Isocitrate Dehydrogenase Mutations in Glioma

Subjects: Medicine, General & Internal

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Mutations in isocitrate dehydrogenase (IDH) are commonly observed in lower-grade glioma and secondary glioblastomas. IDH mutants confer a neomorphic enzyme activity that converts α-ketoglutarate to an oncometabolite D-2-hydroxyglutarate, which impacts cellular epigenetics and metabolism. IDH mutation establishes distinctive patterns in metabolism, cancer biology, and the therapeutic sensitivity of glioma. Thus, a deeper understanding of the roles of IDH mutations is of great value to improve the therapeutic efficacy of glioma and other malignancies that share similar genetic characteristics.

Keywords: IDH mutation ; glioma ; cancer ; therapy resistance

1. Introduction

In 2008, compelling research showed that mutations in isocitrate dehydrogenase (*IDH1* and *IDH2*) are frequently identified in the World Health Organization (WHO) grade II/III gliomas and secondary glioblastomas (GBMs). In contrast, these mutations are rare in primary GBM patients [1]. In 2009, Yan et al. [2] showed that *IDH1* and *IDH2* mutations frequently occur in WHO grade II/III astrocytomas and oligodendrogliomas. Besides gliomas, *IDH* mutations also occur in other non-central nervous system (CNS) malignancies, including acute myeloid leukemia (AML) [3][4], intrahepatic cholangiocarcinoma [5][6], chondrosarcoma [7], and melanoma [8][9]. The mutations are confined to a single arginine residue (Arg^{132}) in *IDH1* or two arginine residues (Arg^{172} and Arg^{140}) in *IDH2* [10][11]. The mutations commonly cause amino acid substitutions, which localize at the active sites of the enzymes and alter the catalytic functions of *IDH* enzymes. In contrast to wild-type *IDH*, which transforms isocitrate into α-ketoglutarate (α-KG), the mutated *IDH*s convert α-KG into D-2-hydroxyglutarate (D-2-HG) [12]. The altered catalytic activity that occurs because of cancer-associated *IDH* mutations was later termed “neomorphic activity”. The overproduction of the oncometabolite D-2-HG leads to widespread physiological consequences, including profound effects on cellular metabolism [13][14], epigenetic shift [15][16][17][18], genomic instability [19][20][21][22][23], and redox homeostasis [24][25][26][27][28][29]. *IDH* mutations are considered founder events for oncogenesis, through which an ancestor glial cell commits to malignant transformation. On the other hand, the mutant *IDH* enzyme brings about substantial changes in cancer biology, thereby establishing novel therapeutic vulnerabilities that are not commonly identified in other neoplasms.

2. Clinical Indications Involving the Discovery of *IDH*-Mutated Glioma

2.1. Clinical Classification of Gliomas

The 2016 WHO classification of CNS tumors has suggested the use of integrated phenotypic and genotypic characterization, which provides an increased level of objectivity [30]. In particular, *IDH* mutations have become some of the most important parameters in the differential diagnosis of gliomas. For example, diffuse astrocytomas often harbor *IDH* mutations, followed by other mutations such as *TP53* and *ATRX*. Oligodendrogliomas are characterized by *IDH* mutations along with 1p/19q co-deletion (potentially along with *CIC* and *FUBP1* mutations). The *IDH* mutation status is also useful for the differential diagnosis of primary and secondary GBMs [30][31][32]. Moreover, as *IDH* mutations frequently induce genome-wide DNA and histone hypermethylation, the introduction of methylation profiling allows for further improving the accuracy of glioma classification. Recently, Jaunmuktane et al. [33] demonstrated a diagnostic algorithm that integrated histology, molecular signature, and methylation array, and improved the diagnostic approach. Thus, the *IDH* mutation status is of great value in glioma classification and the selection of appropriate therapeutic strategies.

2.2. Radiology—D-2-HG Imaging

D-2-HG is a novel metabolite that accumulates in extremely high levels in glioma cells, but is absent in normal brain cells. The drastic contrast in cellular D-2-HG levels suggests that this oncometabolite could be an ideal biomarker for clinical

monitoring and diagnosis among patients with *IDH*-mutated cancers [34]. Several hallmark studies have developed noninvasive radiologic methods for the detection of D-2-HG, such as magnetic resonance spectroscopy (MRS). In *IDH* mutant gliomas, D-2-HG accumulates to sufficient levels as a brain metabolite, which renders its visibility on MRS. These levels are 2–3 orders of magnitude higher than those found in the adjacent normal brain tissues [34]. Andronesi et al. [35] reported that D-2-HG was detected unambiguously in mutant *IDH1* glioma in vivo using 2D correlation spectroscopy (COSY) and J-difference spectroscopy. Several other studies have also reported that D-2-HG is detected among glioma patients or in animal models using the short echo times (TEs) method [36][37][38][39]. On the other hand, D-2-HG levels were detected in glioma patients using long TE methods and J-difference spectroscopy with 100% sensitivity [40][41]. The application of long TE methods in D-2-HG detection has been confirmed in several subsequent reports, with increased sensitivity and specificity [42][43]. Overall, the noninvasive detection of D-2-HG has been proven to be a valuable diagnostic and prognostic biomarker. D-2-HG imaging provides a useful approach to the clinical management of patients with *IDH*-mutated glioma. Fluctuations in D-2-HG levels may provide crucial longitudinal data for the determination of disease progression and therapy response [34].

2.3. Disease Outcomes—Prolonged Survival

In 2008, Parsons et al. [1] first reported that mutations in *IDH1* occurred in most patients with secondary GBM, and were associated with better overall survival (OS). Similar trends were reported in numerous studies using various datasets [44][45][46][47][48][49]. For example, using a large clinical dataset, Yan et al. [2] reported that GBM patients harboring *IDH1* or *IDH2* mutations tend to have a prolonged median OS compared with patients with *IDH* wild-type GBM. Similar findings were also observed among patients with anaplastic astrocytoma. The median OS was 65 months for patients with *IDH* mutant disease, compared with 20 months for those with *IDH* wild-type disease. Moreover, the progression-free survival (PFS) was also improved among GBM patients with *IDH* mutations compared with their counterparts [45]. Secondary genetic alterations, such as *TP53*/*ATRX* mutations and 1p/19q co-deletion, predispose patients with *IDH*-mutated gliomas to slightly different OS and disease-free survival (DFS; Figure 1A,B). Several studies have reported that *IDH* mutations are associated with younger age at diagnosis and limited genome alterations among patients with WHO grade II/III gliomas and GBMs, which may bias the disease outcome (Figure 1C,D) [1][2][50][51]. However, in a multivariate analysis, Sanson et al. [45] showed that the *IDH* mutation status is an independent predictor of favorable outcomes among glioma patients.

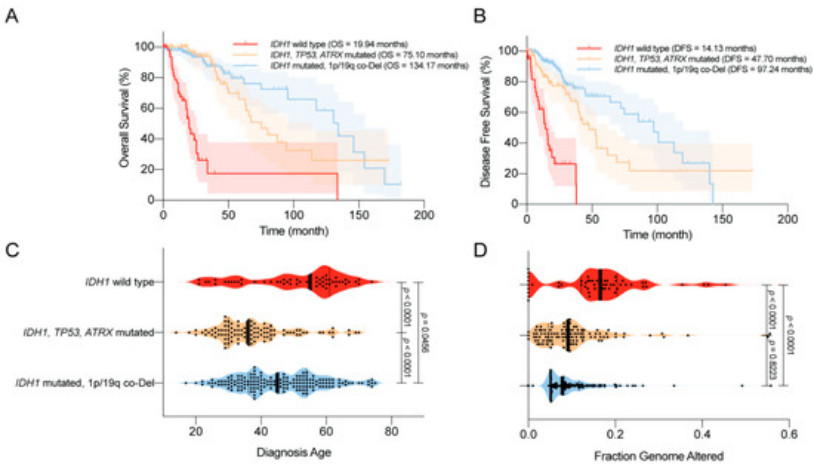

Figure 1. Clinical features of the World Health Organization (WHO) grade II/III *IDH*-mutated glioma. (**A**) Overall survival (OS) of glioma patients according to *IDH1* status. *IDH1* mutations are associated with prolonged OS. (**B**) Disease-free survival (DFS) of glioma patients according to *IDH1* status. *IDH1* mutations are associated with prolonged DFS. (**C**) Age at diagnosis among glioma patients according to *IDH1* status. *IDH1* mutations are associated with a younger age at diagnosis. (**D**) The distribution of genome alterations in glioma according to *IDH1* status. *IDH1* mutations are associated with fewer genome alterations. The data are visualized in cBioPortal [52][53].

2.4. Complications—Epilepsy and Secondary GBM

Epileptic seizure is one of the most common complications among patients with glioma, particularly those with LGGs (up to 90%) [54][55][56][57]. Severe seizures impair the quality of life and neurocognition function among glioma patients [58]. Considering the high incidence of *IDH* mutations in LGG, it is likely that the epileptic changes are relevant to the unique patterns in the tumor microenvironment, which is associated with *IDH* mutants. Numerous studies have indicated that mutations in *IDH* are associated with a high prevalence of epilepsy [59][60][61][62][63]. For example, Chen et al. [62] showed that *IDH* mutations are independently correlated with seizures, regardless of WHO grade. A recent study suggested that D-2-HG overproduction in the tumor microenvironment plays a major role in glioma-related epilepsy. D-2-HG is structurally

similar to glutamate, which is the predominant excitatory neurotransmitter in the CNS. Thus, D-2-HG may act as an analog of glutamate, which leads to the abnormal firing of neurons through activating N-Methyl-d-aspartic acid (NMDA) receptors, and hence epileptic changes. Treating cultured rat cortical neurons with exogenous D-2-HG resulted in an elevated firing rate [62]. By mimicking the activity of glutamate, the increased level of D-2-HG mediates the abnormal neuronal activity and leads to glioma-related epilepsy [35][64][65]. However, three millimolar D-2-HG induced an elevated burst frequency in the neuronal network in vitro [62], whereas this dose is over 30 times higher than the glutamate concentration for excitotoxicity [66]. More effort is urged in order to elucidate the detailed molecular mechanism of the epileptic changes in *IDH*-mutated glioma. Because of the association between *IDH* mutations and seizures, therapies that target mutant *IDH*, such as mutant *IDH* inhibitors, could diminish D-2-HG production and potentially reduce epileptic seizures [67].

2.5. Sensitivity to Radiotherapy and Chemotherapy

Clinical data have shown that *IDH* mutant gliomas tend to exhibit a better disease outcome compared with wild-type *IDH* tumors. Several studies have explained that the favorable prognosis of *IDH* mutant gliomas is due to their increased sensitivity to radiotherapy and chemotherapy [68][69]. *IDH* mutant gliomas likely harbor defects in multiple DNA repair pathways, which render them vulnerable to radiotherapy- or chemotherapy-induced DNA damage [19][22]. These findings indicate that *IDH* mutation could serve as an important predictive factor for treatment response among glioma patients. For example, Houillier et al. [69] reported that *IDH1* mutation is an independent predictor of temozolomide response among LGG patients. *IDH1* mutations combined with 1p/19q co-deletion further improved the treatment response. Hartman et al. [70] also reported that *IDH1* status is an important predictor of disease-free survival (DFS) and OS among patients undergoing adjuvant therapy. In another study conducted by van de Bent et al. [71], no correlation was found between *IDH1* mutations and disease outcome in response to procarbazine (Matulane), lomustine (CCNU), and vincristine (Oncovin) chemotherapy.

3. Novel Molecular Targeting for *IDH*-Mutated Glioma

3.1. IDH Mutant Inhibitors

Because of the critical roles played by *IDH* mutations in the malignant transformation of glioma, targeting the neomorphic activity of *IDH* mutants has been heavily proposed as a direct therapeutic approach. In the past decade, several attempts have been made to develop small molecular compounds that directly inhibit mutant *IDH* enzymes. In 2012, the first-in-class mutant *IDH* inhibitor was discovered, which showed a specific and potent inhibitory effect on D-2-HG production in *IDH* mutant U87 cells and xenograft models [72]. Later, Rohle et al. [67] reported a novel synthetic inhibitor of *IDH* mutant, AGI-5198, which blocked D-2-HG production and subsequently reversed the malignant transformation effect of *IDH* mutations. Besides glioma, the inhibition of mutant *IDH* promotes differentiation in leukemia harboring *IDH* mutations [6]. With the promising findings regarding AGI-5198, second-generation mutant *IDH* inhibitors are under development and are undergoing evaluation in clinical studies. For example, ivosidenib (AG-120) and vorasidenib (AG-881) have been tested in AML and glioma with *IDH* mutations [73][74][75][76]. In a recent phase I clinical study with ivosidenib in *IDH1*-mutated advanced glioma conducted by Mellinghoff et al. [77], the mutant *IDH* inhibitor appeared to be well-tolerated throughout the experiment, which paved the way for subsequent clinical studies to evaluate its therapeutic efficacy. Although the *IDH* mutant enzyme inhibitors suppress malignancy, several studies have suggested that this inhibitor reduces D-2-HG production and relieves the burden on the DNA repair pathway, resulting in chemoresistance to other therapies, such as PARP inhibitors [23][78]. More effort is urged to explore the strategy of combining *IDH* mutant inhibitors with other glioma therapies in order to improve the clinical outcome.

3.2. Targeting Hypermethylation Phenotype

Genome-wide DNA and histone hypermethylation is a unique signature in *IDH*-mutated glioma, which is closely related to gliomagenesis by promoting oncogene expression and inhibiting tumor suppressors [79]. This rectification of the epigenetic shift could be a reasonable strategy for halting D-2-HG-driven oncogenesis and the malignant phenotype. DNA-demethylating agents such as 5-azacytidine or 5-aza-2′-deoxycytidine (decitabine) irreversibly bind to DNA methyltransferases (DNMTs) and inhibit the process of DNA methylation. The D-2-HG-induced hypermethylation phenotype was reversed by demethylating compounds, and cell proliferation was suppressed in vitro and in vivo [80][81][82]. Several clinical trials are evaluating the therapeutic effects of 5-azacytidine among patients with recurrent gliomas with *IDH* mutations (NCT03666559 and NCT03684811). On the other hand, inhibitors targeting histone methyltransferases inhibitors are also being investigated for *IDH*-mutated gliomas, as an alternative strategy to rectify the D-2-HG-associated hypermethylation phenotype. It is reported that H3K9 methyltransferase G9a is correlated to the development and progression of glioma, and its inhibitor BIX-01294 showed repressive effects on gliomas cells [83].

3.3. Targeting DNA Repair Pathways

As previously mentioned, *IDH* mutant gliomas exhibit defects in multiple DNA repair pathways. High levels of D-2-HG inhibit the activity of DNA oxidative demethylases, such as AlkB homolog 2/3 (*ALKBH2*/*3*) [19]. Several seminal studies have also indicated that D-2-HG compromises HR DNA repair, establishing a “BRCAness” in this type of malignancy [23][84]. In addition, *IDH* mutation-associated G-CIMP resulted in the methylation of the promoter region of O-6-methylguanine-DNA methyltransferase (MGMT), which reduced MGMT expression and led to increased sensitivity to alkylating agents [46][85][86]. Our recent study indicated that *IDH* mutations led to defects in NAD metabolism, which compromised PARP-associated HR, as PARP repairs DNA damage in an NAD^+ dependent manner [22][87]. With the identification of the DNA repair deficiency in *IDH*-mutated glioma, numerous studies have attempted to evaluate DNA repair inhibitors, which may serve as a potential sensitization strategy. Several other groups and as well as ours reported that a combination of PARP inhibitors, such as olaparib, with temozolomide or radiotherapy, led to synergistic lethality in *IDH* mutant glioma cells [21][22][23]. Several phase I/II clinical trials are currently recruiting patients to investigate the therapeutic effect of the PARP inhibitors, pamiparib (BGB-290) or olaparib, combined with temozolomide in *IDH* mutant gliomas (NCT03914742, NCT03749187, and NCT03212274).

3.4. Targeting Anti-Oxidative Pathways

Redox homeostasis has been reported to be greatly impacted by *IDH* mutations, highlighted by profoundly elevated levels of oxidative stress [24][25][26][27][28]. As a result, ROS scavenging pathways are widely mobilized in the context of *IDH* mutation, so as to maintain cellular metabolism, thereby supporting cellular growth and survival. These findings suggest that the antioxidant pathway plays an essential role in *IDH*-mutated glioma. Targeting anti-oxidative pathways may be more effective in glioma with *IDH* mutations. Our recent study showed that NRF2-governed anti-oxidative pathways, such as that regarding de novo glutathione synthesis, were widespread in *IDH* mutant gliomas. The blockade of NRF2 using natural compound inhibitors, brusatol, or triptolide significantly increased oxidative damage and subsequently suppressed the growth of *IDH* mutant xenografts with prolonged OS [25][27][28][88]. The concept of targeting redox homeostasis in *IDH* mutant cancers has shown a potential therapeutic value. The development of pharmacological grade NRF2 inhibitors is needed urgently for potential clinical translation.

3.5. Targeting Metabolic Reprogramming

D-2-HG is a metabolite that is absent in normal cells. The production of large quantities of D-2-HG inevitably depletes a substantial amount of carbohydrate from the Krebs cycle. Several hallmark studies have demonstrated the presence of depleted metabolic pathways in *IDH*-mutated cells. For example, glutamate metabolism is greatly altered in *IDH* mutant glioma, as mentioned before. The glutamate level is significantly lower in *IDH* mutant cancers, which leads to an increased dependence on glutaminolysis to compensate for the metabolism [29][89][90][91]. Several studies have reported that a blockade of glutaminase activity results in the suppression of *IDH* mutant glioma and AML. Seltzer et al. and Emadi et al. [89][90] reported that bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide (BPTES), an inhibitor of glutaminase, selectively suppresses tumor growth in *IDH* mutant glioma and AML by targeting the fragile glutamine metabolism. Another glutaminase inhibitor (CB-839) was also reported to induce selective radio-sensitivity in *IDH* mutant cancers [29] and terminal differentiation in *IDH* mutant AML [91]. An ongoing phase I clinical trial is investigating the side effects and the best dose of CB-839, in combination with radiation therapy and temozolomide, for treating *IDH*-mutated diffuse or anaplastic astrocytoma (NCT03528642). In addition, *IDH* mutations lead to the depletion of NAD^+ because of the increased methylation of the promoter region of *NAPRT1*, the rate-limiting enzyme in NAD^+ biosynthesis, and suppression of the expression of NAPRT1. This renders the *IDH* mutant glioma vulnerable to inhibition through the nicotinamide phosphoribosyltransferase (NAMPT) catalyzed NAD^+ salvage pathway [92]. Moreover, Tateishi et al. [93] showed that NAMPT inhibitors further sensitized *IDH* mutant cancer cells to alkylating agents, such as temozolomide, as PARP activation consumes NAD^+ during the base excision repair of chemotherapy-induced DNA damage. With the substantially exhausted metabolic pathways, distinctive metabolic vulnerabilities are established in *IDH*-mutated malignancies. Effectively targeting these metabolic pathways may induce selective cytotoxicity to cancer cells, but a lesser extent than that occurs in normal somatic cells with an intact metabolic network.

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