG from glutamine. Glutaminase inhibition lowered glutamate and α -KG levels in *IDH1* wildtype and mutant cells, but D-2-HG levels were not reduced, indicating the presence of a compensatory mechanism [37■■].

Changes in the other metabolites following BPTES treatment supported this hypothesis including increases in glycolytic intermediates and decreased levels of TCA cycle intermediates which were seen in both wildtype and mutant *IDH1*-expressing cells [37■■]. Consequently, α -KG might be produced or diverted away from the TCA cycle to compensate for inhibition of α -KG produced from glutaminase. Therefore, metabolic inhibition has been shown as a potential approach for selective targeting of *IDH1/2* mutant tumors. However, glutaminase inhibition alone is not sufficient as a therapeutic strategy and will require additional components for an effective therapeutic response.

Changes in fatty acid metabolism may also result from *IDH1/2* mutant expression. Mutant *IDH1*-expressing cells exhibit decreased levels of citrate compared with wildtype-expressing *IDH1* cells, coupled with increases in acetyl-CoA and triglyceride and phospholipid precursors [36■,37■■]. The combination of decreased citrate and increased lipid precursors may indicate that *IDH1* mutant expressing cells shuttle citrate out of the TCA cycle to produce lipids required for cell growth. Increases in fatty acid/lipid synthesis are a common characteristic of many cancers, including gliomas [46], and it is possible *IDH1/2* mutation may contribute to this phenotype. In addition, mutant *IDH1* may lead to decreased fatty acid oxidation in two ways: reducing available cofactors for peroxisomal β -oxidation and by decreasing carnitine biosynthesis for mitochondrial fatty acid transport.

Oxidation of α -phytanic acids and β -oxidation of certain fatty acids within peroxisomes requires both NADPH and α -KG, products of wildtype *IDH1* activity. *IDH1* has been shown to be the sole source of these molecules within the peroxisomes [47]. Mutant *IDH1* has

decreased the ability to produce NADPH and α -KG, suggesting that mutation of *IDH1* may lead to decreased levels of these substrates within peroxisomes and potentially decreased rates of fatty acid oxidation. Chowdhury *et al.* [38] demonstrated that high levels of D-2-HG can inhibit γ -butyrobetaine hydroxylase 1, the last enzymatic step in carnitine biosynthesis. Carnitine is required for activation and transport of fatty acids into the mitochondria to undergo β -oxidation. Consistent with this finding, levels of propionylcarnitine (a carnitine ester which sustains endogenous carnitine pools) were decreased in *IDH1/2* mutant and D-2-HG-treated cells [36]. Therefore, *IDH1/2* mutations may contribute to tumorigenesis by priming cells for growth by increasing fatty acid synthesis and reducing oxidation of certain fatty acids.

***IDH1/2* MUTATIONS AND ANTICANCER METABOLISM BASED THERAPY**

The discovery of the *IDH1/2* mutation has profound implications for the understanding and treatment of cancer. Elevated D-2-HG levels are characteristic of *IDH1/2* mutant tumors and could serve as a biomarker to identify *IDH1/2* mutational status or monitor tumor growth or treatment efficacy. Studies in AML have shown that D-2-HG can be detected in serum, and increased D-2-HG levels correlate with *IDH1/2* mutational status [19,40]. The use of D-2-HG as a biomarker in gliomas is currently under investigation; however, detection may be technically challenging as the degree of D-2-HG diffusion from solid glial tumors into serum, cerebrospinal fluid, or urine is unknown. Alternatively, D-2-HG can be detected by magnetic resonance spectroscopy (MRS), allowing for noninvasive monitoring of tumor progression or classification of *IDH1/2* mutational status [48].

As it is unclear whether mutant *IDH1/2* protein is important for tumor growth or maintenance, targeting the mutant enzymes may not be therapeutically beneficial. Additionally, it is unknown whether changes in methylation status in *IDH1/2* mutant cells are reversible by disrupting mutant protein function. The distinct metabolic alterations resulting from *IDH1/2* mutations reveal a potential opportunity for therapeutic intervention. Therefore, targeting unique metabolic pathways with *IDH1/2* mutant tumors may be an alternative strategy. One potential strategy for the treatment of *IDH1/2* mutant tumors is inhibition of α -KG synthesis from glutamine. Studies from our group have demonstrated that inhibition of this pathway can specifically slow the growth of mutant *IDH1*-expressing cells [37]. However, compensatory mechanisms and the mutational background of glioma cells suggest that multiple metabolic components may need to be targeted for the development of a successful therapeutic strategy. Further investigation of the role of *IDH1/2* and D-2-HG on the epigenome and the metabolome will likely reveal additional targets.

CONCLUSION

IDH1/2 mutations are central to the development of a particular subset of gliomas, and further studies could identify targeted treatments for individuals with these mutations. Epigenetic and metabolic alterations in *IDH1/2* mutant cells provide clues to the mechanism by which these mutations lead to tumor development and/or maintenance; however, the relative contribution of these changes to each process is currently unknown.

To our knowledge, cell lines and animal models derived from a tumor with a naturally occurring *IDH1/2* mutation have not been established. The literature and our experience suggest that *IDH1/2* mutant tumors are resistant to cell culture establishment using standard protocols [49]. Therefore, studies of *IDH1/2* mutations have been conducted in genetic and metabolic backgrounds which have not developed in concert with an *IDH1/2* mutation. Although these efforts have yielded useful insights, cell culture systems and animal tumor models derived from tumors with naturally occurring *IDH1/2* mutations need to be developed to better understand the role of mutant *IDH1/2* in tumorigenesis and tumor maintenance.

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KEY POINTS

- *IDH1/2* mutations occur frequently and early in the development of low-grade gliomas and secondary GBM.
- *IDH1/2* mutations produce high levels of D-2-HG, which can inhibit α -KG-dependent enzymes potentially leading to genome-wide epigenetic alterations and altered cellular metabolism.
- Mutant *IDH1/2* enzymatic activity leads to metabolic alterations including changes in glutamine, N-acetylated amino acid, and fatty acid metabolism.
- Targeting the altered metabolism in *IDH1/2* mutant gliomas may be a useful therapeutic strategy.

FIGURE 1.

Epigenetic and metabolic alterations in *IDH1/2* mutant tumor cells. *IDH1/2* mutant enzyme activity results in high intracellular D-2-hydroxyglutarate (D-2-HG) levels and alterations in glutamine metabolism, citrate and acetyl-coA levels, and fatty acid metabolism. Simultaneously, D-2-HG is able to compete with α -ketoglutarate for binding to histone demethylases and DNA hydroxylases likely contributing to a hypermethylated phenotype.

Table 1Pathways potentially altered by *IDH1/2* mutations in glioma

Tissue studied		Alteration	
Methylation	<i>IDH1</i> mutant gliomas	Hypermethylated pathways	Hypomethylated pathways
		Methane metabolism	Protein kinase A signaling
		Pregnane X receptor/retinoid X receptor activation	Angiopoietin signaling
		Retinol metabolism	Ras-related nuclear protein signaling
		Phenylalanine metabolism	Retinol transport
		Starch and sucrose metabolism	Cell cycle regulation
		Pentose and glucuronate interconversion	Methylated-DNA-protein-cysteine methyltransferase (MGMT)
		Androgen and estrogen metabolism	Fatty acid binding
Transcription	G-CIMP-positive gliomas	Increased	Decreased
		Transcriptional regulation	Polysaccharide binding
		Nucleic acid synthesis	Heparin binding
		Metabolic processes	Glucosaminoglycan binding
		Cadherin based cell adhesion	Collagen
		Zinc finger transcription factors	Thrombospondin
			Cell morphogenesis
			Retinoic acid signaling
			Fatty acid binding
Metabolism	<i>IDH1/2</i> mutant cells or cells treated with D-2-HG	Increased	Decreased
		D-2-HG	NAAG
		Glycerol-3-phosphate	NAA
		Glycerol-2-phosphate	2-Methyl butyryl carnitine
		Glycine	Isobutyl carnitine
		Asparagine	α-Aminoadipate
		Glutamine	Phosphocholine
		Serine	Propionylcarnitine
		Threonine	Malate
		Phenylalanine	Fumarate
		Tyrosine	Citrate
		Tryptophan	
		Methionine	

D-2-HG, D-2-hydroxyglutarate; NAA, N-acetylated aspartic acid; NAAG, N-acetyl-aspartyl glutamate. Data from [20,35,36,37,44].