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The Distribution and Significance of *IDH* Mutations in Gliomas

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Abstract

In 2009, the discovery of isocitrate dehydrogenase (IDH) mutations in gliomas is a powerful example of understanding of the relationship between tumor genetics and human diseases. IDHs, catalyze the oxidative decarboxylation of isocitrate to α -ketoglutarate with production of NADH/NADPH, is the key enzymes in the Krebs cycle. IDH mutations, which occur early in gliomagenesis, change the function of the enzymes, causing them to produce 2-hydroxyglutarate, and to not create NADPH. Gliomas with mutated IDH have improved prediction of patient outcomes compared to its with wild-type IDH. Thus, the WHO Classification of Tumors of the Central Nervous System was revised in 2016 to incorporate molecular biomarkers (including the IDH mutations) – together with classic histological features – in an integrated diagnosis, in order to define distinct glioma entities as precisely as possible. The aim of this chapter is to review the findings on the epidemiology and significance of IDH mutations in human gliomas, from discovery to the current knowledge about their molecular pathogenesis.

Keywords: *IDH* mutation, gliomas, Isocitrate dehydrogenase, significance, therapies

1. Introduction

Isocitrate dehydrogenase (IDH) is a key enzyme in the Krebs cycle and plays an important role in energy metabolism. This enzyme is involved in a number of cellular processes, such as mitochondrial oxidative phosphorylation, regulation of cellular redox status, glutamine metabolism as well as lipogenesis or glucose sensing.

In 2008, Parsons et al. discovered a link between *IDH* mutations and gliomas. After that, further studies showed that *IDH* mutations are not only common but also closely related to the diagnosis, treatment and prognosis of gliomas. Therefore, the WHO classification of Tumors of the Central Nervous System of 2016, gliomas are subdivided based on combined classical histological with molecular markers (including the *IDH* mutations). This reclassification is expected to guide treatment decisions and improve outcome prediction.

The aim of this chapter is to review the findings on the epidemiology and significance of *IDH* mutations, from current knowledge about molecular pathogenesis to the value these mutations in gliomas.

2. IDH enzymes

2.1 Normal enzymes

2.1.1 Genetics and classification enzymes

IDH is a small molecule protein which is mainly distributed in the liver, heart muscle and skeletal muscle. In humans, there are three isozymes of IDH, which differ in subcellular localization, structural organization, allosteric regulation, catalytic mechanism and cofactor requirement. These are IDH1, IDH2 and IDH3.

These isozymes are encoded by five separate genes. IDH1, encoded by *IDH1* gene on 2q33.3, is configured as a homodimer with two enzymatically active sites and most of its activity is detected in the cytosol and in peroxysomes, Main function of IDH1 is believed to be the synthesis of NADPH, required for reducing reactions and for lipid synthesis [1–3].

IDH2, which is found in mitochondrial, encoded by the *IDH2* gene on 15q26.1, in [4]. Similar to IDH1, this enzyme is structured as a homodimer. Recent findings show that the IDH2 may be the main catalyst for the oxidation of isocitrate (ICT) to α -ketoglutarate (α -KG) in the citric acid cycle (TCA) in [5]. IDH3 is composed of three subunits encoded by *IDH3A* (subunit alpha), on 15q25.1-q25.2, *IDH3B* (subunit beta) on 20p13 and *IDH3G* (subunit gamma), on Xq28 [6–8].

IDH3 is a multi-tetrameric enzyme ($2\alpha 1\beta 1\gamma$) with α – subunits being catalytic and the β - and γ - subunits being believed to be regulatory [9, 10]. Since *IDH3* mutations do not occur with a significant frequency in glioma [11] this chapter focuses on the roles of IDH1 and IDH2 in glioma biology and uses IDH to refer to both IDH1 and IDH2 but not IDH3 (Figure 1).

2.1.2 Mechanism and function of IDH enzymes

IDH exists in NADP-dependent forms [2]. Both IDH1 and IDH2 exist as homodimers, share considerable sequence similarity (70% identity humans). IDH1 is highly expressed in the mammalian liver (IDH1 provides NADPH for peroxisomal fat and cholesterol synthesis) with only moderate to absent expression in other tissues, whereas IDH2 is highly expressed in heart, muscle, and activated lymphocytes [13].

The main function of IDH is to catalyze the oxidative decarboxylation of ICT to α -KG. This reaction also produces a molecule called NADPH, which is necessary for

Figure 1. IDH1 is localized in the cytoplasm and peroxisomes, whereas IDH2 is founded within the mitochondrial matrix [12].

multiple cellular processes. The NADPH is involved in the breakdown of lipids for energy, and also protects cells from potentially harmful molecules called reactive oxygen species.

By providing mitochondrial NADPH for NADPH-dependent antioxidant enzymes, IDH maintains a pool of reduced glutathione and peroxiredoxin [14]. These molecules protect mitochondria from ROS-mediated oxidative damage, ensuring lipid peroxidation and DNA damage, and from stress induced by heat shock, cadmium, excess fructose, or tumor necrosis factor- α (TNF- α) [13, 14]. These data suggest that IDH is important for cell stress responses, mitochondrial bioenergetics, and macromolecular synthesis to support cell survival and growth.

2.2 Molecular pathogenesis of IDH mutations

IDH1 mutations almost occur at Arginine 132 resulting in amino acid exchange, including R132H (most common, 88%), R132C, R132L, R132S, and R132G. *IDH2* mutations typically occur at R140 or R172. Of *IDH2* mutations, R172K is most common. *IDH1* and *IDH2* mutations are mutually exclusive [15].

2.2.1 Enzymatic properties of mutant IDHs

Mutations in *IDH* are neomorphic gain-of-function mutations, which affect cofactor binding affinity and conformation of the enzymes' active center. When mutated, the enzymes' binding affinity to ICT decreases, while affinity to NADPH increases. Mutations result in a dominant gain-of-function that catalyzes the NADPH-dependent reduction of α -KG to D-2-hydroxyglutarate (D-2HG or R-2HG) but not further carboxylated [16]. D-2HG is a competitive inhibitor of multiple α -KG-dependent dioxygenases, including histone demethylase. As a result, D-2HG makes histone methylation and blocks cell differentiation. Therefore, D-2HG is called oncometabolite.

All *IDH* mutant enzymes produce D-2HG; their allelic frequency, enzymatic property, and association with overall prognosis, however, are markedly different. For example, while the *IDH2*Arg140 mutation is exclusively found in myeloid malignancies [17], the *IDH1*Arg132 and *IDH2*Arg172 mutations are common in gliomas.

In addition, due to essential roles of IDHs in producing cytoplasmic and mitochondrial NADPH, tumor cell survival may also be dependent on basal IDH activities to maintain cytoplasmic and mitochondrial redox homeostasis.

2.2.2 Mutant IDH enzymes control cellular growth

A large body of evidence indicates that IDH mutation inhibits cell proliferation [18–20]. Theoretically, D-2HG inhibits ATP synthase, resulting in decreased mTOR (mammalian target of rapamycin) signaling and cell growth. Moreover, by inhibiting the FTO (fat mass and obesity-associated) demethylase activity, D-2HG promotes cell-cycle arrest, thereby increasing N6-methyladenosine modification of MYC/CEBPA (CCAAT/enhancer binding protein alpha) transcripts for destabilization and, thus, decreasing proliferative signaling [20].

There is a study in mice indicating that *IDH1*R132H homozygous expression in neural progenitor cells (NPCs) results in extensive cerebral hemorrhage and perinatal lethality [21]. On molecular levels, high-level accumulation of D-2HG inhibits prolyl-hydroxylation and subsequent maturation of collagen. Immature collagens accumulate, resulting in an aberrantly formed basement membrane and the initiation of an endoplasmic reticulum (ER) stress response. As a result, mice developed hydrocephalus and grossly dilated lateral ventricles.

Collectively, these studies provide strong evidence that IDH mutation targets various signaling pathways to inhibit glial cell proliferation.

2.3 IDH mutation involvement human cancers

Mutations in *IDH1* and *IDH2* have recently been discovered in CNS cancers like gliomas, and a number of types of leukemia, including acute myeloid leukemia. This discovery has been extended to prostate cancer, intrahepatic cholangiocarcinoma, colon cancer, and thyroid cancer as well since 2009.

Mutations targeting IDH in different types of tumors share four distinct biochemical features. First of all, *IDH* mutations are almost somatic and rarely germline. In addition, predominantly all reported cases have been frameshifts or deletions, whereas nonsense mutations have not been observed in cancer.

Second, the vast majority of *IDH* mutations (Mut) are heterozygous with a wild-type (Wt) allele [22, 23]. The existence of wild type-mutant (Wt-Mut) and mutant-mutant (Mut-Mut) dimers in addition to wild type-wild type (Wt-Wt) dimer in a cell heterozygous for *IDH* mutation has been reported [24]. An illustration of the three dimer types allele is provided in **Figure 2**.

From what has been mentioned so far, the most likely model is as follows: substitution of two arginine residues on both monomers inactivates both forward oxidative decarboxylation and reverse reductive carboxylation reactions while the presence of one arginine fully inhibits the forward oxidative decarboxylation reaction but changes the product of the reverse reductive carboxylation reaction to be D-2HG instead of ICT.

It is conceivable that the Mut-Mut dimer is totally, while the Wt-Mut dimer increases the production of D-2HG from 2KG through the reverse reaction and does not interconvert ICT and 2KG. Since D-2HG is thought to inactivate 2KG utilizing enzymes, it is possible that it also inhibits the Wt-Wt dimer form and that might explain the dominant negative effect of heterozygous arginine substitution (**Figure 3**) [24, 25].

Third, nearly all *IDH* mutations cause a single amino acid replacement, Arg132 in *IDH1* (into one of six amino acid residues -His, Cys, Leu, Ile, Ser, Gly

Figure 2.
The three dimer types formed in a cancer cell heterozygous for IDH mutation.

Figure 3.
The model gains of function and dominant negative effect exerted by heterozygous IDH mutation. (D)-2HG (d) 2-hydroxyglutarate, ICT: isocitrate, Mut: mutant, Wt: wildtype.

and Val), as well as Arg172 in *IDH2* (into one of four other residues -Lys, Met, Gly and Trp), and Arg140 in *IDH2* to either Gln or Trp. Rarely *IDH1* mutations also are reported, including R100A in adult glioma, G97D in colon cancer cells and a pediatric glioblastoma. The synthesis of cancer-associated *IDH* mutations in the functional region of the enzyme suggested that these mutations might give the mutant protein with a new and possibly oncogenic enzymatic activity.

Lastly, the mutual exclusivity seen in mutant *IDH1* and *IDH2* alleles in most cases. Obviously, in a cancerous cell transformed by one of these mutant alleles, the forward oxidative decarboxylation reaction catalyzed by the remaining wild-type isoform would still be important for that cell to be able to produce NADPH. In other words, cancerous cells that have mutant *IDH2*, would still need the wild type *IDH1* isoform to catalyze the forward oxidative decarboxylation reaction to produce NADPH. Only rarely, individual tumors have been found to sustain mutations in both the *IDH1* and *IDH2* genes [26].

IDH mutations also exhibit three distinct clinical features. First, they exist in a highly restricted tumor spectrum. For example, they occur frequently in low-grade gliomas and secondary glioblastomas (GBM), but rarely in primary GBM. Likewise, they are often found in genetically normal AML. Second, the *IDH* mutations occur at an early stage in tumor formation, and occur the earliest known mutation in glioma. Finally, in glioma, AML and intrahepatic cholangiocarcinoma, *IDH* mutations alone or in combination with other genetic mutations (in the case of AML) are associated with better prognosis.

2.4 IDH mutations in human gliomas

Glioma stem cells are small numbers of tumor cells that act as stem cells in glial cells. According to the “seed and soil” theory put forward by Paget, if the tumor microenvironment is soil, then glioma stem cells are seeds.

The *IDH* mutations enhance function in glial tumor cells, leading to the accumulation and secretion of large amounts of the oncometabolite, D-2HG, which ultimately inhibits the catalytic activity of α -KG-dependent dioxygenase, damaging the key steps in angiogenesis, hypoxic stress, and mature differentiation of cells. These processes are closely related to the occurrence and development of tumors. However, researches showed that D-2HG is a weak competitive inhibitor

of α -KG. Thus, it can only be observed to inhibit the differentiation of glioma stem cells when the accumulation of D-2HG is high. Therefore, the formation of gliomas requires not only seeds (glioma stem cells) but also soil (tumor microenvironment).

It was found that the *IDH* mutations could promote tumorigenesis microenvironment by increasing the expression of VEGF and making it suitable for glioma stem cell growth.

Interestingly, VEGF is initiated transcription by HIF-1 α , and hypoxia can cause an increase in VEGF. *IDH* mutants can modulate VEGF to promote tumor microchip formation by inhibiting HIF-1 α degradation. Moreover, quick growth of tumors will rapidly consume the surrounding energy and nutrients. Thus, HIF-1 α is a stably expressed surrounding tumor. *IDH* mutations make tumor microenvironments easier to form.

With the appropriate soil, glioma tumor stem cells grow rapidly and continue to invade the surrounding tissues, ultimately accelerating the growth of gliomas.

IDH mutations occur in about 80% of all grade II/III gliomas (low-grade gliomas - LGG) and secondary glioblastomas, which progress from the less malignant grade 2 diffuse astrocytomas or grade 3 anaplastic astrocytomas. In contrast, *IDH* mutations accounted for less than 5% of primary glioblastomas, which arise de novo [27, 28] and approximately 10% of pediatric glioblastomas [26, 29]. This suggests that LGG and secondary GBM are minimally overlapping disease subtypes.

In contrast to diffuse gliomas, *IDH* mutations are rare in many of WHO grade I gliomas, for example gangliogliomas, subependymal giant cell tumors, pilocytic astrocytomas, ependymomas and pleomorphic xanthoastrocytoma.

Aggregate data from multiple preclinical and clinical studies have shown that *IDH* mutations alone are not enough to turn malignant. *IDH* mutations occur early in gliomas formation and often have secondary genetic abnormalities such as mutations in *TP53*, chromosomal region 1p/19q co-deletion or loss of nuclear ATRX reactivity.

These changes relate to the histological classification of the disease. For example, diffuse astrocytomas, mutant *IDH*, often contain *TP53* mutations and lose ATRX. In contrast, almost histologically confirmed *IDH* mutant oligodendrogliomas have 1p/19q co-deletion. In particular, the majority of glioma patients with *IDH* mutation and 1p/19q co-deletion also had a mutation in the promoter regions of

Type of IDH	IDH1/2	IDH1/2	IDH1	IDH1/2	IDH1
Author	Yan et al [29]	Hartmann et al [26]	Ichimura et al [33]	Park et al [34]	Watanabe et al [35]
Pilocytic astrocytoma	0%		0%	0%	10%
Diffuse astrocytoma	90%	74%	59%	>80%	88%
Anaplastic astrocytoma	73%	65%	52%		78%
Secondary glioblastoma	85%		50%	>95%	82%
Primary glioblastoma	5%		3%		5%
Oligodendroglioma	84%	87%	68%	100%	79%
Anaplastic oligodendroglioma	94%	75%	60%		75%
Oligoastrocytoma	100%	83%	50%		94%
Anaplastic oligoastrocytoma	100%	72%	78%		71%

Table 1.
Frequency of IDH mutations in different types of gliomas.

	Author	Yan et al [29]	Hartmann et al [26]	Sanson et al [36]	Pusch et al [37]
Gene	Amino acid change				
IDH1	R132H	83.5%	89.4%	89%	91.5%
	R132C	4.1%	3.9%	3.2%	4.3%
	R132S	2.4%	1.5%	1.9%	1.6%
	R132G	0.6%	1.3%	4.5%	1.9%
	R132L	4.1%	0.3%	1.3%	0.6%
IDH2	R172K	2.4%	2.7%		
	R172M	1.8%	0.8%		
	R172W		0.7%		
	R172G	1.2%			

Table 2.
Frequency of specific IDH mutations in gliomas.

the telomerase reverse transcriptase (*TERT*). These mutations are thought to be mutually exclusive [30–32], thus aiding in distinguishing diffuse astrocytomas from oligodendrogliomas (**Tables 1** and **2**) [38].

3. Clinical indications involving the discovery of IDH-mutated glioma

3.1 Diagnosis

The latest WHO classification of CNS tumors using the integrated phenotypic and molecular parameters (including the *IDH* mutation) have re-established the CNS tumors classification. This classification includes glioblastoma, *IDH*-wildtype, *IDH*-mutant or NOS; diffuse astrocytoma, *IDH*-wildtype, *IDH*-mutant or NOS; anaplastic astrocytoma, *IDH*-wildtype, *IDH*-mutant or NOS; oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted or NOS; oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted or NOS; anaplastic oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted or NOS.

There are two features make *IDH* mutations easily detectable, reliable as bio-markers. First, nearly all tumors carry *IDH* mutations located at specific residues, such as Arg132 in *IDH1* or Arg140 and Arg172 in *IDH2*, which are located in a single exon 4 and can be simply identified through PCR-based amplification and sequencing. Second, antibodies specifically recognizing mutant IDH1R132H protein have been developed, thus it may be identified through conventional immunohistochemistry (IHC). Based on these hypotheses, to determine *IDH* mutations, currently, different methods are available to diagnose this status. They analyze either the nucleotide sequence of the gene (as the direct method) or the altered structure of the protein (as the indirect method).

Practical guidelines are available for detection of *IDH* mutations with molecular genetics techniques. In this regard, crucial aspects are the availability of tumor tissue, the tumor cell content and the quality of the respective genomic DNA (gDNA). Among them, conventional Sanger sequencing is a relatively inexpensive method and therefore is widely used in laboratories. As a consequence, it becomes the “gold standard” for the detection of *IDH* mutations. Beside, alternative methods to assess

the *IDH* mutation status exist. They include derived cleaved amplified polymorphic sequence (dCAPS), PCR-based restriction length polymorphism assays, cold PCR high resolution melting (HRM), post-PCR fluorescence melting curve analysis (FMCA) and SNaPshot assays. These are new methods and unapproved for clinical use in determining *IDH* status.

As the indirect method to confirm *IDH* status, immunohistochemistry of the *IDH1* mutant proteins is used. IHC using *IDH1* R132H mutation-specific antibody detects *IDH1* mutation. However, this method can miss about 10% of gliomas carrying an *IDH1* mutation and all gliomas with an *IDH2* mutation [39]. It is conceivable that, when the IHC is negative for *IDH1* R132H, the tumor can carry the *IDH1* mutation in another location or the *IDH2* mutation. In this case, subsequent genetic analysis is recommended.

All of the above methods have in common the need for tissue samples. Thus, surgery or biopsy of the tumor is necessary. This is a diagnostic difficulty. Therefore, recently, studies on non-invasive methods are being carried out, in which diagnosis by magnetic resonance spectroscopy (MRS) and amide proton transfer-weighted (APTw) have been shown to be promising [40–42]. In *IDH* mutant gliomas, D-2HG accumulates to sufficient levels as a brain metabolite, which renders its visibility on MRS. Therefore, this may provide crucial longitudinal data for the determination of disease progression and therapy response.

Identification of *IDH* status allows differential diagnosis between gliomas and non-neoplastic CNS lesions (astrocytoma or therapy-induced changes), between gliomas and non-glial CNS tumors, and within glioma subtypes. As discussed above, *IDH* status may be used to differentiate primary from secondary glioblastomas. In addition, *IDH* status associated with 1p/19q co-deletion became the key in the diagnosis of oligodendroglioma.

3.2 Prognostic

Generally, *IDH* mutations are associated with a better outcome than other types of mutations [43–45]. In 2008, Parsons et al. reported that mutations in *IDH1* occurred in most secondary GBM, and were related with better overall survival (OS) [46]. Similar trends were reported in variety studies using different datasets [29]. For example, in a prospective translational cohort study of the German Glioma Network, patients with anaplastic astrocytoma carry *IDH1* wild-type exhibited a worse overall survival rate than patients with glioblastomas with *IDH1* mutation [47]. *IDH*-mutated astrocytomas harboring ATRX mutation also were shown to form a subgroup of astrocytomas with a favorable prognosis [48].

Furthermore, in the SongTao study, *IDH* mutations were associated with prolonged PFS together with MGMT promoter methylation and 1p/19q codeletion and a higher rate of objective response to temozolomide in secondary glioblastomas [43]. Even in primary glioblastomas, *IDH1/2* mutations define a subgroup of tumors of long-term survival patients [49].

In 2009, using a large clinical dataset, Yan et al. reported that GBM patients with *IDH* mutations tended to prolonged median OS compared with patients carrying *IDH* wild-type GBM. Similar findings were also observed in patients with anaplastic astrocytoma.

The median OS was 65 months for gliomas patients with *IDH* mutant, compared with 20 months for those with *IDH* wild-type. Furthermore, the progression-free survival (PFS) was also improved among GBM patients with *IDH* mutations compared with other patients [29].

Extensive meta-analysis (2,190 cases) confirmed *IDH* mutation as a prognostic biomarker of gliomas [44]. Many other studies have shown that *IDH* mutations are an independent prognostic marker for improved PFS and OS in patients with grade III gliomas [47, 50–52].

Several studies have explained that the favorable prognosis of *IDH* mutant gliomas is due to their increased sensitivity to chemotherapy and radiotherapy [47, 53]. *IDH* mutant gliomas likely harbour defects in multiple DNA repair pathways, which render them vulnerable to radiotherapy- or chemotherapy-induced DNA damage [54, 55]. These findings indicate that *IDH* mutation could serve as an important predictive factor for treatment response among glioma patients.

3.2.1 Novel therapies

Glioma is the most frequent brain tumor and has a notably high mortality and disability rate. For its complex pathogenesis, the surgical and drug-assisted treatments do not seem to be effective. Therefore, it is of great significance to find new targets for diagnosis and treatment. The detection of *IDH* mutations in gliomas offers bases to research new therapies.

Some studies indicated that *IDH*-mutated gliomas maintain the *IDH*-mutated allele even after acquiring oncogenic driver mutations [56, 57]. This may show that *IDH*-mutated gliomas may remain vulnerable to the targeted therapies developed specifically for *IDH* mutations even at progression or after malignant transformation to higher grade glioma. The therapeutic effects may be further enhanced by combining different targeted therapies or with traditional chemotherapeutics or radiation.

3.2.2 *IDH*-mutated inhibitors

Since the neomorphic activity of *IDH* mutants is correlated with malignant transformation, direct targeting of the mutant enzymes becomes a heavily pursued strategy.

Over the past decade, several attempts have been made to find and develop small molecular compounds that directly inhibit the *IDH*-mutated enzymes. Some synthetic inhibitors reported as AGI-5198, ivosidenib (AG-120) and vorasidenib (AG-881), demonstrated effective and safe in treating *IDH*-mutated myeloid malignancies and solid tumors, including glioma [58–60]. BAY1436032, another *IDH*-mutant inhibitor, had shown tumor-suppressing effects as experimental therapeutics for the treatment of AML and astrocytoma in animal models [61, 62]. Recently, ivosidenib and vorasidenib have been approved by the Food and Drug Administration as a therapeutic option for *IDH*-mutated AML.

Despite the promising success of the *IDH*-mutated inhibitors, a number of studies have indicated the potential limitations of their application. As discussed above, *IDH*-mutated enzymes enhance sensitivity to chemotherapy and radiotherapy. So that, using these inhibitors reduces D-2HG production and relieves the burden on the multiple DNA repair pathways, resulting in chemoresistance. For example, AGI-5198 might increase their resistance to genotoxic therapies, such as radiation and chemo agents [63, 64].

Overall, targeting *IDH*-mutated activity is a straightforward strategy and has shown efficacy gliomas in humans. However, whether inhibition of mutant *IDH* and subsequent reduction in D-2HG production are sufficient to halt tumor growth in gliomas and other solid tumors remains unclear. In addition, whether these drugs will cross the blood brain barrier for admission to *IDH* mutant glioma cells is a question that requires further studies.

3.2.3 Targeting redox homeostasis

Redox homeostasis has been reported to be greatly affected by IDH mutations, notably elevated levels of oxidative stress. Targeting redox homeostasis may be effective in gliomas with IDH mutations. In fact, in IDH-mutated gliomas, the synthesis of NAD is largely compromised. As a result, tumor cells rely on a path of salvation to create NAD. Consequently, the IDH-mutated gliomas cells can be extremely sensitive to the blockade of the salvage pathway.

In addition, one study demonstrated that levels of glutamate, glutamine and glutathione decreased in tumor regions in patients with IDH-mutated glioma, compared with levels in contralateral regions. Furthermore, the glutathione level negatively correlates with the level of D-2HG, suggesting that glutathione is required for IDH-mutated cells to maintain redox homeostasis [65]. An animal preclinical study has shown that inhibiting glutamine metabolism using the glutaminase inhibitor CB-839 leads to impaired redox homeostasis and makes IDH-mutated glioma sensitivity to radiotherapy [66].

Since the disruption of redox homeostasis results in potent cytotoxicity accompanied by tumor suppression, current therapeutic compounds are mostly at the preclinical stage and show considerable systemic toxicity. Nevertheless, developing the next generation of therapeutic compounds with both potency and selectivity will be of great help for targeting redox imbalance in IDH-mutated malignancies.

3.2.4 Immunotherapies

With evidence that IDH mutation is an early event in tumorigenesis and is present homogeneously in all glioma tumor cells at specific codons. These mutations are ideal immunotherapy targets.

In fact, there are increasing evidences that the IDH mutation might play critical roles in altering the immunological microenvironment of the tumor, as shown by an inhibition of tumor-infiltrating lymphocytes, cytotoxic T cells and natural killer cells [67, 68]. Additionally, the presence of IDH mutation correlates with a decrease in the expression of PD-L1 (Programmed Death-Ligand 1). Decreased expression of PD-L1 in IDH-mutated gliomas implies a stronger T cell activation, because PD-L1 is a cellular surface protein that modulates the immune system and promotes self-tolerance through inhibition T cell activity [69].

The combination with the IDH-mutated inhibitors shows an improvement in the efficacy of PD-1-resistant derived immunotherapy, which induces intracellular CD4 + T-cell proliferation. The result is a reduction in tumor size and a prolonged survival. Further studies are currently under investigation, promising to bring positive results.

3.2.5 Vaccines

Vaccination is the most effective measure of disease prevention and control. In many low-grade glioma patients, the spontaneous immune response to IDH1 mutation has been found [70]. The use of the self-immune response to tumor treatment has also been a heavily researched subject in recent years and provides evidences that is worth the wait. For example, in animal experiments, it was found that the vaccine not only was able to prevent from IDH1 mutant cells growing in the brain, but also did not destroy the normal physiological function of the IDH1 enzyme [70].

Specifically, a phase 1 clinical trial is ongoing to confirm the safety and therapeutic efficacy of the IDH1 R132H mutant peptide vaccine (NOA-16)

in newly diagnosed grade III and IV gliomas with IDH1 mutation. The first reported results demonstrated the safety and immunogenicity of NOA-16, with 80% of patients having mutation-specific T cell immune responses, and 87% of the patients displaying humoral immune responses; no deaths have been reported [71].

It is difficult to completely remove gliomas by surgery and drugs, so they often recur. Moreover, the recurrent gliomas after clearance generally tend to be more resistant and invasive. Vaccines can play a maintenance role in these cases. So finding a suitable vaccine will greatly benefit patients and help them escape the magic spell of glioma recurrence.

3.2.6 Other therapies

In addition to the treatments outlined above, there are other methods based on vulnerability of IDH-mutant cells to NAD⁺ depletion, hypoxia-inducible factor-1 α (HIF-1 α) pathway of IDH mutation or mammalian target of rapamycin (mTOR) signaling pathway. These are all new methods, are preclinical models and promise to bring about a change in treatment for gliomas with IDH mutations.

It is generally known that trials of IDH mutant inhibitors, vaccines, immunotherapies and so on in IDH mutant gliomas and recurrent gliomas have been conducted. Meanwhile, old drugs for other tumors have also been developed to treat gliomas with IDH mutations, such as azacitidine, nivolumab, and temozolomide.

In summary, targeting the distinctive vulnerabilities of IDH-mutated glioma has been shown to be successful, as cancer cells are less likely to compensate for the loss of essential biological pathways. However, development of further studies is needed for more convincing evidence to apply these novel therapies to treatment.

4. Conclusion

The discovery of the IDH mutation not only adds to the landscape of glioma genetics but also supports diagnosis and prognosis. For IDH-mutated gliomas, numerous attempts have been made to define selective and effective therapeutics that target the biological signatures, with the aim of improving standard treatments.

From the above mentioned biological bases, IDH mutation is an important target for the prevention and treatment of gliomas. However, due to the short and uncertain clinical trial duration, most clinical trials of vaccines, IDH inhibitors or other methods are still underway. Much research still needs to be completed. However, we believe that the great potential of these new treatments offers hope in patients with gliomas.

Finally, a major obstacle in IDH-mutated glioma is that the critical oncogenic drivers of this disease remain controversial. One of the main questions remains the molecular pathogenesis of WHO grade II and III gliomas without IDH mutations, which often do not show changes in genes typically associated with gliomas. In-depth investigation of critical molecular pathways will be of great importance to develop highly potent and selectivity treatment.

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