Chapter

IDH-Mutant Gliomas

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Abstract

Isocitrate dehydrogenase (*IDH*) mutation is one of the most critical genomic alterations in lower grade and secondary glioblastoma patient. More than 90% of *IDH* mutation is located at codon R132 of *IDH1* gene. *IDH* mutation produces oncometabolite "2-hydroxyglutarate" and induces epigenetic alteration, such as DNA global methylation and histone methylation. As a result, *IDH* mutation promotes early gliomagenesis. Since *IDH* mutation is the earliest genomic event and almost always retained during tumor progression, *IDH* mutation is expected as novel therapeutic target. Herein, we review the clinical characteristics of *IDH*-mutant gliomas, biological role of *IDH* mutation for gliomagenesis, and current and future therapeutic approach for *IDH* mutant tumors.

Keywords: *IDH* mutation, glioma, 2-hydroxyglutarate, tumor biology, cancer metabolism, target therapy

1. Introduction

The WHO 2016 classification integrates molecular and histological features in the diagnosis of gliomas. Among numerous genomic alterations, the *isocitrate dehydrogenase* (*IDH*) mutation is one of the most important genetic alterations found in this kind of tumor. As *IDH* mutation is a ubiquitous mutation in lower grade gliomas, the development of molecular target therapies against *IDH* mutations is expected. Here, we review *IDH*-mutant gliomas, focusing on their role in tumorigenesis and as novel therapeutic targets.

2. Discovery of *IDH* mutations in cancers

The presence of an *isocitrate dehydrogenase* (*IDH*) mutation was first discovered in colorectal cancers [1]. Parsons et al. [2] found mutations of the *IDH1* (2q.33) in 12% of the glioblastomas (GBMs). Other large scale studies validated that *IDH1* and *IDH2* (*IDH*) mutations were found in the majority of secondary GBM and lower grade (WHO grade II and III) gliomas, whereas these were rarely found in adult primary and pediatric GBMs [2–4]. Almost all of the *IDH1* mutations occur at codon 132, >90% of them exhibit a c.395G>A (R132H) substitution, followed by R132C [3, 5, 6]. Although the frequency was low, *IDH2* mutations were also identified at codon 172 in gliomas [4, 7].

Besides, *IDH* mutation was found in hematopoietic cancers, including acute myeloid leukemia (AML; 10–15%, *IDH2*) [8, 9], angioimmunoblastic T-cell lymphoma (AITL, 20%) [10], chondrosarcoma (~50%) [11–13], intrahepatic cholangiocarcinoma (15–20%, *IDH1*) [13], and at lower frequency in other hematopoietic

and solid cancers, such as B-acute lymphoblastic leukemia (B-ALL), esophageal cancer, colorectal cancer, melanoma, prostate carcinoma, and breast adenocarcinoma [1, 4, 14–16].

3. Tumorigenesis of *IDH*-mutant gliomas

3.1 Genomic characteristics of *IDH*-mutant glioma

The discovery of *IDH* mutations allowed the distinction of primary GBM, which is genetically characterized by *TERT* promoter mutation, gene alteration of epidermal growth factor receptor (*EGFR*), phosphatase and tensin homolog (*PTEN*) mutation or deletion, trisomy 7, monosomy 10, and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) homozygous deletion, from secondary GBM (GBM, *IDH*-mutant) [3, 5, 17, 18].

In astrocytic tumors, most of the tumor cells have co-mutations in *IDH1, TP53*, and *ATRX*. Moreover, WHO 2016 [19] defined the presence of *IDH* mutation and co-deletion of chromosome1p and 19q as necessary for the diagnosis of oligodendroglial tumors. Also, in oligodendroglial tumors, *TERT* promoter mutation is almost always present (>95%), while *CIC and FUBP1* are commonly (>40%) observed. These genetic abnormalities for astrocytic and oligodendroglial tumors are mutually exclusive [20–24]. Importantly, the *IDH* mutation is the earliest genetic alteration observed; it is commonly retained during tumor progression [25–28], but in a subset of mutants, *IDH1* was either deleted or amplified at tumor recurrence [29], indicating the critical role of *IDH* mutation for tumorigenesis. It has also been shown that *IDH* mutations do not select or create *ATRX* or *TERT* promoter mutations [30].

3.2 Developmental hierarchy in *IDH*-mutant gliomas

Two recent large scale single cell RNA-sequencing studies revealed a developmental hierarchy in *IDH1*-mutant gliomas [31, 32]. Accordingly, *IDH1*-mutant astrocytoma and oligodendroglioma shared a similar developmental hierarchy, consisting of three subpopulations of malignant cells: nonproliferative astrocytic and oligodendrocytic cells, proliferative, and undifferentiated neural stem/progenitor cells. In contrast, tumor micro environment (TME) was different in the abundance microglia/macrophage cells between astrocytic and oligodendroglial tumors. TME also differs between astrocytic tumors of different grades. Though TME and genomic alterations are distinctive, evidence indicates the existence of common progenitor cells in *IDH1*-mutant gliomas. In higher grade tumors, undifferentiated glioma stem/progenitor cells were increased [32]. In addition, almost all proliferating cancer cells were composed of subpopulations of undifferentiated cells (stem-like) in oligodendroglioma [31], suggesting a significant role for undifferentiated cells in cell proliferation and malignant progression.

3.3 *IDH*-mutant xenograft model

Although *IDH1* mutation induced proliferation *in vitro* [33], *IDH1* mutation did not promote xenograft formation [34–36]. Intriguingly, Bardella et al. [37] demonstrated that $IDH1^{R132H}$ overexpression in the murine subventricular zone induced the formation of early gliomagenesis, where stem and transit amplifying/progenitor cell populations were expanded, indicating the pivotal role of *IDH1* mutation in glioma formation. Moreover, Wakimoto et al. demonstrated that "tertiary mutations," such as *PIK3CA* mutation, *PDGFRA* amplification, and *MYC* amplification, promote

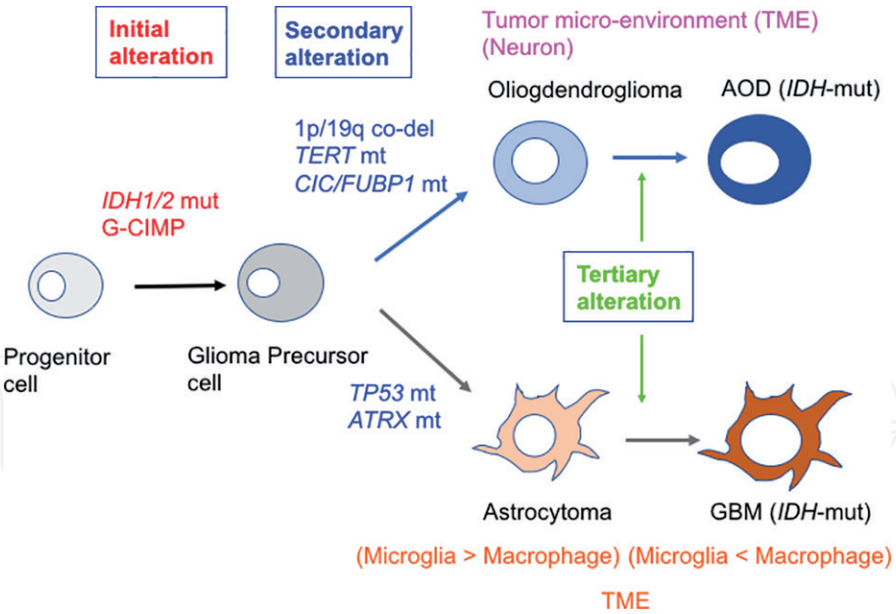

Figure 1.
Genomic alteration and tumor microenvironment in IDH-mutant astrocytic and oligodendroglial tumors.

IDH1-mutant glioma formation in xenograft models. Importantly, tumor harboring tertiary mutations were associated with unfavorable prognosis in *IDH1*-mutant glioma patients [38]. Recently, large genomic analyses demonstrated that malignant progression in *IDH1*-mutant glioma is associated with the *PI3K* pathway and *MYC* activation [39, 40]. Thus, *IDH* mutation induces gliomagenesis, whereas tertiary mutations are critical to promote tumor progression in lower grade gliomas (**Figure 1**).

4. The 2016 WHO classification

The 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) integrated phenotypic and genotypic parameters for CNS tumor classification. According to this classification, all diffusely infiltrating gliomas are grouped as diffuse astrocytic and oligodendroglial tumors. These tumors were histologically and genetically classified based on the presence of *IDH* mutation, co-deletion of chromosome1p and 19q, or *ATRX* and *TP53* mutations. Accordingly, gliomas are classified as follows: (1) diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (AA, WHO grade III): *IDH*-mutant, -wildtype, or not otherwise specified (NOS); (2) oligodendroglioma (WHO grade II) or anaplastic oligodendroglioma (WHO grade III): *IDH*-mutant and 1p/19q-codeleted or NOS; (3) oligoastrocytoma (grade II) and anaplastic oligoastrocytoma (WHO grade III): NOS; (4) GBM (WHO grade IV): *IDH*-mutant, -wildtype, or NOS; and (5) diffuse midline glioma (WHO grade IV): H3K27M-mutant.

IDH-wildtype GBM (about 90% of cases) is known as primary GBM, while *IDH*-mutant GBM (about 10% of cases) corresponds to secondary GBM [19].

5. Epidemiology of *IDH*-mutant gliomas

5.1 Age distribution of *IDH*-mutant gliomas

According to some statistical analyses, the *IDH*-mutant GBM or anaplastic astrocytoma patients were more than 20 years younger than those with

IDH-wildtype GBM [4]. In contrast, *IDH*-mutant GBM patients were only 4 years older than those with *IDH1*-mutant grade II and III astrocytoma [41]. This indicates that *IDH*-mutant glioma arises earlier than *IDH*-wildtype glioma (mostly GBM).

5.2 Prognosis of *IDH*-mutant gliomas

Parsons et al. [2] initially demonstrated that *IDH1*-mutant GBM patients survived about threefold longer than those with *IDH1*-wildtype GBM. Other groups verified that *IDH1* mutation is a favorable prognostic biomarker in gliomas [4, 42, 43]. In addition to GBM, large amounts of clinical studies indicated that the *IDH* mutation was an independent prognostic factor in grade II and III gliomas [4, 28, 43–47]. Notably, the prognosis of *IDH1*-mutant GBM is better than of *IDH1*-wildtype AA [48]. Also, a prospective randomized study (NOA-04) revealed that *IDH1* mutation, hypermethylation of the *O^6-methylguanine DNA-methyltransferase* (*MGMT*) promoter, age, extent of resection, and oligodendroglial histology are independent prognostic factors in anaplastic gliomas [44]. Among them, the impact of *IDH1* mutation conferred a stronger favorable prognosis than 1p/19q co-deletion, *MGMT* promoter methylation, and histology [44]. Collectively, *IDH1* mutation is a convincing prognostic factor in gliomas, irrespective of tumor grade and histology.

5.3 Prognostic classification for gliomas

Suzuki et al. [28] distinguished lower grade gliomas on the basis of the presence of *IDH1* mutation, *TP53* mutation, and 1p/19q co-deletion. Accordingly, tumors were classified into three groups: type I (*IDH1*-mutant with 1p/19q co-deletion; favorable prognostic group), type II (*IDH1*-mutant with TP53 mutation; intermediate prognostic group), and type III (*IDH1*-wildtype; poor prognostic group). Eckel-Passow et al. [47] classified gliomas into five groups based on the mutation status of *IDH1* and *TERT* promoter and on 1p/19q co-deletion. This group also demonstrated that *TERT* promoter mutations and *ATRX* alterations provided additional information for a tailored prognostic classification [49]. Besides, Arita et al. [50] proposed a classification of grade II–IV gliomas based on the mutations in *IDH* and the hotspot in *TERT* promoter.

Among *IDH*-mutant astrocytic tumors, *CDKN2A/B* homozygous deletion was demonstrated to be an unfavorable prognostic molecular marker [51]. Similarly, another group demonstrated that *PIK3R1* mutation and altered retinoblastoma pathway genes, including *RB1* and *CDKN2A*, were independent predictors of poor survival in astrocytic tumors. In oligodendrogliomas, NOTCH pathway inactivation and PI3K pathway activation were associated with poor prognosis [52, 53]. Collectively, these molecular markers could predict prognosis in glioma patients.

6. The mechanism of tumorigenesis in *IDH1*-mutant gliomas

6.1 *IDH* mutation drives production of oncometabolite D-2-hydroxyglutarate

In humans, IDH is composed of three types of isozymes (IDH1, IDH2, and IDH3). IDH1 is located in the cytoplasm and peroxisomes, whereas IDH2 and IDH3 are localized in the mitochondria and are involved in the TCA cycle. IDH1 and IDH2 are NADP+ dependent, whereas IDH3 is NAD+ dependent. IDH converts isocitrate into α-ketoglutarate (α-KG). No mutation in *IDH3* has been detected in human cancers. If *IDH* is mutated, it blocks normal enzymatic activity and instead produces D-2-hydroxyglutarate (2-HG) from α-KG in an NADPH dependent manner,

irrespective of the substituted amino acid [54–56]. Compared with *IDH*-wildtype cells, the 2-HG level in *IDH*-mutant cells is 50–100-fold higher [54, 57]. *IDH* mutations are almost always heterozygous, and both mutant and wildtype *IDH1* alleles are required for 2-HG production in glioma cells [58].

6.2 *IDH*-mutation induced epigenetic alterations

6.2.1 IDH-mutation inducible DNA hypermethylator phenotype

Since the structure of 2-HG is similar to that of α-KG, 2-HG inhibits a variety of α-KG-dependent dioxygenases [59, 60]. Among them, 10–11 translocation-2 (TET2) induces global demethylation of DNA by catalyzing the conversion of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC). Forced mutant *IDH1* caused increased 5mC concentrations, instead of decreased 5hmC [37, 61]. *IDH* mutation also promotes methylation of DNA by TET2 inhibition, resulting in a glioma CpG island methylator phenotype (G-CIMP), a specific DNA methylation pattern in *IDH*-mutant tumor cells [61–63]. Indeed, forced overexpression of mutant *IDH* ($IDH1^{R132H}$ and $IDH2^{R172K}$) produced high concentrations of 2-HG and increased global 5-mC levels [61]. Similarly, *TET2* mutations, which are mutually exclusive to *IDH* mutations, induce a global hypermethylation signature [61]. Turcan et al. [64] demonstrated that a G-CIMP-like phenotype and G-CIMP positive proneural glioblastomas were formed after the introduction of an *IDH1* mutation into normal human astrocytes (NHA). These data indicate that mutant *IDH* induced TET2 suppression, followed by G-CIMP, in cancer cells. Consistent with *IDH*-mutant glioma patients, glioma patients with G-CIMP are younger at diagnosis and survive longer than those without G-CIMP [62]. Intriguingly, about 10% of G-CIMP tumors were relapsed as G-CIMP low tumors with poor clinical outcome [65].

The Cancer Genome Atlas (TCGA) performed comprehensive transcriptome analysis. Accordingly, GBM was classified into four groups (classic, mesenchymal, proneural, and neural groups). Aberrations and gene expression of *EGFR* and *NF1* define the classical and mesenchymal subtypes, whereas tumors with an *IDH1* mutation were classified within the proneural group. The proneural group is also accompanied by a *PDGFRA* gene abnormality and the G-CIMP feature [66]. DNA methylation induced by the *IDH1* mutation caused hypermethylation at cohesion and CCCTC-binding factor (CTCF) binding sites and compromised the binding of the insulator protein. As a result, loss of CTCF at a domain permits a constitutive enhancer to interact aberrantly with the receptor tyrosine kinase gene *PDGFRA* [67].

6.2.2 IDH mutation promotes global histone methylation

IDH mutation is also known to increase histone methylation. Lysine methylation of histone tails modifies chromatin structure and regulates gene expression. By competition with α-KG, 2-HG inhibits histone demethylases including members of the Jumonji transcription factor family (JMJD2A, JMJD2C/KDM4C, and JHDM1A/FBXL11), resulting in histone hypermethylation [68]. Indeed, hypermethylation in H3K4me1, H3K4me3, H3K9me2, H3K27me2, H3K79me2, H3K27me3, H3K9me3, and H3K36me3 was observed in cells with exogenous 2-HG or mutant *IDH1* induction [60, 63, 64, 69]. Sasaki et al. [63] also demonstrated that $IDH1^{R132H}$ knock in mice showed significantly increased early hematopoietic progenitors, histone hypermethylation, and DNA methylation. Interestingly, the elevation of H3K9me3 levels was observed earlier than the DNA methylation

change in NHA upon $IDH1^{R132H}$ induction [69], suggesting that histone methylation may be an early event in *IDH1*-mutant cancers. The hypermethylation of histones blocks cell differentiation in cancer cells [60, 63, 64, 69]. Using a histone demethylating agent or a specific mutant IDH1 inhibitor, suppressed cell differentiation can be restored [70, 71]. Besides, 2-HG impairs collagen maturation, which leads to basement membrane aberrations that play a part in glioma progression [72]. Taken together, these data show that DNA hypermethylation and histone methylation promote tumorigenesis through a wide range of gene function changes (**Figure 2**).

6.3 *IDH* mutation inducible metabolic alterations

In addition to the epigenetic changes, *IDH1* mutation is known to alter hypoxia inducible factor 1α (HIF-1α) activity. Under oxidative conditions, α-KG-dependent prolyl hydroxylases (PHDs), which form the Egl nine homolog (EglN) families, induce HIF-1α hydroxylation. Hydroxylated protein is then bound by the von Hippel-Lindau tumor suppressor protein (VHL), ubiquitylated, and degraded via proteasome. In contrast, under hypoxia, the hydroxylation reaction is inhibited and HIF-1α is upregulated. HIF-1α then activates the transcription of several genes to mediate a switch from oxidative to glycolytic metabolism and induces angiogenesis by regulating the expression of vascular endothelial growth factor (VEGF) [73, 74]. Koivunen et al. [33] demonstrated that *IDH1* mutation attenuates HIF-1α through the activation of HIF prolyl 4-hydroxylase (EGLN), enhancing the proliferation and soft agar growth of NHA.

While several studies demonstrated that the *IDH1* mutation induced aerobic glycolysis via HIF-1α activity [59, 75], other group reported that HIF-1α responsive genes, including lactate dehydrogenase (LDHA) were downregulated; silenced LDHA was associated with increased methylation of the LDHA promoter [76]. Another group showed that *IDH1* mutation reduces pyruvate flux to lactate and suppresses monocarboxylate transporters MCT1 and MCT4, which mediate lactate transmembrane transport [77]. *IDH* mutation also alters pyruvate metabolism, including pyruvate dehydrogenase and pyruvate carboxylase enzymes, resulting in anaplerosis of the TCA cycle [78, 79].

Cancer cells are known to depend on reductive carboxylation (RC) of glutamine-derived α-KG for *de novo* lipogenesis under hypoxia [80]. It is worth noticing

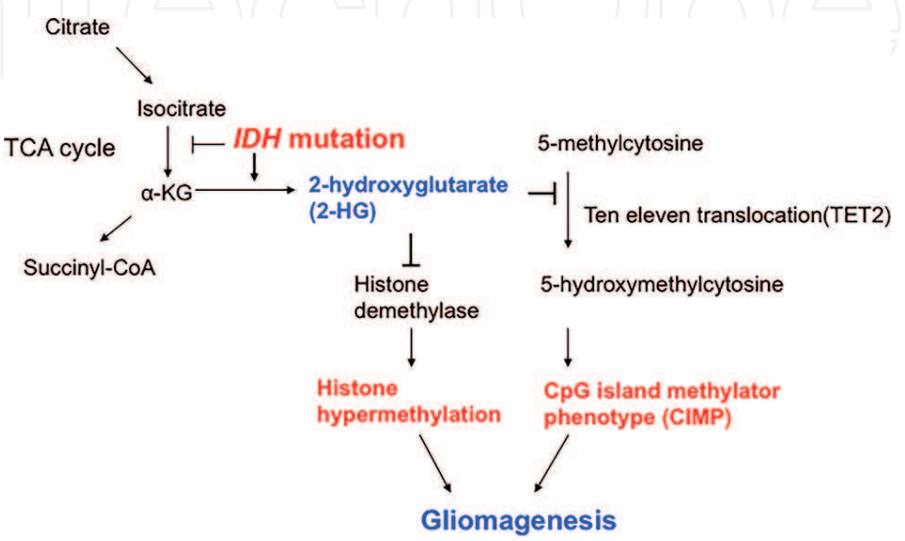

Figure 2.
Biological role of IDH mutation to induce gliomagenesis.

that the RC pathway is inhibited by *IDH* mutation [55]. Under hypoxia, *IDH1* mutation upregulated the contribution of glutamine to lipogenesis [81, 56].

Altered amino acids, glutathione, choline derivatives, and tricarboxylic acid (TCA) cycle intermediates were observed in *IDH*-mutant cells [82, 83]. Glutamate dehydrogenase (GDH)1 and GDH2 were overexpressed in *IDH1*-mutant tumors, and the orthotopic growth of an *IDH1*-mutant glioma is inhibited by a double GDH1/2 knockdown [84]. Another group demonstrated that GDH2 was critical for IDH1-mutation induced metabolic alterations and IDH1-mutant glioma growth [85]. The presence of 2-HG also inhibited ATP synthase and mTOR signaling [41].

Importantly, branched-chain amino acid transaminase (BCAT), which catalyzes the α-KG to glutamate conversion, was expressed at lower levels in *IDH1*-mutant gliomas than in *IDH1*-wildtype [86, 87]. As a result, the glutamate level was decreased, and cell proliferation and invasiveness were suppressed in *IDH*-mutant gliomas [87].

7. Role of extensive resection in *IDH1*-mutant gliomas

There is a huge amount of evidence showing that surgical resection has a pivotal role in survival benefit of glioma patients. Extensive resection is known to prolong survival in low grade glioma and also in GBM (*IDH1*-wildtype) [88–91]. In *IDH1*-mutant gliomas, an MRI study demonstrated that *IDH1*-mutant tumors were rarely located in high risk areas of the brain and show unilateral patterns of growth, sharp tumor margins, and less contrast enhancement [92, 93]. Indeed, radiographic atlas revealed *IDH1*-mutant gliomas were frequently located at frontal lobe [94]. A diffusion-tensor imaging study demonstrated that *IDH*-mutant GBM has a less invasive phenotype than *IDH*-wildtype GBM [95]. Intriguingly, patients with *IDH1*-wildtype gliomas had a reduced neurocognitive function and lower performance score than those with *IDH1*-mutant gliomas [96]. In addition, lesion volume was not associated with neurocognitive function for patients with *IDH1*-mutant tumors, but associated for those with *IDH1*-wildtype tumors [96]. Consequently, *IDH1*-mutant gliomas may be relatively less invasive to the surrounding eloquent area than *IDH*-wildtype GBM.

In addition, Beiko et al. [97] reported that extensive resection, including nonenhancing area, prolonged survival in *IDH1*-mutant anaplastic astrocytoma and glioblastoma. They also mentioned, since *IDH1*-mutant gliomas were predominantly located at frontal lobe, that maximal resection was relatively amenable. Another group independently demonstrated that gross total resection extended survival in grade III *IDH1*-mutant gliomas without 1p/19q co-deletion [98]. In contrast, survival advantage was controversial in grade II astrocytoma [99, 100]. These results suggest that for *IDH1*-mutant gliomas, especially grade III astrocytoma, maximal resection should be considered.

8. Prediction of *IDH* status

To establish *IDH* status-based treatment strategies, including surgery, advanced preoperative or intraoperative molecular analysis is important. Magnetic resonance spectroscopy (MRS) can be used to detect 2-HG and glutamate changes [101–107]. A recent MRS study demonstrated that 2-HG peaks rapidly decrease in accordance with tumor regression, whereas they increase with tumor progression in *IDH*-mutant gliomas [108], suggesting that 2-HG concentration, measured by MRS, may be a reliable approach to evaluate disease states in *IDH*-mutant gliomas.

In addition, several MR techniques, including diffusion tensor imaging and MR methods for determining relative cerebral blood volume, have been proposed to detect mutant *IDH1* noninvasively [109–111]. Moreover, T2-FLAIR mismatch sign was found as a highly specific imaging marker for *IDH*-mutant astrocytoma [112–114]. Intraoperative technologies to assess *IDH1* mutation have also been established [115–117]. These advanced technologies may allow the development of tailored surgical strategies for *IDH*-mutant gliomas. Other group demonstrated that urinary 2-HG is increased in patients with *IDH1*-mutant gliomas [118]. These findings indicate the possibility of application of indirectly assessed 2-HG as a clinical biomarker.

9. Treatment vulnerability in *IDH*-mutant gliomas

9.1 Radiotherapy for *IDH*-mutant gliomas

It has been shown that there is a higher relative sensitivity to radiotherapy and concurrent temozolomide (TMZ) in *IDH1*-mutant GBM patients than in those with *IDH1*-wildtype GBM [119], although there is no prospective clinical evidence of radiation therapy to extend survival in glioma patients with *IDH1* mutation. As described above, *IDH* mutation inhibits NADPH and glutamate production, resulting in reduced glutathione levels and increased reactive oxygen species (ROS) [120–123]. Conversely, radiosensitivity in *IDH1*-mutant tumors was diminished by IDH1 inhibitor [124]. These findings support selective vulnerability to radiation therapy in *IDH*-mutant gliomas.

9.2 Chemotherapeutic evidence for *IDH*-mutant gliomas

9.2.1 Temozolomide

Current standard management of GBM consists of surgical tumor resection, following local radiotherapy with temozolomide treatment [125]. Additionally, adjuvant TMZ prolonged survival in anaplastic astrocytoma [126]. Several studies demonstrated *IDH1*-mutation as a predictive biomarker for TMZ sensitivity in low grade gliomas and secondary GBM [127, 128].

Cytotoxicity of TMZ is provoked by the formation of O^6-methylguanine (O^6G)-DNA adducts. O^6G-DNA adducts induce DNA strand break and apoptosis through the O^6G-thymine-mediated mismatch repair pathway [129, 130]. It has also been established that the activation of DNA repairing pathways, including methylguanine methyltransferase (MGMT) repair enzyme, together with mismatch repair (MMR) system proteins deficiency, such as mutation-induced MSH2 and MSH6, result in drug resistance [131–133]. *MGMT* promoter methylation is highly methylated in *IDH1*-mutant gliomas, particularly oligodendrogliomas, compared with *IDH*-wildtype [43].

Some preclinical studies demonstrated that forced *IDH* mutation sensitized cells to chemotherapy by increased ROS [134–136]. Conversely, forced *IDH1* mutation revealed that *IDH1* mutation-induced temozolomide (TMZ) resistance and rapid G2 cell cycle arrest through increased RAD-51-mediated homologous recombination (HR) [137, 138]. Importantly, among DNA adducts, O^6G represents less than 10%, while the majority of TMZ-induced DNA lesions are N^7-methylguanine (60–80%) and N^3-methyladenine (10–20%) adducts, which are immediately repaired through poly(ADP-ribose)polymerase (PARP)-dependent base excision repair (BER) [129, 139, 140]. We have recently shown that there are lower steady state NAD+ levels in *IDH1*-mutant gliomas [141],

and that TMZ immediately induces NAD+ consumption through PARP activation-mediated BER in *IDH1*-mutant gliomas [142]. Besides, Lu et al. [143] reported that the PARP associated DNA repair pathway was extensively compromised in *IDH1*-mutant cells due to decreased NAD+ availability, thus, cells were sensitive to TMZ, suggesting that deregulated NAD+ metabolism may be related with chemosensitivity. Taken together, these studies show that *IDH* mutation may increase susceptibility to chemotherapy; however, it remains unclear if *IDH* mutation itself promotes TMZ sensitivity.

In contrast, TMZ-induced hypermethylation is a critical problem. Long-term TMZ exposure induces MMR inactivation, followed by DNA hypermutation phenotype. Among numerous mutations, gene alterations in RB and AKT-mTOR pathways promoted malignant progression in *IDH1*-mutant gliomas [27].

9.2.2 Other chemotherapeutic agents

Sulkowski et al. [144] demonstrated that 2-HG inhibits KDM4A and KDM4B, histone demethylases that play a critical role in double strand repair. As a result, *IDH1* mutation suppresses HR and induces PARP inhibitor sensitivity. Additionally, *IDH1*-mutant downregulates the DNA double strand break sensor ATM by altering histone methylation, resulting in impaired DNA repair. As a result, *IDH1* mutation causes DNA damage susceptibility to radiation and daunorubicin and reduces self-renewal of hematopoietic stem cells in acute myeloid leukemia [145].

10. Novel therapeutic target in *IDH1*-mutant tumors

10.1 Specific IDH inhibitor

In 2013, specific inhibitors for *IDH1* and *IDH2* mutations were discovered [70, 146]. In *IDH2*-mutant AML cells, an $IDH2^{R140Q}$ inhibitor induced both histone and DNA demethylation [147]. These effects reversed blocked cell differentiation and resulted in cytotoxicity *in vitro* [146, 147]. It is interesting to note that histone hypermethylation is more rapidly reversed than DNA hypermethylation [147]. In *IDH1*-mutant AML cells, differentiation and DNA demethylation were also induced by a next generation IDH1 inhibitor [148]. Since the *IDH2* mutation is crucial for proliferation and maintenance of leukemia cells [149], an IDH inhibitor may be used as a novel and efficient chemotherapeutic agent against *IDH*-mutant AML cells. Indeed, clinical trials demonstrated durable response for *IDH1/2*-mutant refractory AML patients [150, 151].

In *IDH1*-mutant glioma cells, Rohle et al. [70] reported that a specific IDH1 inhibitor, AGI-5198, blocked 2-HG production, histone demethylation, cell differentiation, and inhibited cell growth in endogenous *IDH1*-mutant glioma cells. Other group demonstrated that BAY 1436032, a pan inhibitor of IDH1 mutation, promoted mild cytotoxic effects *in vivo* [152]. In contrast, we established that, even with a long-term IDH1 inhibitor treatment, 2-HG depletion does not induce demethylation of global-DNA and histones, cell differentiation, nor cytotoxicity [141]. Studies using another IDH1 inhibitor also revealed minimal cytotoxicity despite a rapid decrease in 2-HG levels in glioma cells [153, 154]. Similarly, treatment with an IDH1 inhibitor did not contribute to cytotoxicity, and the CpG island methylation status as well as histone trimethylation levels were largely retained in malignant glioma and chondrosarcoma [155, 156]. Intriguingly, in immortalized human astrocytes with an inducible $IDH1^{R132H}$ expression system, a specific IDH1 inhibitor induced demethylation and inhibited tumorigenesis when forced expression was prior or concomitant to inhibitor treatment, but these effects were

not observed if the treatment was delayed [157]. These results indicate that 2-HG depletion or blocked mutant *IDH1* might be insufficient to control tumor growth and reprogramming of epigenomic alterations in progressed *IDH1*-mutant gliomas. Indeed, preliminary results indicate that the 6-month progression-free survival of *IDH1*-mutant glioma, chondrosarcoma, and cholangiocarcinoma is 25, 56, and 43%, respectively, suggesting that the potential of the IDH1 inhibitor may be weaker in *IDH1*-mutant gliomas than in other cancers [158].

10.2 Other treatment strategies

10.2.1 DNA demethylating agents

In addition to IDH1 inhibitor treatments, other strategies to control *IDH1*-mutant tumor cells have been proposed. Because the *IDH1* mutation promotes proliferation by blocking DNA demethylation, treatment with DNA demethylating agents reverses DNA methylation and inhibits proliferation in *IDH1*-mutant cells [71, 159]. Intriguingly, treatment with both the DNA demethylating agent 5-azacytidine (5-Aza) and TMZ demonstrated extensively prolonged survival in an *IDH1*-mutant orthotopic xenograft model [160].

10.2.2 Bcl-2 family inhibitors

Since 2-HG suppresses the activity of cytochrome c oxidase in mitochondrial complex IV, the mitochondrial threshold for apoptosis was decreased after BCL-2 inhibition in *IDH1* and *IDH2*-mutant AML [161]. Similarly, another Bcl-2 family member, the Bcl-xL inhibitor, induced apoptosis in *IDH*-mutant cells, including endogenous *IDH1*-mutant glioma cells [162]. Together, inhibition of Bcl-2 family members may be targetable to control growth in *IDH*-mutant cells.

10.2.3 DNA damaging agents

Because PLK1 activation provokes a rapid bypass through the G2 checkpoint after TMZ treatment in *IDH1*-mutant tumors, combination treatments with TMZ and a PLK1 inhibitor significantly suppressed tumor growth in an *IDH1*-mutant *in vivo* model [138]. In tumors with ATRX mutation-associated alternative lengthening telomeres (ALT), ATR inhibitor is highly sensitive [163], implying that such inhibition may be useful for treatments of *IDH1*-mutant astrocytic tumors with positive ALT. *IDH1* mutation blocked HR, so-called "BRCA ness" phenotype provided specific sensitivity for PARP inhibitor both *in vitro* and *in vivo* [144].

10.2.4 DLL-3 targeting therapy

Since Notch ligand DLL-3 is overexpressed in *IDH*-mutant gliomas, anti-DLL3 antibody-drug conjugate (ADC), rovalpituzumab tesirine (Rova-T), is a potent therapeutic agent for *IDH*-mutant gliomas [164].

10.2.5 Vaccination therapy

Schumacher et al. [165] reported an immunological approach to control *IDH1*-mutant cells. They showed that an epitope derived from the *IDH1*-mutant amino acid sequence is presented in HLA class II molecules of antigen-presenting cells, which elicit a strong immune response via CD4 + T cells. In addition, they showed that constitutive stimulation with synthetic peptides having the *IDH1*-mutation

sequence developed an immune response that eradicated *IDH1* mutated tumors in a mouse model with human HLA molecules. Thus, vaccine therapy targeting for *IDH1*-mutation is expected to develop for future clinical trial [165, 166]. Moreover, *IDH1*-mutation caused downregulation of leukocyte chemotaxis, resulting in repression of the tumor-associated immune system including immune cells, such as macrophages [167]. Additionally, tumor infiltrating lymphocytes (TILs) and programmed death ligand 1 (PD-L1) were expressed at low levels in *IDH1*-mutant gliomas [168]. In contrast, Kohanbash et al. [153] demonstrated reduced expression of cytotoxic T lymphocyte-associated genes and IFN-gamma inducible chemokines in *IDH1*-mutant cells; these results were reversed by specific IDH1 inhibitor. Therefore, combination treatments with vaccine immunotherapy and IDH1 inhibitor result in enhanced toxicity in *IDH*-mutant tumors.

10.2.6 Target for altered metabolism

IDH1 mutation induced altered metabolism is also expected as a novel therapeutic target. Based on the fact that the main carbon source for α-KG and 2-HG synthesis in *IDH1*-mutant cells is glutamine from glutaminolysis, a suitable target therapy would be the use of glutaminase (GLS) inhibitor or anti-diabetic drug metformin via the inhibition of mitochondrial complex I in the electron transport system [83, 169–171]. Since reduced glutamate blocks glutathione synthesis, inhibition of glutaminase specifically sensitizes *IDH*-mutant glioma cells to oxidative stress and radiation [86].

Mutant *IDH1* alters steady state levels of NAD+ through inhibiting NAPRT1, one rate limiting enzyme for NAD+ biosynthesis. Therefore, inhibition of nicotinamide phosphoribosyltransferase (NAMPT), another rate limiting enzyme, induced high cytotoxicity in *IDH1*-mutant patient-derived glioma cells [141]. Since TMZ rapidly consumes NAD+ through PARP activation, combination treatments with TMZ and NAMPT inhibitor further enhanced NAD+ depletion-mediated cytotoxicity in *IDH1*-mutant cancers [142]. Similarly, Lu et al. [143] reported that the PARP-associated DNA repair pathway was extensively compromised in *IDH1*-mutant cells due to decreased NAD+ availability, thus sensitive to TMZ.

Because of the relationships between *IDH1* mutation and *MYC* activation [38, 40, 172], target therapy to regulate *MYC*, by using bromodomain and extra-terminal (BET) inhibitors, CDK7 or MYC-induced glycolysis may be used for *IDH*-mutant gliomas [40, 173–175]. Given the results of these studies, *IDH1* mutation-specific biological alterations and metabolic feature may be expected as novel therapeutic targets.

11. Conclusions

In summary, investigations on *IDH* mutations enabled distinctive tumor classification and may allow the development of specific therapeutic strategies. Further preclinical and clinical studies are warranted to overcome the outcomes of cancer development in *IDH*-mutant glioma patients.

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