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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 chromosome 1p 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, IDHI 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 IDH1R132H 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
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 oligodendrogial tumors. These tumors were histologically and genetically classified based on the presence of IDH mutation, co-deletion of chromosomes 1p 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 O6-methylguanine DNA-methyltransferase (MGMT) promoter, age, extent of resection, and oligodendrogial 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 IDH1-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 (IDH1R132H and IDH2R172K) 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 IDHI 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 IDHI 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 IDHI 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 IDHI induction [60, 63, 64, 69]. Sasaki et al. [63] also demonstrated that IDHI 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\textsuperscript{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.](image-url)
that the RC pathway is inhibited by IDH mutation [55]. Under hypoxia, IDH 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 IDHI-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 \textit{IDH1} noninvasively [109–111]. Moreover, T2-FLAIR mismatch sign was found as a highly specific imaging marker for \textit{IDH}-mutant astrocytoma [112–114]. Intraoperative technologies to assess \textit{IDH1} mutation have also been established [115–117]. These advanced technologies may allow the development of tailored surgical strategies for \textit{IDH}-mutant gliomas. Other group demonstrated that urinary 2-HG is increased in patients with \textit{IDH1}-mutant gliomas [118]. These findings indicate the possibility of application of indirectly assessed 2-HG as a clinical biomarker.

9. Treatment vulnerability in \textit{IDH}-mutant gliomas

9.1 Radiotherapy for \textit{IDH}-mutant gliomas

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

9.2 Chemotherapeutic evidence for \textit{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 \textit{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\textsubscript{6}-methylguanine (O\textsubscript{6}G)-DNA adducts. O\textsubscript{6}G-DNA adducts induce DNA strand break and apoptosis through the O\textsubscript{6}G-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 \textit{IDH1}-mutant gliomas, particularly oligodendrogliomas, compared with \textit{IDH}-wildtype [43].

Some preclinical studies demonstrated that forced \textit{IDH} mutation sensitized cells to chemotherapy by increased ROS [134–136]. Conversely, forced \textit{IDH1} mutation revealed that \textit{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\textsubscript{6}G represents less than 10%, while the majority of TMZ-induced DNA lesions are N\textsubscript{7}-methylguanine (60–80%) and N\textsubscript{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 \textit{IDH1}-mutant gliomas [141],
and that TMZ immediately induces NAD+ consumption through PARP activation-mediated BER in \textit{IDH1}-mutant gliomas [142]. Besides, Lu et al. [143] reported that the PARP associated DNA repair pathway was extensively compromised in \textit{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 \textit{IDH} mutation may increase susceptibility to chemotherapy; however, it remains unclear if \textit{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 \textit{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, \textit{IDH1} mutation suppresses HR and induces PARP inhibitor sensitivity. Additionally, \textit{IDH1}-mutant downregulates the DNA double strand break sensor ATM by altering histone methylation, resulting in impaired DNA repair. As a result, \textit{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 \textit{IDH1}-mutant tumors

10.1 Specific \textit{IDH} inhibitor

In 2013, specific inhibitors for \textit{IDH1} and \textit{IDH2} mutations were discovered [70, 146]. In \textit{IDH2}-mutant AML cells, an IDH2\textsuperscript{R140Q} inhibitor induced both histone and DNA demethylation [147]. These effects reversed blocked cell differentiation and resulted in cytotoxicity \textit{in vitro} [146, 147]. It is interesting to note that histone hypermethylation is more rapidly reversed than DNA hypermethylation [147]. In \textit{IDH1}-mutant AML cells, differentiation and DNA demethylation were also induced by a next generation IDH1 inhibitor [148]. Since the \textit{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 \textit{IDH}-mutant AML cells. Indeed, clinical trials demonstrated durable response for \textit{IDH1/2}-mutant refractory AML patients [150, 151].

In \textit{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 \textit{IDH1}-mutant glioma cells. Other group demonstrated that BAY 1436032, a pan inhibitor of \textit{IDH} mutation, promoted mild cytotoxic effects \textit{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\textsuperscript{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 IDH1-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 IDH1-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 IDH1-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 IDH1-mutant glioma patients.
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