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REVIEW

Advances in the Immunotherapeutic Potential of Isocitrate Dehydrogenase Mutations in Glioma

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Abstract Isocitrate dehydrogenase (IDH) is an essential metabolic enzyme in the tricarboxylic acid cycle (TAC). The high mutation frequency of the *IDH* gene plays a complicated role in gliomas. In addition to affecting gliomas directly, mutations in *IDH* can also alter their immune microenvironment and can change immune-cell function in direct and indirect ways. *IDH* mutations mediate immune-cell infiltration and function by modulating immune-checkpoint gene expression and chemokine secretion. In addition, *IDH* mutation-derived D2-hydroxyglutarate can be absorbed by surrounding immune cells, also affecting their functioning. In this review, we summarize current knowledge about the effects of *IDH* mutations as well as other gene mutations on the immune microenvironment of gliomas. We also describe recent preclinical and clinical data related to IDH-mutant inhibitors for the treatment of gliomas. Finally, we discuss different types of immunotherapy and the immunotherapeutic potential of IDH mutations in gliomas.

Keywords *IDH* mutation · Tumor immune microenvironment · Immunotherapy · Glioma

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Introduction

Gliomas are the most common and most lethal primary tumors of the central nervous system (CNS) [1]. The 2007 World Health Organization (WHO) classification system for CNS tumors categorizes gliomas from grade I to grade IV (glioblastomas, GBMs). Typically, patients with grade II or III gliomas (also known as lower-grade gliomas, or LGGs) survive from 2 to 3 years to more than 5 years, while those with GBMs generally survive no more than 1 year [2]. According to the data from the cancer genome atlas (TCGA)-LGG and TCGA-GBM cohorts, there are high frequencies of genetic alteration in gliomas [3]. Among these genes, mutation frequencies of gene isocitrate dehydrogenase (*IDH*), tumor protein P53 (*TP53*), phosphatase and tensin homolog (*PTEN*), ATRX chromatin remodeler (*ATRX*), titin (*TTN*), epidermal growth factor receptor (*EGFR*), and capicua transcriptional repressor (*CIC*) are each $> 20\%$ in LGGs or GBMs (Table 1). These mutations generate glioma heterogeneity and regulate the development, evolution, immune evasion, and therapeutic response of gliomas [4–9]. A better understanding of gene mutations in gliomas is crucial for tumor classification and therapy.

In 2016, the WHO classification system for CNS tumors incorporated molecular parameters into the definitions of tumor entities, with gliomas classified as *IDH*-mutant or wild-type [10]. Most LGGs and almost all secondary GBMs exhibit *IDH* mutations [11]. Due to the high frequency of *IDH* mutations and because they exhibit different biological characteristics, the new 2021 WHO classification of CNS tumors divides adult diffuse gliomas into *IDH*-mutant; *IDH*-mutant and 1p/19q-codeleted; and *IDH*-wild type [12]. In this classification, all *IDH*-mutant diffuse astrocytic tumors are considered a single type

Table 1 Top-30 Mutated Genes in LGGs and GBMs

LGGs		GBMs	
Gene names	Mutation frequency (%)	Gene names	Mutation frequency (%)
IDH1	76.80	PTEN	33.50
TP53	48.40	TP53	31.50
ATRX	37.70	TTN	25.70
CIC	21.00	EGFR	23.70
TTN	12.30	MUC16	15.40
FUBP1	9.30	FLG	13.60
PIK3CA	8.20	NF1	11.60
NOTCH1	7.40	RYR2	10.80
MUC16	7.00	PIK3R1	9.80
EGFR	6.80	PIK3CA	9.60
NF1	6.00	SPTA1	9.60
SMARCA4	4.90	RB1	9.60
PTEN	4.70	ATRX	9.30
FLG	4.50	SYNE1	8.60
PIK3R1	4.30	OBSCN	7.60
RYR2	4.10	MUC17	7.30
IDH2	4.10	LRP2	7.30
OBSCN	3.90	PCLO	7.10
ZBTB20	3.90	HMCN1	6.80
ARID1A	3.70	PKHD1	6.80
NIPBL	3.50	COL6A3	6.50
PCLO	3.50	AHNAK2	6.30
HMCN1	3.30	IDH1	6.30
MUC17	3.10	DNAH5	6.00
APOB	2.90	DNAH2	6.00
BCOR	2.90	USH2A	5.50
LRP2	2.90	FLG2	5.50
ADGRV1	2.70	FAT2	5.50
TCF12	2.70	LAMA1	5.30
ZNF292	2.50	CFAP47	5.30

(astrocytoma) and are then graded as CNS WHO grade 2, 3, or 4. *IDH*-mutant and 1p/19q-co-deleted gliomas are regarded as oligodendroglioma (grade 2, 3). GBMs or *IDH*-wildtype LGGs in the presence of microvascular proliferation or necrosis or TERT promoter mutation or EGFR gene amplification or +7/−10 chromosome copy number changes are also diagnosed as *IDH*-wild type (GBMs, grade 4) [12]. Although glioma patients harboring *IDH* mutations have longer survival times than those without *IDH* mutations, these mutations are also believed to be an early event during the progression of LGGs to higher-grade gliomas [13, 14]. Hence, it is vital to explore the role of *IDH* mutations in the development and progression of glioma.

IDHs, including IDH1, IDH2, and IDH3, are essential metabolic enzymes in the tricarboxylic acid cycle (TAC), which converts isocitrate into α-ketoglutarate (α-KG), NAPDH, and CO_2 [15]. IDH1 is localized to the cytoplasm and peroxisomes, while IDH2 and IDH3 are localized to the mitochondria [16]. Among these three IDHs, mutations in *IDH1* and *IDH2* have been found in gliomas, *IDH1* being the most frequently mutated metabolic gene [17]. *IDH* mutations involve the replacement of a single amino-acid in IDH1 (arginine 132 residue, R132) and IDH2 (analogous residue arginine 172, R172; or arginine 140, R140) [18]. These are gain-of-function mutations, mediating the transformation of α-KG into D2-hydroxyglutarate (D2-HG) [19]. D2-HG is a homolog of α-KG, and functions as a competitive inhibitor of α-KG-dependent dioxygenases [5, 20].

It is known that D2-HG regulates gene expression *via* three mechanisms: transcriptional, post-transcriptional (including translation), and post-translational modifications (Fig. 1). First, D2-HG can inhibit the activity of the ten-

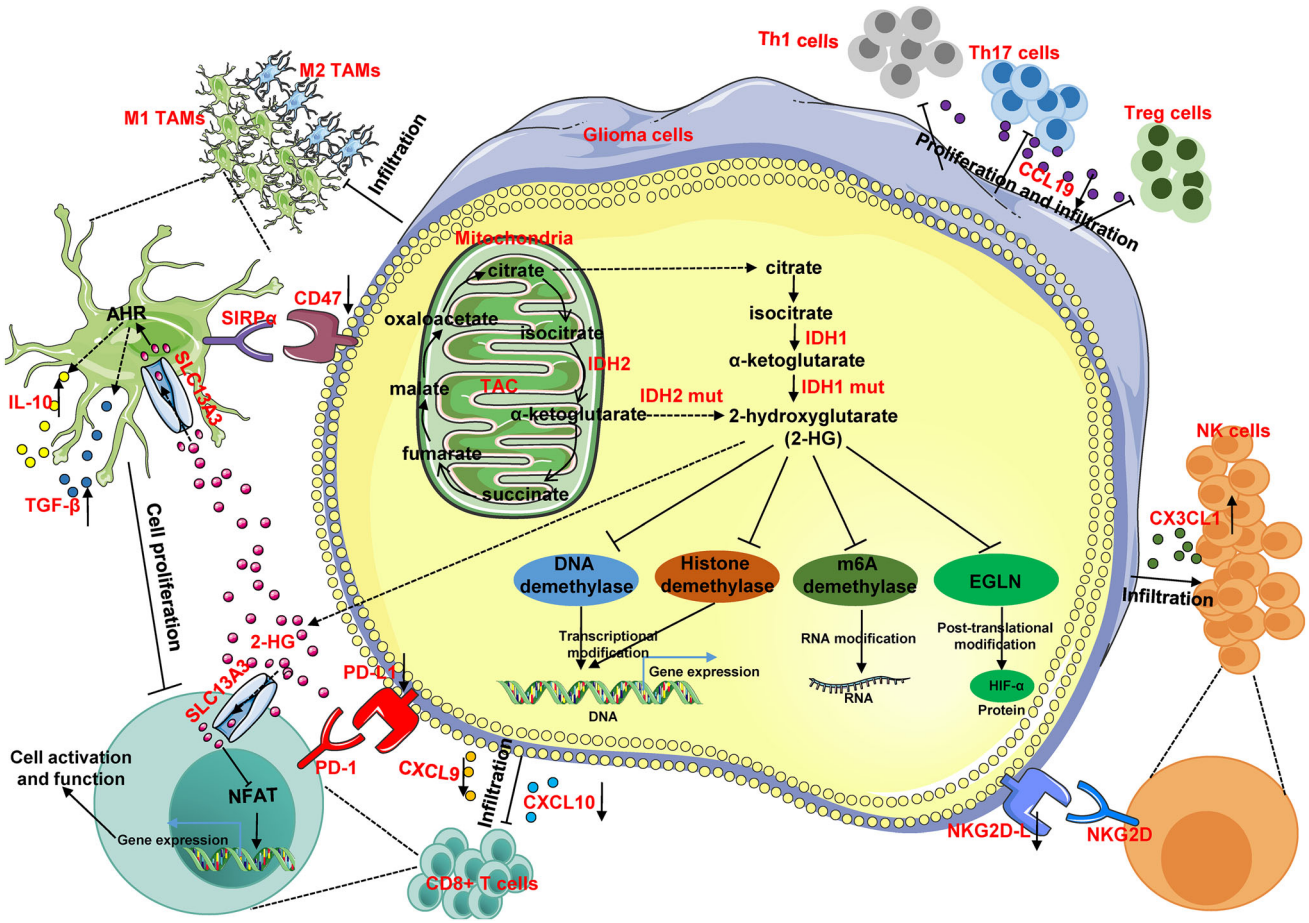


Fig. 1 A model for the influence of *IDH* mutations on glioma cells and their surrounding immune microenvironment. In glioma cells, *IDH* mutations regulate gene expression *via* three mechanisms: transcriptional (*via* inhibition of DNA and histone demethylases), post-transcriptional (*via* inhibition of m6A demethylases), and post-translational (*via* inhibition of EGLN) modifications. In addition, *IDH* mutations affect the immune microenvironment of gliomas, modifying immune cell infiltration and functioning in direct (*via* regulating immune-related gene expression) and indirect ways (*via* IDH mutation-derived D2-HG).

eleven translocation (TET) family of methylcytosine hydroxylases, which mediates DNA demethylation by transforming 5-methylcytosine to 5-hydroxymethylcytosine [5]. Inhibition of the TET family of methylcytosine hydroxylases remodels the methylome to establish a CpG-island hypermethylated phenotype, which results in a reorganization of the methylome and transcriptome [21, 22]. Similarly, D2-HG can impair the activity of histone demethylases, thereby inhibiting histone demethylation, which, in turn, modulates gene transcription [5, 23]. Abnormalities in DNA and histone methylation regulate gene expression in a transcriptional manner. Messenger RNA N6-methyladenosine (m6A) methylation is the most common RNA modification [24]. N6-methyladenosine methylation is generally mediated by "writers" (methyltransferases, such as METTL3), "readers" (binding proteins, such as IGF2BP3), and "erasers" [demethylases, such as fat mass and obesity-associated protein (FTO)] [25]. D2-HG has been shown to increase the methylation levels of m6A by inhibiting the activity of demethylases like FTO, which eventually regulates gene expression in a post-transcriptional manner [26–28]. Our previous study found that mutations in *IDH1* significantly upregulates the protein level of the transcription factor, hypoxia-inducible factor 1-alpha (HIF-1α) [29]. A subsequent study showed that D2-HG maintains HIF-1α protein stability by inhibiting its ubiquitination, which is mediated by the α-KG-dependent dioxygenase, EGLN, indicating that D2-HG can also regulate gene expression in a post-translational manner [30].

In the immune microenvironment of gliomas, myeloid cells, including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells, neutrophils, and dendritic cells, represent the largest immune subset [31]. Infiltration by these myeloid cells favors glioma progression and induces resistance to glioma treatment [32]. Although immunotherapies targeting inhibitory checkpoint molecules have been revolutionary for the treatment of

solid tumors, the high infiltration of monocytes and low infiltration of lymphocytes induced by glioblastoma (GBM) cells establishes an immunosuppressive microenvironment that is responsible for resistance to immunotherapy [32–35]. Recent glioma studies have indicated that mutations in *IDH* also affect immune-cell infiltration, which, in turn, mediates the distinctive immune responses of *IDH*-mutant *versus* wild-type gliomas. Here, we summarize advances in our knowledge of the immune microenvironment and immunotherapy for *IDH*-mutant gliomas.

Alterations in Immune Cell Infiltration in *IDH*-mutant Gliomas

Tumor-associated Macrophages

TAMs are the most common immune cells in the CNS, accounting for 30%–50% of all immune cells [36]. Originally, TAMs were subdivided into microglia (resident macrophages of the CNS) and peripheral blood-derived macrophages [37]. However, it was difficult to distinguish between these two subpopulations because of a lack of unique markers. In 2016, TMEM119 and CD49D/ITGA4 were identified as specific markers for microglia and peripheral blood-derived macrophages, respectively [38, 39]. TAMs play a critical role in both innate and adaptive immunity and have both pro- and anti-glioma functions. Traditionally, TAMs are divided into pro-inflammatory M1 signature and anti-inflammatory M2 signature. M1 signature TAMs are activated by IFN-γ, TNF-α, and TLR and contribute to inflammation [40]. In contrast, M2 signature TAMs occur after exposure to IL-4, IL-10, and IL-13 and promote an anti-inflammatory response, tissue repair, and tumor progression [36, 41]. Recently, results of single-cell RNA-sequencing of the TAMs have shown that both M1 and M2 signature genes are frequently co-expressed in individual cells [42]. Despite the fact that M2 signature TAMs secret TGF-β and IL-10 to promote glioma tumorigenesis and establish an immunosuppressive microenvironment, IL-1β and IL-6 derived from M1 signature TAMs have also been found to facilitate glioma cell growth and invasion [43–48]. In addition, high levels of TAM infiltration are indeed associated with an aggressive tumor subtype and predict a poor prognosis in glioma patients [49]. Hence, targeting TAMs may be a promising approach to the treatment of gliomas.

Mutant *IDH1* has been shown to suppress immune-response-related pathways in an unbiased RNA-sequencing study, indicating that *IDH1*-mutant and wild-type gliomas exhibit different patterns of immune-cell infiltration and responses to immunotherapy [50, 51]. In both *IDH1*-mutant human and mouse glioma tissues, it has been reported that the infiltration of TAMs is lower than in *IDH1*-wild-type gliomas [52]. Another study found that, although the total number of TAMs is lower in *IDH1*-mutant GBM samples, the remaining TAMs are more pro-inflammatory [53]. In contrast, longitudinal single-cell profiling and mass cytometry studies have reported that TAMs from patients with *IDH*-mutant gliomas exhibit a more immunosuppressive phenotype than *IDH*-wild-type samples [54]. Apart from that, the microenvironment is also significantly different between IDH-mutant-1p/19q-co-deleted and IDH-mutant gliomas, and in particular in the abundance of TAMs. Gliomas harboring IDH-mutant-1p/19q-co-deleted present lower TAM infiltration with respect to the IDH-mutant [55–57].

Mutation in IDH1 not only alters the ratio of M1 and M2 signatures in TAMs, but also promotes TAM migration *in vitro* and *in vivo*. When glioma cells are co-cultured with human primary TAMs for 24 h, *in vitro* assays have showed that the IDH1 mutation increases the expression of M1 signature markers (CD40, CD80, TNF-α, and IL-12) and downregulates the expression of M2 signature markers (CD206, CD163, and IL10) in TAMs. Moreover, a conditioned medium derived from IDH1-mutant glioma cells significantly promotes TAM migration compared with that from IDH1-wild-type glioma cells. In orthotopic xenografts, isogenic human U87 *IDH1*-wild-type and -mutant glioma cells have been transplanted into BALB/c immunodeficient (SCID) mice and retain innate immune functions. Similar to the *in vitro* results, the *IDH1*-mutant glioma cells have increased TAM recruitment, which promotes the anti-tumor functions of TAMs *in vivo* [50]. Further results have suggested that *IDH1* mutations increase TAM recruitment and the expression of phagocytosis markers through the inhibition of ICAM-1 expression by mediating hypermethylation in its promoter [50].

The oncometabolite D2-HG also plays an important role in mutant *IDH1*-mediated TAM activation. In human primary TAMs, D2-HG selectively increases the expression of IL-12, but not other markers, and also activates M1-type TAMs [50]. In murine BV2 microglial cells, co-culturing with conditioned media from *IDH*-wild-type GL261 glioma cells increases the expression of pro-inflammatory genes (IL-6, IL-1β, TNF-α, CCL2, and CXCL10) as well as anti-inflammatory markers, indicating activation of BV2 cells. D2-HG treatment abolishes this conditioned media-mediated pro-inflammatory response in activated BV-2 microglial cells by suppressing the AMPK/mTOR/NF-κB signaling pathway [58]. However, this study did not assess the effects of D2-HG on the anti-inflammatory response. Further studies have shown that D2-HG is taken up by TAMs through solute carrier 13A3

(SLC13A3). When taken up by TAMs, D2-HG acts as an allosteric activator of tryptophan-2,3-dioxygenase 2, which promotes the conversion of L-tryptophan into L-kynurenine (L-Kyn), a ligand of the aryl hydrocarbon receptor (AHR). Increased AHR activity then induces secretion of the immunosuppressive factors IL-10 and TGF-β in TAMs. Interestingly, co-culture of D2-HG-pretreated macrophages with T cells has been shown to promote L-Kyn accumulation and AHR activity in TAMs, resulting in a dose-dependent suppression of T-cell proliferation [54, 59].

CD8+ Cytotoxic T Lymphocytes

CD8+ T cells are one of the most vital immune cells in the adaptive immune response. CD8+ T cells can be classified into three types according to their state of differentiation: naïve, effector, and memory T cells [60]. Naïve CD8+ T cells have not yet received an antigen presentation signal, whereas effector and memory CD8+ T cells have been activated by antigens. During antigen presentation, CD8+ T cells carrying an antigen-specific T-cell receptor (TCR) specifically recognize tumor antigenic peptides on the cell surface, a process that is mediated by MHC class I molecules [61, 62]. Once activated, CD8+ T cells mainly function by secreting pro-inflammatory cytokines, binding to the Fas receptor on target cells *via* the Fas ligand, and releasing granzymes, thus causing the lysis of target cells [63]. CD8+ T cells obtained from glioma tissue have been shown to be phenotypically CD8+ CD25−, indicating a lack of T-cell activation. In addition, GBM patients with high CD8+ T-cell infiltration at the time of diagnosis are more likely to have a better overall survival than patients with focal CD8+ T-cell infiltration [64]. Therefore, triggering T-cell activation is a promising strategy for glioma treatment.

Decreased CD8+ T-cell numbers have been identified using immunofluorescence assays in *IDH*-mutant, lower-grade gliomas than in *IDH*-wild-type gliomas. Sequence data from the TCGA database has demonstrated that LGG tissue harboring *IDH* mutations has fewer infiltrated CD8+ T cells and lower IFN-γ–induced chemokine gene expression than *IDH*-wild-type tissue [6, 65]. In a murine glioma model, *IDH*-mutant gliomas also show lower infiltration of CD8+ cytotoxic T cells than *IDH*-wild-type gliomas [66]. An *in vitro* study found that co-culture with conditioned medium from IDH^{R132H} gliomas reduces the migration of CD8+ T cells by inhibiting chemokine secretion mediated by signal transducer and activator of transcription 1 (STAT1) signaling [65].

There are two enantiomers of the metabolite 2-HG, named D2-HG and L2-HG. Unlike D2-HG driven by IDH1/2 mutations, L2-HG accumulation occurs in the context of hypoxia and mitochondrial dysfunction [67, 68]. Several studies have found that the two enantiomers play crucial roles in mediating the infiltration and function of CD8+ T cells. The D2-HG produced by *IDH*-mutant glioma cells can also be taken up by CD8+ T cells. The imported D2-HG impairs only the activation of these T cells but has no effects on T-cell apoptosis or proliferation [6]. When taken up by T cells, D2-HG interferes with Ca^{2+}-dependent transcriptional activity of nuclear factor of activated T cells and inhibits ATP-dependent TCR signaling and polyamine biosynthesis in T cells, which results in a suppression of T-cell antitumor immunity. Similar results have also been reported in tumor models. L2-HG can be produced by CD8+ T cells in response to TCR triggering and environmental hypoxia. Adoptively transferred CD8+ T cells treated with L2-HG exhibit an increased capacity to proliferate *in vitro* and persistence *in vivo*, indicating enhanced anti-tumor efficacy [69]. In gliomas, D2-HG maintains HIF-1α protein stability by inhibiting EGLN [30]. In CD8+ T cells, HIF-1α activation increases their production of L2-HG. Autocrine L2-HG alters CD8+ T-cell differentiation by mediating hypermethylation [69].

Tumor-infiltrating CD4+ T Cells

CD4+ T cells represent a diverse cell population expressing CD4 cell surface markers that are associated with both innate and adaptive immune responses to pathogens and tumors [70]. CD4+ T cells are classified into Th1, Th2, Treg, Th17, and natural killer (NK) T cells based on their functions and cytokine secretion patterns [71]. Similar to TAMs, CD4+ T cells play both anti-tumor and pro-tumor roles depending on the cell subtype [72]. For example, CD4+ Th cells directly recognize antigens on MHC-II-expressing tumor cells and produce lymphokines that impair tumor growth and induce cell death. However, CD4+ Tregs function without this antigenic stimulation and mediate immune suppression by directly producing inhibitory cytokines or by influencing the state and function of dendritic cells (DCs) and other immune-cell subtypes [71]. During glioma progression and growth, CD4+ Tregs have been found to accumulate in both murine and human tumor tissues and to act as potent suppressors of anti-glioma immunity [73]. Targeting CD4+ T cells in combination with DC vaccination can lead to long-term immunity against experimental gliomas [74].

In both human and mouse glioma tissues, fewer CD4+ T cells, including Tregs, are found in *IDH*-mutant samples than in *IDH*-wild-type samples [52, 66, 75]. A study reported that the migration, proliferation, differentiation, and cytokine secretion of Th1, Th17, and Treg cells are significantly inhibited by D2-HG [75]. In that study, CD4+ T cells from *IDH*-wild-type glioma mice were isolated, activated by monoclonal CD3 and CD28 antibodies, and then treated with or without D2-HG. It was found that the

proliferation of polarized Th1s, Th17s, and Tregs was significantly inhibited in cells treated with D2-HG. D2-HG promoted the differentiation of these cells at a concentration of 30 mmol/L. In addition, D2-HG suppressed T-cell migration by downregulating CCL19 secretion [75]. Interestingly, the IDH1-mutant protein contains an immunogenic peptide, which has been shown to be suitable for mutation-specific vaccination. MHC-II molecules are responsible for presenting this specific immunogenic epitope to Th1 cells and inducing the Th1 cell response [76]. Since *IDH* mutations occur in the majority of LGGs and secondary GBMs, a mutation-specific anti-IDH vaccine may be a promising immunotherapeutic strategy for *IDH*-mutant gliomas.

Natural Killer Cells

NK cells are effective cytotoxic lymphocytes that fight various virus-infected and cancer cells [77]. NK cells are divided into five groups based on their migratory behavior and cytotoxic responses: i. NK cells that kill all target cells; ii. NK cells that do not kill target cells, iii. NK cells that interact with target cells; iv. NK cells that randomly kill target cells based on the net balance of stimuli detected by activating and inhibitory receptors, and v. exhausted NK cells [78]. The functioning of NK cells is modulated by an array of activating (NKp30, NKp44, NKp46, NKp80, NKG2D, CD2, and DNAM-1) and inhibitory (KIRs and NKG2A) receptors. Among these receptors, inhibitory receptors specifically bind to MHC-I molecules to inhibit NK cell cytotoxicity [79].

Unlike TAMs and T cells, a higher infiltration of NK cells has been reported in *IDH*-mutant gliomas, in which, D2-HG upregulates CX3CL1 expression, with a high expression level of this chemokine inducing NK-cell recruitment by targeting the CX3CL1 receptor. In addition, the higher infiltration of NK cells in *IDH1*-mutant gliomas is associated with a better prognosis [80]. Interestingly, *IDH*-mutant glioma cells and astrocytes are resistant to NK-cell-mediated cytolysis. Furthermore, *IDH*-mutant glioma cells escape NK-cell immune surveillance by downregulating NKG2D ligand expression. The inhibition of DNA methyltransferases increases NKG2D ligand expression in *IDH*-mutant glioma cells and restores the NK-mediated lysis of *IDH*-mutant glioma cells in an NKG2D-dependent manner [81]. Hence, targeting DNA methylation may represent a novel strategy to sensitize *IDH*-mutant gliomas to NK-cell-mediated immune lysis. Demethylation and epigenetic modifications *via* DNA methyltransferase has been shown to suppress *IDH1*-mutant glioma growth in combination with temozolomide in a mouse model [82].

Immune Checkpoint Alterations in IDH Mutant Gliomas

PD-1/PD-L1

Programmed cell death 1 (PD-1) is a receptor expressed in activated T cells. This immune inhibitory receptor is involved in regulating T-cell function and differentiation [83, 84]. Similarly, programmed cell death 1 ligand 1(PD-L1) is an immune receptor expressed in both hematopoietic and non-hematopoietic cells, including various tumors [85]. When PD-L1 interacts with its receptor, PD-1, T-cell activation is abolished [86, 87]. In tumors, this interaction provides a means for tumor cell immune escape *via* cytotoxic T-cell inactivation [88, 89]. Hence, targeting the PD-1/PD-L1 pathway is another potential treatment strategy for gliomas [90].

Anti-PD-1/PD-L1 immunotherapy has been a breakthrough that has prolonged survival times for patients with a variety of cancers [91]. However, patients with GBMs have had limited efficacy with anti-PD-1 therapy, except for in isolated case reports [92]. The low efficacy of immunotherapy for gliomas is likely due to multiple reasons, including the unique immune environment of the brain [91]. However, patients with recurrent GBMs have been shown to benefit from neoadjuvant anti-PD-1 immunotherapy, with intratumoral and systemic immune responses [92]. In *IDH*-mutant gliomas, the expression levels of PD-L1 and PD-1 are lower than in *IDH*-wild-type gliomas due to promoter methylation [93–96]. Whether this low PD-L1/PD-1 expression can alter the immune response to immunotherapy remains to be elucidated. Three clinical-phase studies (NCT03557359, NCT03718767, and NCT03925246) related to nivolumab (anti-PD-1) treatment for *IDH*-mutant, recurrent, or progressive gliomas and *IDH*-mutant gliomas with or without hypermutator phenotypes are ongoing.

CD47

Cluster of differentiation 47 (CD47), also known as integrin-associated protein, is a ubiquitously-expressed receptor belonging to the immunoglobulin (*Ig*) superfamily. CD47 possesses a single extracellular V-set IgSF domain, a five transmembrane domain, and a short cytoplasmic domain [97, 98]. Through interactions with its ligand, signal regulatory protein alpha (SIRPα), CD47 alters the phagocytosis of TAMs *via* the “don’t eat me” signal. In addition, CD47 regulates the activation of T cells, B cells, and dendritic cells by binding with other ligands, such as thrombospondin-1 and integrins [98–100]. In gliomas, CD47 is abnormally upregulated in tumor

tissue and cell lines [101]. Disrupting the CD47/SIRPα axis has been shown to induce tumor phagocytosis and to elicit a potent anti-glioblastoma effect [102, 103]. Moreover, treatment with anti-CD47 antibody also has antitumor effects in gliomas and glioma stem cells, indicating that CD47 may be a target for tumor therapy [104].

Compared with *IDH1*-wild-type glioma cells, CD47 expression is decreased in *IDH*-mutant cell lines. In *IDH1*-wild-type glioma cells, the PKM2/β-catenin/BRG1/TCF4 co-factors bind to the CD47 promoter and modulate CD47 transcription. However, when *IDH1* is mutated, recruitment of PKM2 and β-catenin to the TCF4 site is diminished, resulting in low CD47 expression. In addition, microglia co-cultured with *IDH1*-mutant glioma cells exhibit increased phagocytosis [105]. These findings reveal that mutations in *IDH1* not only affect the microglial signature and infiltration but also alter microglial phagocytosis.

CTLA-4

Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is a member of the Ig superfamily and transmits an inhibitory signal to T cells [106]. In an orthotopic glioma model, CTLA-4 blockade has been shown to eradicate glioma cells by reshaping oligoclonal T-cell infiltration [107]. Furthermore, systemic CTLA-4 blockade ameliorates glioma-induced changes in the CD4+ T-cell compartment without affecting regulatory T-cell function [108]. In gliomas, lower CTLA-4 expression and higher methylation of the CTLA-4 promoter have been found in patients with *IDH* mutations [94, 109]. Whether lower expression of CTLA-4 affects the efficacy of anti-CTLA-4 immunotherapy in *IDH*-mutant gliomas requires further exploration.

Alterations in Immune Cell Infiltration and Immune Checkpoint in Other Gene-mutant Gliomas

TP53 Mutant Gliomas

The protein TP53 is known as a tumor suppressor and acts as a transcriptional regulator to regulate the tumor cell cycle, apoptosis, and autophagy [110, 111]. Somatic alterations in the *TP53* gene in gliomas are of two types: loss-of-function (common) and gain-of-function (rare) [112, 113]. In *TP53*-mutant GBM pathologic specimens, immune checkpoint CTLA4 presents higher levels than in *TP53*-wild-type GBMs, indicating a correlation between *TP53* mutation and immunologic markers [114]. Further research found that loss of *TP53* by mutation might cooperate with the induction of SPARC to promote tumor cell escape from immune surveillance through modulating TAM recruitment and activation [115]. In contrast, gain-of-function mutation of *TP53* is positively correlated with the tumor-associated myeloid signature *via* upregulating cytokines ccl2 and TNFα to promote TAM and other myeloid-derived immune cell infiltration [112].

PTEN Mutant Gliomas

PTEN protein acts as a tumor suppressor in gliomas, and suppressed expression of PTEN is prevalently found in PTEN-mutant gliomas [116]. Mutation in *PTEN* not only increases expression of the PD-L1 protein in gliomas, but also induces T-cell apoptosis [117, 118]. Subsequent results of a PD-1 immune checkpoint clinical trial have demonstrated that *PTEN* mutation promotes resistance to GBM immunotherapy *via* altering the immunosuppressive environment in GBM patients [119].

EGFR Mutant Gliomas

EGFR is a prominent driver in a variety of tumors as well as GBMs, and it has been reported that amplification and over-expression of *EGFR* is $> 50\%$ in GBMs [120]. Activated EGFR induced by EGF stimulates cell proliferation and migration, and inhibits apoptosis *via* various key signaling pathways such as the JAK/STAT3 and PI3K/AKT pathways [121]. Among *EGFR* amplifications, *EGFRvIII* (deletion of exons 2–7) mutation is the most prevalent and accounts for $\sim 66\%$ [122, 123]. Mutations in *EGFR* can remodel vessel walls and govern the recruitment of leukocytes, myeloid cells, and lymphocytes [124]. In addition, mutant EGFR protein also has immunogenic activity, and vaccines targeting EGFRvIII indeed induce potent T- and B-cell immunity in GBMs to eliminate tumor cells [121, 125].

Ongoing Clinical Trials of IDH Mutant Inhibitors

Considering the crucial role of *IDH* mutations in both glioma cells and the tumor microenvironment, targeting mutant IDH protein is also a promising strategy for glioma therapy. In this section, we summarize the IDH-mutant inhibitors that are being tested in ongoing clinical trials of patients with gliomas. Other IDH-mutant inhibitors are listed in Table 2 [126–131].

IDH-305

IDH-305 is an oral, selective, brain-penetrating IDH1 inhibitor. The IC_{50} values of IDH-305 for $IDH1^{R132H}$, $IDH1^{R132C}$, and *IDH1*-wild-type gliomas are 27, 28, and

Table 2 Mutant IDH Inhibitors

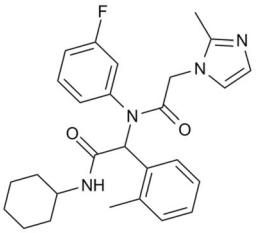
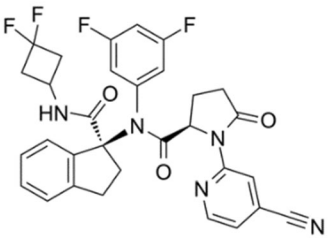
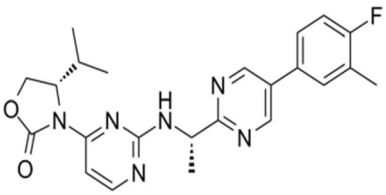
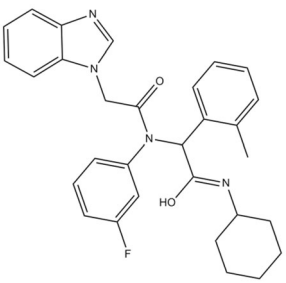
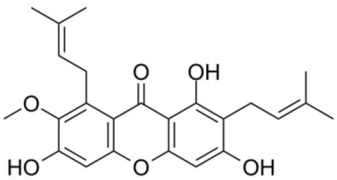
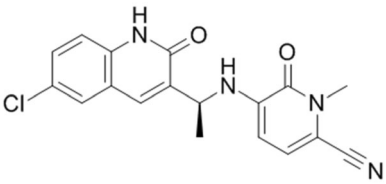
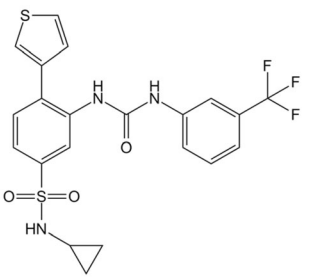
Drug names	Structure	Introductions
AGI-5198		AGI-5198 (IDH-C35) is the first highly effective and selective mutant IDH1 inhibitor, with an IC_{50} = 0.07 and 0.16 μmol/L for $IDH1^{R132H}$ and $IDH1^{R132C}$, respectively.
IDH1 Inhibitor 3		IDH1 Inhibitor 3 is a mutant IDH1 inhibitor, with an IC_{50} of 45 nmol/L for $IDH1^{R132H}$.
IDH-889		IDH-305 is an oral and brain-penetrating inhibitor of mutant IDH1, with an IC_{50} = 0.02, 0.072, and 1.38 mol/L for recombinant $IDH1^{R132H}$, $IDH1^{R132C}$, and wild-type IDH1, respectively.
Mutant IDH1-IN-1		Mutant IDH1-IN-1 is a selective inhibitor of mutant $IDH1^{R132H}$, with IC_{50} = 81.5 nmol/L.
α-Mangostin		α-Mangostin is an inhibitor of mutant $IDH1^{R132H}$ with a Ki of 2.85 μmol/L; IC_{50} = 2.85 μmol/L.
FT-2102		FT-2102 is a mutant IDH1 inhibitor, with an IC_{50} = 9 and 39 nmol/L for $IDH1^{R132H}$ and $IDH1^{R132C}$, respectively, in U87 glioma cells.
AGI-6780		IDH2/R140Q mutation inhibitor

Table 2 continued

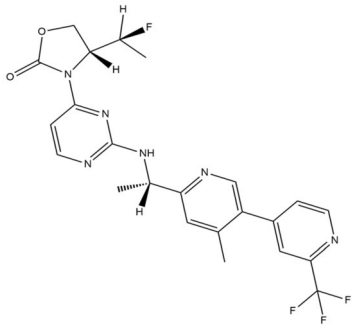
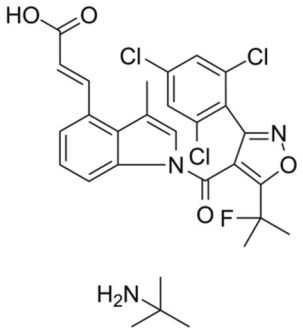
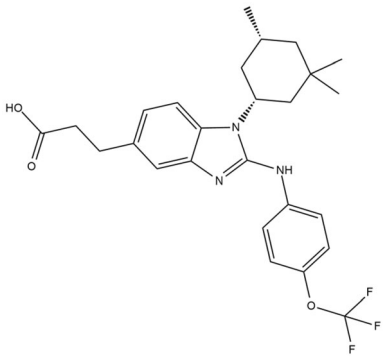
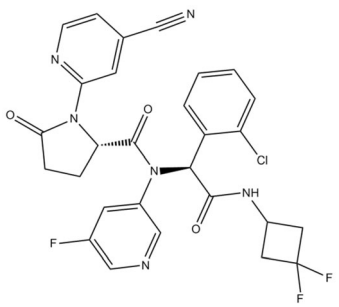
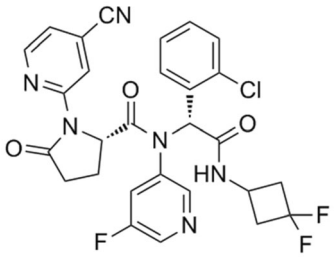
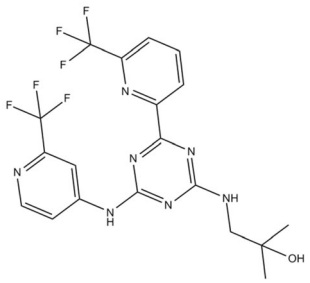
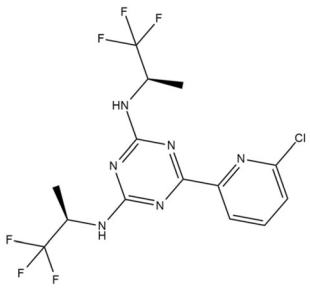
Drug names	Structure	Introductions
IDH-305		IDH-305 is an oral and brain-penetrating inhibitor of mutant IDH1, with an IC_{50} = 27, 28, and 6,140 nmol/L for recombinant $IDH1^{R132H}$, $IDH1^{R132C}$, and wild-type IDH1, respectively.
DS-1001b		Seen in the main manuscript
BAY-1436032		Seen in the main manuscript
AG-120		Seen in the main manuscript

Table 2 continued

Drug names	Structure	Introductions
(R,S)-AG-120		Seen in the main manuscript
AG-221		Seen in the main manuscript
AG-881		Seen in the main manuscript

6.14 μmol/L, respectively [132]. IDH-305 decreases D2-HG production and inhibits MCF-10A-*IDH1*^{R132H} cell growth in a concentration-dependent manner. IDH305 has been shown to suppress D2-HG production in an HCT116-*IDH1*^{R132H} mouse xenograft model at a dose of 200 mg/kg. Moreover, at 300 mg/kg, it reduces the concentration of D2-HG and inhibits tumor progression in an HMEX2838-*IDH1*^{R132C} patient-derived melanoma mouse xenograft model [132]. These results indicate that IDH-305 may be a candidate for *IDH1*-mutant glioma treatment. A Phase I trial of IDH305 in patients with advanced malignancies harboring *IDH1*^{R132} mutations is currently ongoing (NCT02381886).

DS-1001b

DS-1001b is an oral selective inhibitor of mutant IDH1^{R132} that is designed to penetrate the blood-brain barrier and has potential anti-tumor activity. DS-1001b inhibits the proliferation of *IDH1*-mutant chondrosarcoma cell lines *via* demethylation of H3K9me3 and decreased D2-HG levels. Continuous administration of DS-1001b impairs tumor growth in xenograft mice [133, 134]. There have been two clinical trials of DS-1001b (NCT03030066 and NCT04458272) related to the treatment of *IDH1*-mutated gliomas. A first-in-human, multicenter, Phase I study (NCT03030066) included 45 eligible patients with recurrent/progressive *IDH1*-mutant gliomas who received DS-1001b twice daily (bid), continuously. Recurrent/progressive *IDH1*-mutant glioma patients responded to this treatment. During treatment, DS-1001b was well tolerated at dosages up to 1400 mg bid with a favorable brain distribution, and the maximum tolerated dose was not reached. Most adverse events (AEs) were grade 1 to 2 and no grade 4 or 5 AEs or serious drug-related AEs were reported [134]. A Phase II study of DS-1001b in patients with *IDH1*-mutated, WHO grade II gliomas is currently ongoing (NCT04458272). This study is being conducted to

assess the efficacy and safety of DS-1001b in patients with chemotherapy- and radiotherapy-naïve, *IDH1*-mutated, WHO grade II gliomas.

AG881

AG-881 is an orally available, brain-penetrating, second-generation dual mutant IDH1/2 inhibitor. The IC_{50} of AG-881 ranges from 0.04 to 22 nmol/L against $IDH1^{R132}$, 7 to 14 nmol/L against $IDH2^{R140Q}$, and 130 nmol/L against $IDH2^{R172K}$ [135, 136]. AG-881 inhibits the transformation of α-KG into D2-HG, resulting in a reduction in D2-HG production. *In vitro* and *in vivo* studies have found that AG-881 readily crosses the blood-brain barrier, induces cell differentiation, and suppresses tumor growth *via* inhibition of D2-HG-mediated signals [136, 137]. At present, a clinical-phase study (NCT02481154) of orally administered AG-881 is being performed in patients with advanced solid tumors, including gliomas, with *IDH1* and/or *IDH2* mutations. The purpose of this Phase I, multicenter study is to evaluate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of AG-881 in gliomas harboring an *IDH1* and/or *IDH2* mutation.

AG-120

AG-120 is an orally active IDH1 inhibitor with potential anti-tumor activity, while (R, S)-AG-120 is an enantiomer of AG-120 with less activity [138]. In *IDH1*-mutant TF-1 cells and *ex vivo* cultures of samples from primary human acute myeloid leukemia (AML) patients with mutant *IDH1*, AG-120 reduces intracellular D2-HG, inhibits growth factor-independent cell proliferation, and restores cell differentiation induced by erythropoietin [139]. In 2018, AG-120 was approved by the U.S. Food and Drug Administration for the treatment of patients with relapsed or refractory AML who have a susceptible IDH1 mutation. Meanwhile, clinical development for the treatment of AML, cholangiocarcinoma, glioma, myelodysplastic syndromes, and solid tumors is ongoing worldwide [140]. For gliomas, a multicenter, open-label, Phase I, dose-escalation and expansion study of AG-120 has been completed. In this study of 66 patients with advanced mutant-*IDH1* gliomas, AG-120 was well tolerated at 500 mg once per day orally in 28-day cycles. The grade 3 and 4 AE rates were no more than 20%, and only two patients experienced AEs that were considered treatment-related. Among these AG-120-treated patients, stable disease was achieved in 85.7%, and the median progression-free survival was 13.6 months for non-enhancing gliomas. Furthermore, AG-120 reduced the volume and growth rates of non-enhancing tumors in an exploratory analysis. Hence, AG-120 has a favorable safety profile for *IDH1*-mutant advanced glioma patients [141]. Two Phase I clinical trials (NCT03343197 and NCT02073994) have been performed to further evaluate the safety and effectiveness of AG-120 in *IDH*-mutant glioma patients. Moreover, a Phase II study (NCT04056910) focused on the combination of the IDH1 inhibitor, AG-120, and the PD-1 inhibitor, nivolumab, in *IDH1*-mutant gliomas and advanced solid tumors is ongoing.

AG-221

AG-221 is a mutant IDH2 inhibitor with an IC_{50} of ∼ 16 nmol/L. AG-221 reduces D2-HG by > 90%, reverses *in vitro* histone and DNA hypermethylation, and induces the differentiation of leukemia cells. In addition, human-specific CD45+ blast cells proliferate in a dose-dependent manner following treatment with AG-221 [142, 143]. The efficacy of AG-221 has been well studied in a primary human AML xenograft model with an IDH2 mutation. AG-221 potently reduces D2-HG levels in the plasma, bone marrow, and urine of engrafted mice. Moreover, treatment with AG-221 has a significant and dose-dependent survival benefit [143]. A Phase I/II, multicenter, open-label, dose-escalation study (NCT02273739) of AG-221 in patients with advanced solid tumors, including gliomas and angioimmunoblastic T-cell lymphomas who harbor an *IDH2* mutation, was completed on February 23, 2021. The results of this multicenter study have not yet been published.

Conclusion and Perspectives

Mutations in *IDH* frequently occur in gliomas and can affect both glioma cells and the immune microenvironment. In glioma cells, *IDH* mutations alter cell proliferation, apoptosis, autophagy, and temozolomide sensitivity *via* transcriptional, post-transcriptional, and translational modifications. *IDH* mutations also affect the immune microenvironment of gliomas, modifying immune cell infiltration and functioning in direct and indirect ways. These *IDH* mutations affect immune cell migration and function *via* regulating the secretion of related chemokines and the expression of vital immune checkpoints in glioma cells, respectively. In contrast, *IDH* mutation-derived D2-HG can be taken up by immune cells, which, in turn, alters their functioning (Fig. 1).

Although mutant *IDH* affects the immune microenvironment of gliomas, its role in immune cells is complicated. The interaction of PD-L1 with its receptor, PD-1, inhibits CD8+ T-cell activation and cytokine production, with PD-L1 expression decreased in *IDH*-mutant gliomas. Though *IDH*-mutant glioma samples with lower PD-L1 expression should have higher levels of activated CD8+ T cells, other studies have found that exogenous D2-HG

taken up by CD8+ T cells impairs T-cell activation and antitumor immunity. Interestingly, apart from *IDH*-mutant gliomas, activated CD8+ T cells also auto-secrete D2-HG to regulate CD8+ T cells differentiation.

Similar to CD8+ T cells, the role of *IDH* mutations in TAMs is also controversial. Several studies have found that mutations in *IDH* decrease TAM infiltration, while the remaining cells are more commonly of the M1 type and express higher levels of phagocytosis markers. In addition, mutations in *IDH* also decrease TAM-inhibitory molecular CD47 expression, and microglia co-cultured with *IDH1*-mutant glioma cells exhibit increased phagocytosis. In contrast, D2-HG can also be taken up by TAMs *via* SLC13A3. In TAMs, D2-HG induces the secretion of the immunosuppressive factors IL-10 and TGF-β to establish an immunosuppressive environment, which results in resistance to immunotherapy. Moreover, co-culture of D2-HG-pretreated TAMs with T cells suppresses T-cell proliferation in a dose-dependent manner. It seems that blockade of D2-HG secretion by *IDH*-mutant glioma cells is a promising immunotherapy target. Despite the fact that *IDH*-mutant inhibitors, which decrease D2-HG secretion, have been designed to suppress glioma growth *in vitro* and *in vivo*, the role of these inhibitors in influencing the immune environment of gliomas requires further exploration.

Current immunotherapeutic strategies for glioma can be divided into four types: vaccination, immune checkpoint blockade, chimeric antigen receptor (CAR)-T cell therapy, and oncolytic viral therapy [33]. Vaccine therapy depends on dendritic cell-mediated presentation of the released lysate such as peptides and antigens derived from tumors to induce the activation of CD8+ cytotoxic T cells, which eventually kills glioma cells [144]. It has been reported that the IDH1-mutant protein contains an immunogenic peptide, which has been shown to be suitable for mutation-specific vaccination [76]. Results of a multicenter, single-arm, open-label, first-in-humans phase I trial demonstrated that $IDH1^{R132H}$ vaccine indeed induces immune responses and improves the two-year progression-free rate in most *IDH1*-mutant glioma patients [145]. A mutation-specific anti-IDH vaccine is a feasible immunotherapeutic approach for IDH-mutant gliomas. Furthermore, mutations in IDH also alters immune checkpoint molecular expression and immune-cell infiltration, and combination of IDH inhibitors with immune checkpoint inhibitors is also promising for IDH-mutant glioma immunotherapy. Apart from vaccines and immune checkpoint inhibitors, genetically-modified T cells is another interesting immunotherapeutic strategy for gliomas. Briefly, T cells are engineered to express CARs, which recognize domains of antibodies linked to the T cell receptor CD3 ζ-chain and co-stimulatory receptors (such as CD28 and/or TNFRSF9). The engineered CAR T cells also possess antigen recognition domains that are specific for tumor-associated antigens [33]. As previously described, IDH-mutant protein harbors an immunogenic peptide, and CAR T cells targeting IDH-mutant also have potential for glioma immunotherapy. Hence, further exploration of the roles of IDH mutations in glioma cells and in the immune environment of gliomas are vital for future IDH-mutant glioma therapy.

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Conflict of interest The authors declare that they have no conflicts of interest.

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