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# Isocitrate dehydrogenase 1 (IDH1): what it means to the neurosurgeon

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## Abstract

Isocitrate dehydrogenase-1 (*IDH1*) mutations have been discovered to be frequent and highly conserved in secondary glioblastoma (GBM) and lower grade gliomas. Although *IDH1* mutations confer a unique genotype that has been associated with a favorable prognosis, the role of the mutated *IDH1* enzyme and its metabolites in tumor initiation and maintenance remains unresolved. However, given that *IDH1* mutations are homogenously expressed and are limited solely to tumor tissue, targeting this mutation could potentially yield novel treatment strategies for patients with GBM.

### Keywords

Isocitrate Dehydrogenase; IDH1; glioma; mutation; genetics

## Introduction

Based on their clinical presentation and molecular phenotype, GBMs can be subdivided into two groups: primary versus secondary. GBMs are considered to be primary when they develop *de novo* and are often found in older patients. Primary GBMs develop with a relatively rapid clinical history and are associated with *EGFR* overexpression as well as alterations in *PTEN*, *CDKN2A*, and *MDM2*. By contrast, secondary GBMs typically develop in younger patients and arise due to transformation from prior lower grade tumors. Although they possess similar histological and morphological features to their primary counterparts, secondary GBMs differ significantly on a molecular basis due to their association with genetic alterations including mutations in *TP53, IDH1/2 and ATRX.*

A genome-wide analysis of somatic mutations occurring in GBMs revealed highly-conserved and tumor-specific mutations in the active-site-encoding portion of the *IDH1* gene.[31] Importantly, *IDH1* mutations have been shown to be expressed at high frequencies (~75%) in almost all glioma subtypes, except primary GBM, as well as other tumors but at a significantly lower incidence. Because mutations in *IDH1* are homogenously expressed in

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all tumor cells—even single infiltrating cells[20]—it has been hypothesized that mutations in *IDH1* might represent some of the earliest genetic events that could drive the malignant transformation of lower-grade tumors. This review will address the function of *IDH1* and its mutant form, the clinical role of *IDH1* in gliomas, how to screen for mutated *IDH1*, therapeutic approaches to targeting mutated *IDH1*, and a novel engineering application of *IDH1* mutational data in the synthesis of nylon.

## What is IDH?

Isocitrate dehydrogenase 1 (IDH1) catalyzes the oxidative decarboxylation of isocitrate to 2-oxoglutarate. The most widely-cited tumor-specific mutation of *IDH1* consists of a missense mutation at amino acid 132 that replaces an active-site arginine residue with histidine; this somatic heterozygous mutation was first discovered in a genome-wide analysis of central nervous system tumors.[31] More specifically, *IDH1* mutations have been described in WHO Grade IV secondary GBMs, WHO Grade II diffuse astrocytomas, WHO Grade II oligodendrogliomas, WHO Grade III anaplastic astrocytomas, WHO Grade III anaplastic oligodendroglioma, and WHO Grade III anaplastic oligoastrocytoma.[4,5,8,31] *IDH* mutations were subsequently observed in several other cancers and syndromes, including acute myeloid leukemia, preleukemic clonal malignancies, central and periosteal cartilaginous tumors, colorectal cancer, prostate carcinoma, adult supratentorial primary neuroectodermal tumor (PNET), paraganglioma, intrahepatic origin cholangiocarcinomas, Ollier disease, and Maffucci syndrome).[1,2,4,14,16,19,23] *IDH1* mutations are rarely found in primary GBM (4.9%) and not found in pilocytic astrocytomas, ependymomas, or medulloblastomas (Table 1).

## IDH1 mutants and their impact on metabolism and tumor initiation

*IDH1* is an enzyme located in the cytoplasm as well as in peroxisomes where it participates in lipid metabolism and glucose sensing. A number of potential hypotheses have been offered that implicate *IDH1* mutations in malignant progression and oncogenesis. The altered *IDH1* enzyme found in tumors is known to consist of a dimer between the wild-type and mutant proteins and thus possesses a function distinct from the normal enzyme. While normal *IDH1* converts isocitrate into alpha-ketoglutarate ($\alpha$KG), mutant *IDH1* instead possesses the catalytic activity to convert $\alpha$KG into 2-hydroxyglutarate (2HG).[11] It has been suggested that 2HG may inhibit a variety of dioxygenases including *PHD* (prolyl hydroxylase), *TET2*, and histone demethylases,[22] which in theory could trigger aberrant angiogenesis and aberrant gene expression (Figure 1). Mutations of *IDH1* may also reduce the cellular level of glutathione synthase (GSH) by depleting NADPH and rendering the cells vulnerable to oxidative DNA damage, leading to the development of mutations in other genes.[21] Moreover, *IDH1* mutations have been proposed to facilitate “glycolytic flux”, where energy is produced predominately by aerobic glycolysis in the cytosol of cancer cells. During glioma progression, this allows the cancer cells to adopt these adaptive mechanisms in environmental conditions where nutrients and oxygen may otherwise be lacking.[30]

Alternatively, 2HG produced by the mutant *IDH1* expression is known to compete with $\alpha$KG to inhibit degradation of HIF-1$\alpha$, a transcription factor crucial to the cellular response to hypoxia. As a result, high levels of HIF-1$\alpha$ may promote the expression of VEGF-mediated angiogenesis, leading to greater tumor growth. Further implicating this pathway, mutant *IDH1* is also known to HIF-1$\alpha$ inducible genes.[32] However, a recent study showed that activation of *EGLN*, a HIF prolyl 4-hydroxylase, by the *R* enantiomer of 2HG (*R*-2HG), and subsequent downregulation of HIF-1α, contributes to the pathogenesis of *IDH* mutant gliomas. This data suggests that *R*-2HG quantitatively shifts the dose–response linking HIF-1 activation to hypoxia, leading to a blunted HIF-1$\alpha$ response for a given level of

hypoxia. This controversial data suggests that modulation of the HIF-1$\alpha$ response over time, perhaps in conjunction with alterations in other enzymes affected by 2HG, results in epigenetic changes that are ultimately responsible for glioma transformation.

## IDH1 as a biomarker

*IDH1* mutations have been shown to be a prognostic indicator, but not predictive of response to therapy.[12,15,26,28,29,31] It has been extensively shown that patients with mutated *IDH1* have a better prognosis (5 year survival rate of 93%) than those without the mutation (5 year survival rate of 51%), in terms of overall and progression free survival.[29] Even though patients with *IDH1* mutation are generally younger, multivariate analysis has shown that *IDH1* mutations are an independent prognostic factor after adjustment for age, grade, *MGMT* status, treatment, and genomic profile.[26] The caveat of these studies arises from the comparison of genetically distinct tumors; gliomas that carry *IDH1* mutations are biologically different and unique, and therefore comparing them with gliomas that do not carry the mutation can be misleading. This difference from other types of gliomas is supported by the fact that the *IDH1* mutation is tightly associated with a distinct, homogenous DNA CpG island hypermethylated phenotype, resulting in reshaping of the epigenome.[10,22,24] Recently, a pivotal genetic study in gliomas also supports the idea of refining the classification of malignant gliomas based on distinct genetic signatures.[17]

A few studies have evaluated the predictive value of *IDH1* mutations in response to therapy. It has been shown that in patients with anaplastic oligodendroglial tumors treated with radiotherapy alone or radiotherapy with adjuvant PCV (procarbazine, lomustine, and vincristine), *IDH1* mutations had no predictive value for outcome to PCV.[29] In another study of patients with dedifferentiated low-grade astrocytomas progressive after radiotherapy, response to temozolomide (TMZ) did not differ between *IDH1* mutant and wild-type tumors.[12] However, in a recent study it was found that in secondary glioblasomas, *IDH1* mutations, *MGMT* promoter methylation status (classically known to predict benefit from alkylating agents), and 1p19q codeletion were strongly correlated with increased overall survival. Three subgroups of different chemosensitivity were identified: patients with both *IDH1* mutation and *MGMT* promoter methylation had the best response rate to TMZ (median progression-free survival of 13.4 months), patients with *IDH1* mutation alone had the second best response rate to TMZ (10.2 months), and patients with none of these genetic alterations had the worst response rate to TMZ (6.1 months).[28]

## Clinical screening for IDH1 mutations

There are several current methods that have proven useful for the diagnosis and biological evaluation of *IDH1* mutation-bearing gliomas, including genotyping of the DNA extracted from the brain tumor specimen. It is a relatively straightforward method that many clinical molecular diagnostic laboratories use to perform *IDH1* and *IDH2* sequencing. The second method includes immunohistochemical analysis of the tumor specimen to detect *IDH1* expression using specific monoclonal antibodies to target mutant *IDH1*. For these purposes, Imab-1, an anti-*IDH1*-R132H-specific antibody has been developed that reacts with mutated *IDH1*.[7,8,20] Interestingly, in immunohistochemical studies using this antibody, every glioma cell in *IDH1*-positive samples stains positive for mutated *IDH1*, even along the infiltrating edge of the tumor into cortex.

Another modality for screening involves magnetic resonance spectrometry of the downstream metabolite of the mutant *IDH1* pathway, 2HG.[3,9,13] This noninvasive modality utilizes the presence of the L-enantiomer of 2HG and enables a detailed molecular characterization of gliomas bearing this mutation. This modality has been implicated in identifying 2HG “hot spots”, guiding biopsy procedures, assisting in diagnostic workup, and

monitoring the response of targeted therapies. No current report exists of increased 2HG in blood, urine, or cerebrospinal fluid of glioma patients harboring *IDH1* mutations.

## Treatment strategies

Gain-of-function mutations in *IDH1*-associated glioma and the potential role of these mutations in the pathogenesis of malignant disease make *IDH1* a promising, novel therapeutic target. The replacement of critical active-site arginine residues by alternative side chains offers an opportunity to develop selective inhibitors of mutant *IDH1* that seek to limit its metabolic function. Certainly, a great deal of effort has been placed on the identification of small molecules that may directly inhibit mutant *IDH1*, which in theory would lead to the reduction of 2HG levels in gliomas, effectively modulating the impact of the metabolite on cancer-relevant processes. However, controversy remains regarding whether a therapeutically relevant impact can be achieved via mutant *IDH1* inhibition alone.[18] Additional strategies to reduce the production of 2HG in malignant cells have been suggested that focus on inhibition of enzymes that metabolize substrates up-stream of *IDH1*, including glutaminase and glutamate carboxypeptidase II (*GCPII*). Seltzer *et al.* targeted glutaminase, an enzyme upstream of the mutated *IDH1* pathway that produces glutamate from glutamine, to determine if inhibiting this enzyme would perturb $\alpha$KG homeostasis and yield an anti-tumor response.[27] *GCPII* has the potential to reduce extracellular glutamate and represents an opportune target for treating cancers. *GCPII* is identical to a tumor marker, prostate-specific membrane antigen, and has drawn significant interest as a potential therapeutic target in cancers where excess glutamate is considered pathogenic. However because these enzymes also have normal functions in pathways of central metabolism, global inhibition may ultimately risk off-target toxicity in even normal, healthy tissues. In addition, given that the *IDH1* mutation is tightly associated with a hypermethylated phenotype, DNA methyltransferase inhibitors and histone deacetylase inhibitors may also have therapeutic efficacy. Although these inhibitors have been studied in a phase 1/2 trial in a handful of patients in AML with limited efficacy[6], they have yet to be pursued in glioma therapeutic targeting.

## Neomorphic IDH mutant activity informs enzyme redesign

Generally, cancer can be thought of a selective biological process by which gain-of-function mutations, like those associated with *IDH1*, may actually lend a “competitive” advantage for tumor cells throughout their growth and development. Interestingly, knowledge of such neomorphic catalytic activities—as well as their associated functional active site alterations—may provide useful insight in the field of metabolic engineering, wherein the need for enzymes with novel catalytic activities is great. A recent advance toward this end is the use of human *IDH1* mutational data to aid in the rapid design of enzymes that satisfy a significant industrial need in the large-scale production of adipic acid, a central substrate precursor in the synthesis of nylon.[25] Studies such as these suggest that an intimate understanding of cancer-derived mutations may not only reveal underlying mechanisms of tumor pathogenesis, but may also have broad, far-reaching, applications in the fields of metabolic engineering and industrial enzyme redesign.

## Conclusion

*IDH1* is a key metabolic enzyme in the glycolytic pathway, in which mutations of this enzyme are consistent and frequent in low grade gliomas and secondary GBM. *IDH1* mutations can currently be detected via immunohistochemistry, genetic analysis, and magnetic resonance spectrometry. Although *IDH1* mutations denote a unique genotype with a favorable prognosis, the role of the mutated *IDH1* enzyme and its metabolites in tumor

initiation and maintenance remains largely unresolved. Since it is a driver mutation expressed early in tumor development and expressed in every tumor cell, the *IDH1* mutation has the potential to be targeted and every tumor cell affected.

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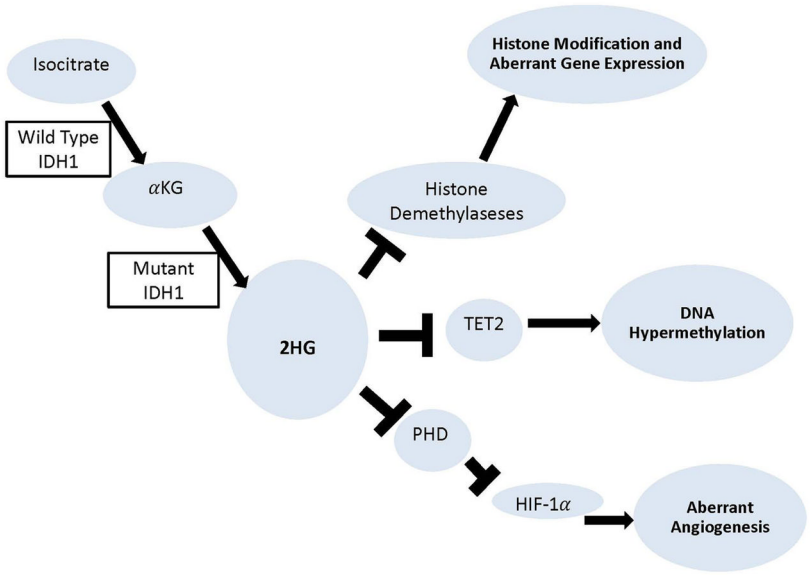


**Figure 1.**
Diagram of the molecular consequences of the *IDH1* mutation.

## Table 1

IDH1 mutation incidence in tumor subtypes.[4,5,14,16,18,21,25,26,29,32,35,36]

| Tumor Type | Mutations (%) and median (range) | Number of mutations/total number of tumors |
|---|---|---|
| Diffuse Astroctyoma | 74% (0–88%) | 307/407 |
| Anaplastic Astrocytoma | 59% (0–78%) | 294/457 |
| Secondary GBM | 83% (50–100%) | 94/121 |
| Oligodendroglioma | 76% (67–84%) | 283/366 |
| Anaplastic Oligodendroglioma | 67% (49–94%) | 237/355 |
| Oligoastrocytoma | 80% (50–100%) | 153/196 |
| Anaplastic Oligoastrocytoma | 75% (63–94%) | 245/345 |
| Ganglioglioma | 37.5% | 3/8 |
| Anaplastic Ganglioglioma | 60% | 3/5 |
| Sporadic Paraganglioma | 2% | 1/66 |
| Primitive Neuroectodermal Tumor | 17% (0–33%) | 3/17 |
| Acute Myelogenous Leukemia | 1% (0–9%) | 21/389 |