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Review Article

Mechanism analysis and targeted therapy of IDH gene mutation in glioma

Xingyuan Ma[1,2], Chao Sun[3], Xiao Ding[4], Jiaqi Xu[5], Yuhang Zhang[1,2], Tingzhen Deng[1,2], Yatao Wang[1,2], Haijun Yang[1,2], Ruiwen Ding[1,2], Haotian Li[1,2], Dawen Wang[1,2], Maohua Zheng[1,2]

[1]The First School of Clinical Medicine, Lanzhou University, Lanzhou 730000, Gansu, China; [2]Department of Neurosurgery, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu, China; [3]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China; [4]The Third Department of Surgery, Armed Police Hospital of Tianjin, Tianjin 300163, China; [5]Edinburgh Medical School, The University of Edinburgh, Edinburgh EH16 4SB, Scotland, UK

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Abstract: Isocitrate dehydrogenase (IDH) is a pivotal enzyme responsible for catalyzing the oxidative decarboxylation of isocitrate into α-ketoglutarate (α-KG). This enzyme serves as a crucial regulator in the tricarboxylic acid cycle (TCA cycle), acting as a rate-limiting step. Its role extends beyond mere metabolic function, influencing cellular homeostasis and overall cell function. In the past decade, prominent research in cancer genetics has revealed that genes responsible for encoding isocitrate dehydrogenase are commonly mutated across various human malignancies. Significant research in the field has shown that these mutations are commonly found in diseases like glioma, acute myeloid leukemia (AML), cholangiocarcinoma (CCA), chondrosarcoma, and thyroid cancer (TC). As research on IDH progresses, deeper insights into the biological effects of IDH mutations have been gained, unveiling their potential role in tumorigenesis. In addition, IDH mutants' unique activities creates new pathways in tumor metabolism, gene rearrangement, and therapeutic resistance. Currently, innovative molecular targeting strategies for genes bearing mutations in IDH have been devised to enhance the therapeutic efficacy against cancers harboring IDH mutations. These methods represent a promising avenue for improving treatment outcomes in IDH-mutated malignancies. This article mainly summarizes the related research on glioma caused by IDH mutation, and focuses on the biological characteristics and transformation of IDH.

Keywords: Brain glioma, IDH, D-2HG, gene mutation, targeted therapy

Introduction

IDH mutations are common in human malignant tumors, especially in gliomas. According to WHO statistics, IDH mutations account for more than 80% of II/III grade gliomas. In IV grade glioblastoma (GBM), according to the statistics of World Health Organization (WHO), in secondary glioblastoma patients, 73% exhibit IDH mutation, while among primary glioblastoma patients, the prevalence of IDH mutation is 3.7%. A subsequent investigation conducted by the WHO revealed that the presence of IDH mutations correlates with extended median survival among glioblastoma patients, thereby positively influencing the progression of the patient's condition [1, 2]. Although gliomas with IDH mutations usually show a better trend of disease progression, the elevated prevalence of IDH mutations observed in secondary glioblastoma suggests that IDH mutations will recur after malignant transformation from low-grade gliomas to advanced gliomas. In addition, gliomas with IDH mutations are more likely to develop into highly mutated gliomas, which indicates that patients are prone to deteriorate prognosis [3]. IDH mutations define WHO grade II and III astrocytomas and oligodendrogliomas, as well as the secondary grade IV glioblastomas that astrocytomas often evolve into. Their presence distinguishes low-grade gliomas from primary glioblastomas, which are mostly IDH wild-type. Detection of these mutations in ambiguous tumor specimens can also be considered as evidence of the presence of diffuse invasive gliomas. This review primarily concen-

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trates on gliomas characterized by mutations in the IDH gene.

The IDH mutations are not uniformly distributed in all organs. In the tumor field, IDH mutations are relatively common in Central nervous system (CNS) tumors such as gliomas. In the case of astrocytoma and oligodendroglioma, the frequency of IDH mutations is relatively high. This may be related to the metabolic characteristics and gene expression regulatory environment of CNS cells [4]. CNS cells have unique metabolic requirements, and IDH plays a key role in the metabolic pathways of these cells, and its mutations may more easily disrupt the normal metabolic and proliferative processes of the cells. However, IDH mutations also have a certain probability of occurrence in tumors of other organs. For example, IDH mutations have also been found in tumors such as CCA, chondrosarcoma. However, compared with glioma, it has low mutation frequency and may have different mutation patterns and biological effects. In CCA, IDH mutations may be associated with abnormal proliferation of bile duct epithelial cells and disturbed bile acid metabolism, whereas in chondrosarcoma, it may affect the differentiation of chondrocytes and the synthesis of extracellular matrix [5, 6].

For a long time, the discovery of novel activities associated with IDH mutation has been demonstrated to significantly influence cellular metabolism, cancer pathophysiology, and the process of tumorigenesis. This review aims to outline the mechanisms underlying IDH mutation, elucidate the notable advancements in understanding the cancer biology of IDH mutant gliomas, and underscore the importance of these insights in driving future therapeutic innovations, particularly in the realm of glioma research. We will also explore significant discoveries from alternative tumor models with IDH mutations, such as AML and CCA. These insights offer valuable perspectives into the molecular mechanisms underlying IDH mutant gliomas.

The mechanism of the IDH mutation

Structure and function of the IDH genes

The-IDH (isocitrate dehydrogenase) genes include IDH1, IDH2, and IDH3. The proteins encoded by the IDH1 and IDH2 genes are mainly localized in the cytoplasm and peroxisomes, and the proteins encoded by the IDH3 genes are located in the mitochondria [7, 8]. The IDH1 gene is located on chromosome 2q33.3, and the IDH2 gene is located at chromosome 15q26.1. They share some structural similarities, both containing multiple exons and introns, and they encode proteins with similar enzymatically active domains [4, 9]. In the case of IDH1, its encoded protein consists of 414 amino acids with a typical NAD (P) binding domain and a substrate binding domain. These domains are essential for the binding and catalytic reactions of the IDH1 protein with the substrate isocitrate and the coenzyme NAD (P). In normal cell metabolism, IDH is one of the key enzymes of the TCA cycle. IDH mainly catalyzes the oxidation and decarboxylation of isocitrate to produce α-KG, and simultaneously reduces NADP to NADPH [4, 10]. This process is important for the cell to produce energy (in the form of ATP) and to maintain a redox balance in the cell. NADPH is an important intracellular reducing agent that is used to maintain the reducing state of antioxidants such as glutathione and protect cells from oxidative stress damage [4, 11]. Meanwhile, α-KG is an important metabolic intermediate and is involved in various biosynthetic reactions, such as amino acid synthesis [4, 12].

The type of the IDH mutation

Among disease-associated IDH mutations such as tumors, point mutations are the most common type. For IDH1, the most representative mutation is that at R132, with the IDH1-R132H mutation being the most common [13, 14]. In this mutation, the arginine (Arg, R) is replaced by a histidine. This single point mutation resulted in an altered activity of the IDH enzyme, enabling a new enzymatic activity to convert α-KG into 2-hydroxyglutarate (2-HG) [4, 15]. For IDH2, the common mutation sites are R172 and R140. Mutations such as IDH 2-R172K (arginine replaced by lysine) can also lead to aberrant changes in enzyme activity, allowing it to produce 2-HG [4, 16]. These point mutations alter the spatial structure of the IDH protein and the chemistry of the enzyme active center, thereby triggering a series of subsequent metabolic and biological changes. Besides point mutations, other types like insertion/deletion mutations exist, but they are relatively rare.

These mutations may cause frameshift mutations in the IDH gene, which can greatly change the encoded protein sequence and affect the folding and function of the protein [16, 17]. However, in contrast to point mutations, the mechanisms and effects of insertion/deletion mutations in IDH mutation-related diseases have not been fully defined.

Mechanism of IDH mutation

In the case of the IDH1-R132H mutation, the structure of the active center of the mutation enzyme protein is altered [18]. Upon substitution of arginine by histidine, the charge distribution and spatial conformation of the active center change. This change changes the substrate preference of the mutated IDH enzyme, changing from preferentially catalyzing the oxidation decarboxylation of isocitrate to form α-KG to using α-KG as a substrate to generate 2-HG after a reduction reaction. From the chemical mechanism, the active center of the mutated IDH enzyme can better bind α-KG and NADPH, enabling α-KG to accept the hydrogen atoms from NADPH, generate 2-HG. This metabolite transition is a critical step in the abnormal cellular metabolism caused by the IDH mutation [19, 20]. The normal function of IDH enzymes depends on the binding and utilization of the cofactor NAD (P). The mutant IDH enzyme may also be altered in its cofactor-binding capacity. For example, the IDH1-R132H mutation may affect the binding affinity of NADPH to the enzyme protein, enabling it to more efficiently utilize NADPH for 2-HG generation reactions in a metabolic environment within the cell [20, 21]. Meanwhile, changes in the cofactor binding ability may also affect the enzyme protein stability and catalytic efficiency [20, 22]. Due to the different utilization of cofactors after IDH mutation, this further disrupts the normal redox balance and metabolic signaling pathways inside the cells, providing the metabolic basis for the malignant transformation of cells and the development of tumors [23].

Mechanism of cell signaling pathway alteration triggered by the IDH mutation

2-HG accumulation caused by IDH mutation is an important factor in triggering altered cellular signaling pathways. 2-HG can act as a competitive inhibitor of α-KG, affecting the activity of the α-KG-dependent dioxygenase family [24, 25]. Among them, the histone demethylases and the 5-methylcytosine hydroxylase of the ten-eleven translocation (TET) family are the key enzymes affected. Inhibition of histone demethylase activity leads to elevated histone methylation levels. For example, in tumor cells, the methylation levels of histone sites such as H3K9 and H3K27 increase, keeping the chromatin in a tight state and inhibiting the expression of some tumor suppressor genes [26, 27]. Decreased activity of TET family enzymes can lead to abnormal DNA methylation status, such as 5-methylcytosine (5 mC) cannot be normally hydroxylated into 5-hydroxymethylcytosine (5 hmC), which increases DNA hypermethylated regions, and also affects the expression of gene and cell differentiation fate [27, 28].

IDH mutations, by changing cell metabolism and epigenetic status, indirectly affect cell proliferation and apoptotic pathways. In terms of cell proliferation, due to altered metabolites and disordered epigenetic regulation caused by IDH mutations, the expression of some genes promoting cell cycle progression (such as cyclin D1, CDK4, etc.) is upregulated, enabling cells to bypass normal cell cycle checkpoints and accelerate cell proliferation [29, 30]. In terms of apoptosis, IDH mutations can cause tumor cells to escape apoptosis by inhibiting the expression of apoptosis-related genes (e.g., Bax, caspase-3, etc.), or by activating anti-apoptotic signaling pathways (e.g., PI3K-Akt pathway). For example, 2-HG produced by IDH mutations can modulate key proteins in the PI3K-Akt pathway, inhibit the transmission of apoptotic signals, and increase the survival ability of tumor cells [31-33].

Metabolic rearrangement and treatment caused by IDH mutation

Metabolic rearrangement

IDH1 and IDH2 mutations are important drivers of gliomagenesis and progression. Patients with IDH mutant gliomas usually have a better prognosis than the wild-type counterparts [4, 8]. In low-grade glioma, the presence of IDH mutations can be used as a marker of good prognosis. For example, the IDH1-R132H mutation is the most common type of mutation, which causes the accumulation of the metabolite 2-HG [34]. 2-HG can competitively inhibit a variety of α-KG-dependent dioxygenases, such

as histone demethylases and 5-methylcytosine hydroxylases of the TET family. This causes changes in histone and DNA methylation status that affect gene expression and thereby promote the proliferation and survival of tumor cells. IDH mutations are also more common in AML [16]. The 2-HG produced by the IDH mutation can interfere with the normal differentiation process of the cells. In normal hematopoiesis, cells need precise epigenetic regulation to achieve differentiation, and 2-HG accumulation caused by IDH mutations disrupts this regulatory mechanism, prevents hematopoietic stem and progenitor cells to differentiate normally into mature blood cells, leading to the proliferation of leukemic cells [35, 36]. IDH mutations are an emerging research hotspot in cholangiocarcinoma. IDH mutations may promote the proliferation, migration and invasion of CCA cells by changing cell metabolism and epigenetic status. Meanwhile, IDH-mutant CCA may have different sensitivity to certain specific therapeutic agents, which provides new targets for the precision treatment of cholangiocarcinoma [37].

Although relatively poorly studied, there are some indications that IDH mutations may be associated with some non-neoplastic diseases of the nervous system. For example, in some studies of neurodegenerative diseases, we found that abnormalities in the IDH metabolic pathway may be potentially linked to the development of diseases [38]. This may be due to the effect of IDH mutations or their related metabolites on neuronal metabolism and function, which in turn leads to neurodegeneration.

IDH mutant enzyme causes the concentration of D-2HG (Dmur-2-hydroxyglutarate, a tumor metabolite that promotes tumorigenesis) up to 5-30 mmol/L in the cytoplasm [37], this leads to the excretion of carbohydrates in the tricarboxylic acid cycle, serving as a compensatory mechanism to address alterations in metabolic pathways (**Figure 1**) [38].

Analysis of metabolic flux has revealed that the oxidative metabolism of IDH1 cells increased in the TCA cycle, while the reductive glutamine metabolism was inhibited. As cellular metabolism diminishes, alternative non-tricarboxylic acid cycle carbohydrates are mobilized to offset the decline in α-ketoglutaric acid, an intermediary metabolite crucial for amino acid, vitamin, organic acid synthesis, and energy metabolism. Waitkus and colleagues showed that glutamate dehydrogenase, a brain-wide enzyme, helps convert glutamate into α-KG. This process plays a crucial role in alleviating the metabolic burden associated with IDH mutations [39]. This discovery validates the heightened sensitivity of IDH mutant glioma cells to inhibition of glutaminase, emphasizing the critical importance of glutamine cleavage as a crucial compensatory pathway for sustaining metabolic balance. McBrayer et al. delved deeper into exploring the reliance of IDH1 mutant cells on glutamate cleavage, and found that D-2HG could inhibit the activity of branched-chain amino acid aminotransferase (BCAT) 1/2 is primarily involved in the metabolic pathway of branched-chain amino acids, enabling the transfer of these amino acids to α-KG. This process results in the production of corresponding α-amino acids and branched-chain keto acids, resulting in a serious decrease in glutamate levels in patients (**Figure 2**) [40].

In addition, the consumption of NADPH by IDH mutants hinders new adipogenesis, resulting in increased dependence of cell growth on exogenous lipid sources, and D-2HG promotes adipogenesis from glutamine sources under hypoxic conditions, ensuring adequate lipid production.

LDHA (lactate dehydrogenase A) plays a role in converting pyruvate, produced during glycolysis, into L-lactic acid [41]. Hence, LDHA expression is regarded as indicative of the Warburg effect in cancer cells, facilitating rapid glycolysis to fulfill the demands of cell proliferation [42]. Despite being prominently expressed in numerous cancer cell types, LDHA is notably absent in glioma tissues and patient-derived glioma cells harboring IDH mutations [41, 42]. Research has revealed a correlation between the lack of expression of LDHA, along with several other glycolytic genes such as carbonic anhydrase 9 (CA9) and VEGFA (vascular endothelial growth factor A), and the hypermethylation of these gene promoter regions in response to D-2HG (**Figure 2**). The overall lack of glycolysis pathway may explain the nature of the slow growth of IDH mutant gliomas exhibit distinct characteristics in comparison to IDH wild-type gliomas [42, 43]. In a recent investigation, the phenomenon known as the Warburg

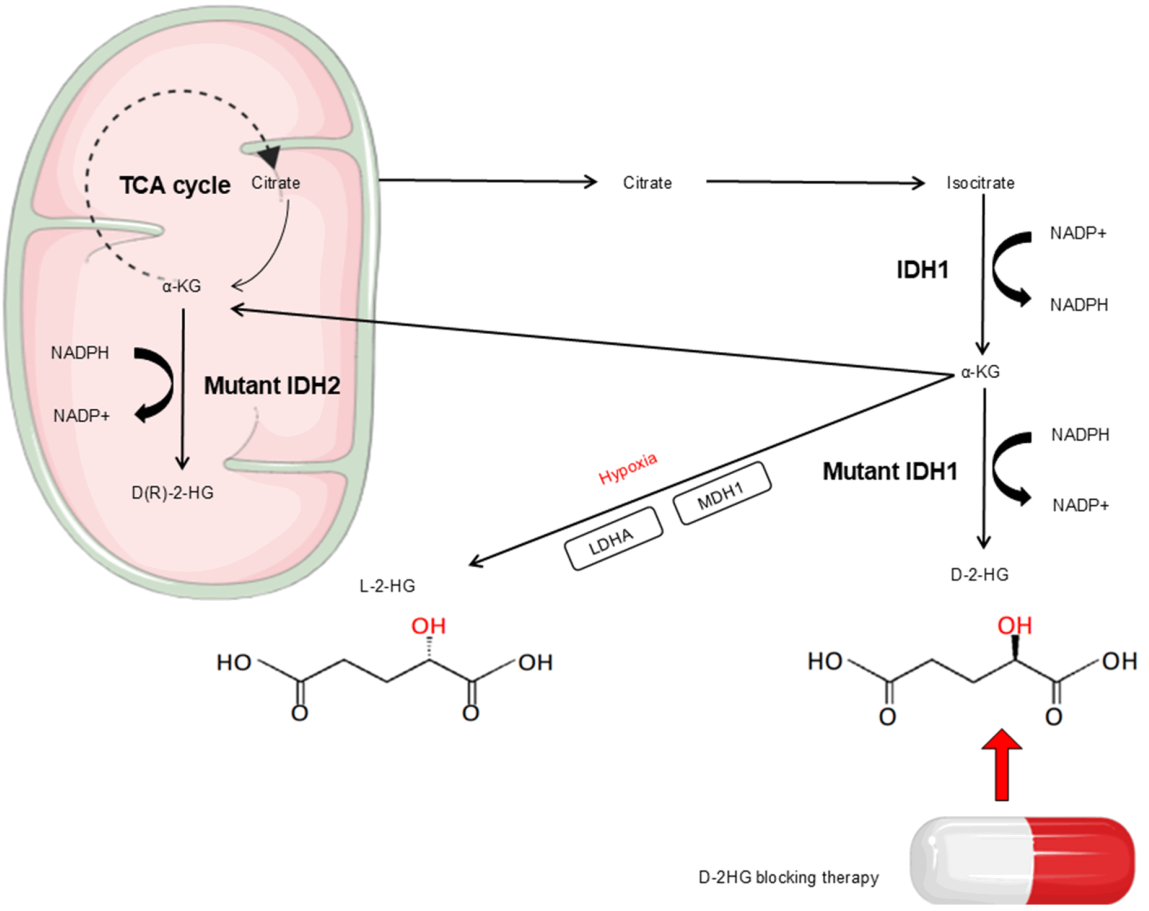

Figure 1. IDH mutation leads to abnormal accumulation of D-2HG in human body. After IDH1/2 mutation, it was transformed into another new enzyme, which used α-KG as a substrate to produce a new metabolite D-2-HG. D-2-HG is produced by α-KG through IDH1/2 mutation. D-2-HG is produced by α-KG through IDH1/2 mutation. 2HG is an endogenous metabolite, which is a 5-carbon dicarboxylic acid with a hydroxyl group on the second carbon or a carbon. According to the chirality of the second carbon atom with hydroxyl group, 2HG can be divided into a pair of chiral isomers (i.e., optical isomers): D-2HG and L-2HG. These stereoisomers have the same physical properties, but they have different three-dimensional spatial configurations, so they can be recognized by different enzymes. Tumors synthesize L-2-HG from α-KG by Malate dehydrogenase (MDH) and LDH enzymes under hypoxic conditions, but the concentration is low. The subtype structure of the two 2-HGs is similar to that of α-KG, which inhibits ATP synthase and α-KG-dependent dioxygenase (such as histone and DNA demethylase). IDH1/2 wild-type tumors synthesize L-2-HG from α-KG by MDH1 and LDHA enzymes under hypoxic conditions, but the concentration is low. The structure of the two subtypes of 2-HG is similar to that of α-KG, which inhibits ATP synthase and α-KG-dependent dioxygenases (such as histone and DNA demethylase).

effect has been shown to be related to the invasiveness of gliomas, and researchers have identified the presence of the CpG island methyl phenotype (G-CIMP) in gliomas, which is the specificity of astrocytomas, while astrocytomas are invasive growth tumors that can evolve into glioblastoma multiforme [44].

Moreover, IDH mutations induce alterations in enzyme activity, reshaping the tricarboxylic acid cycle to generate D-2-hydroxyglutarate. The reduction in α-ketoglutarate levels may impact the abundance of hypoxia-inducible factor subunit hypoxia-inducible factor-1 (HIF-1) [45]. Because α-KG is commonly used the hydroxylation of prolyl hydroxylase (PHD) and for promoting the degradation of HIF. At present, the precise molecular mechanism underlying the regulation of HIF in the context of IDH mutation remains elusive. However, emerging evidence indicates that D-2HG, as opposed to its mirror isomer L-2HG, enhances the activity of PHD2 (prolyl hydroxylase), resulting in diminished expression of HIF1/2 (**Figure 2**) [46].

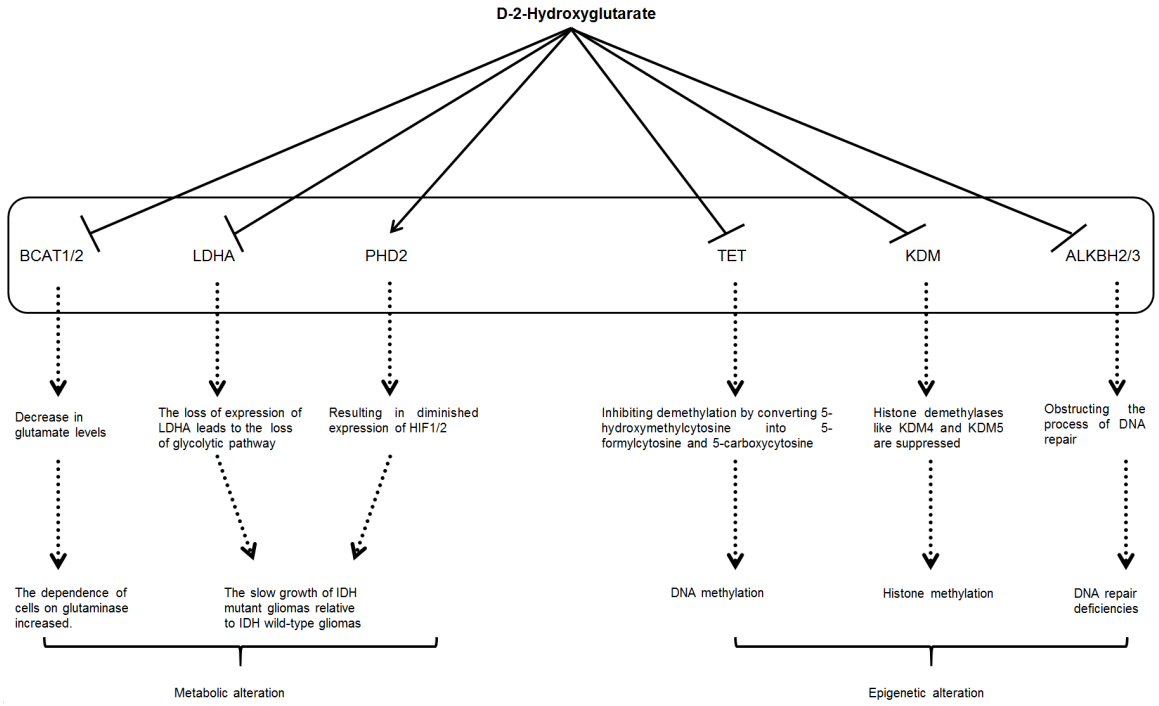

Figure 2. Metabolic and gene rearrangement caused by D-2-hydroxyglutarate. In terms of metabolic rearrangements, D-2HG could inhibit the activity of BCAT1/2 resulting in a serious decrease in glutamate levels in patients, in addition, research has revealed a correlation between the lack of expression of LDHA, and the hypermethylation of these gene promoter regions in response to D-2HG. What is more, emerging evidence indicates that D-2HG, enhances the activity of PHD2, resulting in diminished expression of HIF1/2. The overall loss of glycolytic pathway and the diminished expression of HIF1/2 may explain the slow growth of IDH mutant gliomas relative to IDH wild-type gliomas. In another terms of gene rearrangements, firstly, the presence of D-2HG impedes the activity of TET due to its structural resemblance α-KG. Furthermore, α-KG is essential for the demethylase activity of TET enzymes. Secondly, D-2HG also promotes histone methylation by suppressing histone demethylases like KDM. Histone demethylases like KDM4 and KDM5 are suppressed by increased levels of D-2HG. In the end, D-2HG interferes with the DNA repair pathway by functioning as an inhibitor of DNA repair enzymes such as ALKBH2/3, and by obstructing the process of homologous recombination (HR) DNA repair.

Correlation between IDH mutation and glioma cancer biology

IDH mutation leads to abnormal accumulation of 2-HG, which is the most remarkable metabolic feature of IDH mutant glioma. As a carcinogen metabolite, 2-HG can change the epigenetic state of cells by inhibiting α-KG-dependent dioxygenase. For example, it will affect the activity of histone demethylase, leading to the increase of histone methylation level. In tumor cells, hypermethylated histone can inhibit the expression of some tumor suppressor genes, thus promoting the growth and proliferation of tumor cells. IDH is the key enzyme in TCA cycle, and the mutation of IDH will interfere with the normal operation of TCA cycle [47]. The disorder of TCA cycle will affect the energy metabolism and biosynthesis of cells. In glioma cells, this metabolic disorder can provide growth advantages for tumor cells. For example, abnormal TCA cycle may enable cells to make better use of limited nutrients and synthesize more biomacromolecules, such as nucleic acids and protein, to support the rapid proliferation of tumor cells. 2-HG produced by IDH mutation can inhibit the 5-methylcytosine hydroxylase of TET family, resulting in an increase in DNA methylation level. In glioma cells, hypermethylated DNA regions usually contain many tumor suppressor genes (**Figure 3**) [24, 48]. Hypermethylation of these genes will silence their expression and make tumor cells escape normal growth inhibition signals, thus promoting the occurrence and development of tumors. As mentioned earlier, the inhibition of histone demethylase by 2-HG will lead to the change of histone methylation level. In

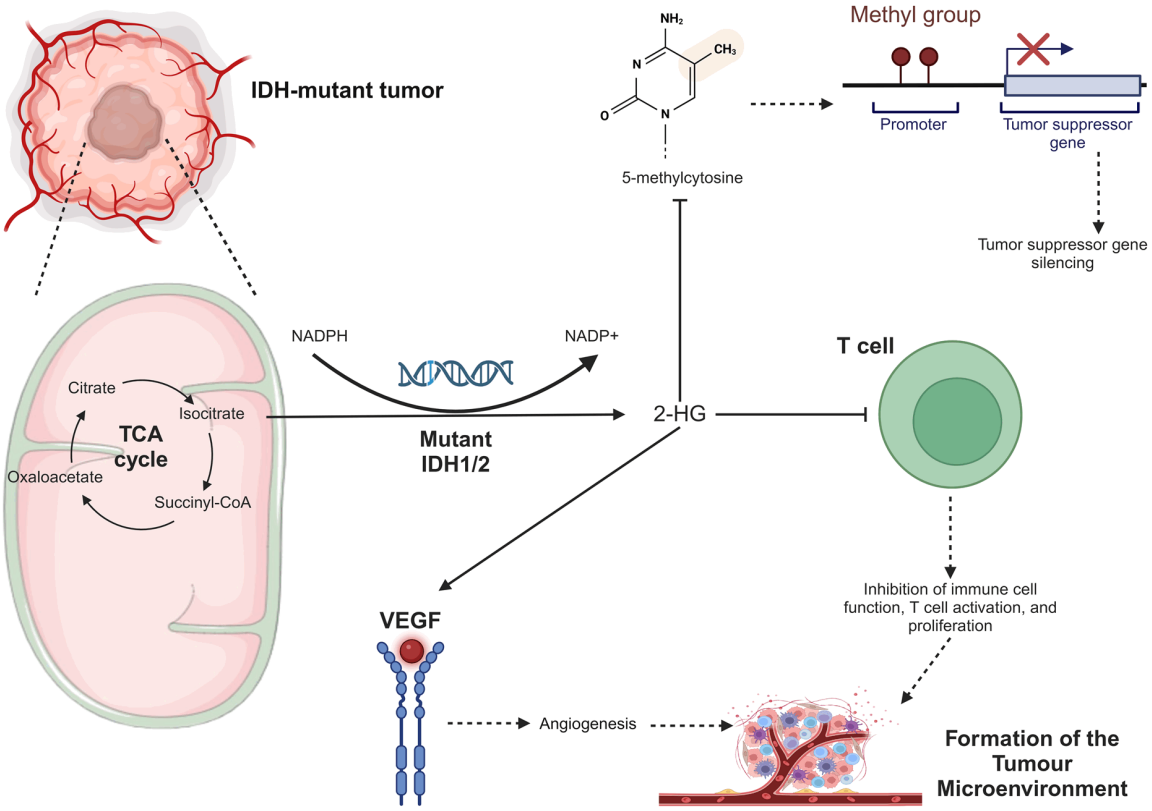

Figure 3. The abnormal accumulation of 2-HG is related to the cancer biology of glioma. IDH mutation leads to the abnormal accumulation of 2-HG, which can inhibit 5-methylcytosine hydroxylase from the TET family, resulting in an increase in DNA methylation levels. In glioma cells, hypermethylated DNA regions typically contain many tumor suppressor genes. The hypermethylation of these genes silences their expression, allowing tumor cells to escape normal growth inhibition signals. In addition, 2-HG can regulate the metabolism of immune cells in the tumor microenvironment, such as the activation and proliferation of T cells. Furthermore, IDH mutant gliomas can promote tumor angiogenesis by secreting certain angiogenic factors, such as VEGF. Ultimately, the abnormal accumulation of 2-HG shapes the tumor microenvironment, thereby promoting tumor initiation and progression.

addition, IDH mutation may also affect the activities of other histone modifying enzymes, such as histone acetylating enzyme and deacetylating enzyme [49]. These changes in histone modification will affect the structure of chromatin and the accessibility of genes, and then regulate the expression of genes. In glioma cells, this disorder of epigenetic regulation can lead to abnormal expression of cell cycle regulation genes and apoptosis-related genes, which is beneficial to the survival and proliferation of tumor cells. IDH mutant glioma can affect immune cells in tumor microenvironment in many ways [50, 51]. On the one hand, the epigenetic changes caused by IDH mutation can affect the expression of surface antigens of tumor cells, so that tumor cells can escape the recognition and attack of the immune system [52, 53]. On the other hand, 2-HG produced by IDH mutation can regulate the metabolism of immune cells in tumor microenvironment [54]. For example, it can inhibit the function of immune cells, such as the activation and proliferation of T cells, and make tumor cells grow and spread more easily in an immunosuppressed environment (**Figure 3**) [55, 56]. IDH mutant glioma can promote tumor angiogenesis by secreting some angiogenic factors. These angiogenic factors can attract endothelial cells to migrate to tumor tissues, and promote the proliferation of endothelial cells and the formation of vascular lumens. The formation of tumor blood vessels can provide more nutrients and oxygen for tumor cells, and also provide a channel for tumor cells to transfer [57, 58]. In IDH mutant glioma, 2-HG may promote angiogenesis by regulating the expression of angiogenesis-

related genes. For example, it may affect the expression and activity of angiogenesis factors such as vascular endothelial growth factor (VEGF), thus playing an important role in tumor angiogenesis (**Figure 3**) [14, 58].

Targeted therapy for metabolic rearrangement pathway

D-2HG blocking therapy: Since IDH mutants are associated with the progression to malignancy of glioma, the most straightforward therapeutic approach now involves directly targeting mutant enzymes. Rohle et al. documented the efficacy of AGI-5198, the first synthesis inhibitor of IDH mutants, can block the production of D-2HG and weaken the formation of IDH1 mutant ectopia in vivo [59]. The FDA has approved the use of second-generation IDH mutation inhibitors, including ivosidenib (AG-120) and vorasidenib (AG-881), as therapeutic options for IDH mutant gliomas. Multiple ongoing clinical trials are evaluating the safety and efficacy of ivosidenib and vorasidenib for the treatment of IDH mutant myeloid malignancies and solid tumors, such as gliomas. Additional IDH mutation inhibitors, like BAY1436032, have demonstrated inhibitory effects on both AML and astrocytoma in animal models [60].

Although IDH mutant inhibitors have achieved great success, certain studies have highlighted potential limitations in the application of these inhibitors. For instance, Johannessen et al. found that the IDH mutation inhibitor AGI-5198 effectively diminished IDH mutations. However, it also triggered hypermethylation. Despite this, patients still exhibited heightened tissue protein-3 methylation, albeit to a minimal extent [61]. Furthermore, Sulkowski and colleagues reported that while AGI-5198 diminishes the burden of DNA damage in cancer cells, it may simultaneously increase cancer cells' resistance to genotoxic treatments such as radiation and chemical agents [62]. Another study confirmed this phenomenon, which showed that AGI-5198 demonstrated radioprotective effects on cancer cells with IDH1 mutations [63]. In general, the direct targeting of IDH mutations represents a promising strategy that has shown effectiveness against human hematopoietic malignancies and various experimental models of solid cancers.

Target essential metabolic enzymes: A large number of reprogrammed cell metabolism in IDH mutant gliomas suggest that specific drug targets may be established for this type of malignant tumor. NAD acts as a crucial cofactor in fundamental biological processes, including electron transport and redox metabolism. It is obtained through both biosynthesis, known as the de novo pathway, and salvage pathways, which involve the utilization of pyridine-containing compounds [64]. In gliomas with IDH mutation, the de novo synthesis of NAD is significantly decreased because nicotinic acid phosphoribosyltransferase (NAPRT1) is silenced. Consequently, cancer cells rely on the salvage pathway for the production of NAD [65]. Disruption in NAD metabolism suggests that IDH mutation-affected cells may be more susceptible to NAMPT-targeting small molecule inhibitors that block the salvage process [66].

Moreover, considering the critical role of glutamine cleavage in metabolic compensation, the metabolism related to glutamine and glutamate has emerged as a potential target in malignant tumors harboring IDH mutations. For instance, inhibiting glutaminase with bis-2-[5-(phenylacetamide)-1,3,4-thiadiazol-2-yl] ethyl sulfide has been demonstrated to suppress glutamine metabolism and impede the progression of IDH1 mutant glioma and AML [67].

According to the screening test, Elhammali found that zaplukast (Zaprinast) has demonstrated the ability to inhibit glutaminase, thereby restricting the growth of IDH mutant tumor cells in vitro [68]. CB-839, a medication administered orally that inhibits glutaminase, demonstrates therapeutic effectiveness in IDH mutated AML by decreasing D-2HG production and facilitating terminal differentiation [69]. Currently, a phase 1 clinical trial is underway to evaluate the concurrent use of CB-839, radiation therapy, and alkylated chemotherapy temozolomide (TMZ) in patients diagnosed with diffuse or anaplastic astrocytomas. These patients specifically harbor IDH mutations (NCT03528642). In summary, inhibition of glutamine/glutamate metabolism is associated with slowing tumor performance in glioma and AML preclinical models. Nevertheless, this strategy often leads to extended incubation periods rather than significant tumor inhibition in vivo. Inhibiting glutamine/glutamate metabolism in conjunction with other cytotoxic treat-

ments like radiation and TMZ may increase the effectiveness of treatment.

Clinical study of targeted therapy of metabolic rearrangement pathways associated with IDH gene mutations: Vorasidenib and ivosidenib inhibit mutant isocitrate dehydrogenase (mIDH) and have shown preliminary clinical activity in mutant IDH gliomas. This study is a perioperative phase 1 clinical trial evaluating the efficacy of vorasidenib and ivosidenib in patients with recurrent low-grade gliomas. The primary endpoint was the change in the concentration of 2-HG in tumor tissue, with results showing that vorasidenib and ivosidenib reduced 2-HG concentrations by 92.6% and 91.1%, respectively. Exploratory analyses indicated that the reduction in 2-HG was associated with DNA methylation, gene expression changes, and decreased tumor cell proliferation. Due to its more consistent 2-HG suppression and better brain penetrance, vorasidenib was selected for phase 3 clinical trials [70]. The follow-up is still ongoing.

In addition, in a double-blind phase 3 clinical trial, the oral IDH1 and IDH2 mutant inhibitor vorasidenib was evaluated in patients with recurrent or residual grade 2 IDH-mutant glioma. The results showed that, compared to the placebo group, vorasidenib significantly improved progression-free survival (27.7 months vs. 11.1 months), with a hazard ratio for disease progression or death of 0.39 ($P<0.001$). Additionally, the time to the next anticancer intervention was significantly prolonged in the vorasidenib group. The incidence of grade 3 or higher adverse events was 22.8% in the vorasidenib group, compared to 13.5% in the placebo group. In the vorasidenib group, 9.6% of patients experienced grade 3 or higher alanine aminotransferase elevation, whereas no patients in the placebo group had this issue [71]. Overall, vorasidenib significantly improved the treatment outcomes for IDH-mutant glioma patients by delaying disease progression and the initiation of subsequent treatments.

In another study evaluating the efficacy and safety of ivosidenib in patients with mIDH advanced gliomas, the results showed that ivosidenib, administered orally at a dose of 500 mg daily, was well tolerated with no dose-limiting toxicities and the maximum tolerated dose was not reached. Among patients with non-enhancing gliomas, 85.7% achieved stable disease, and the median progression-free survival was 13.6 months, significantly longer compared to the 1.4 months observed in patients with enhancing gliomas. Additionally, ivosidenib effectively reduced the volume and growth rate of non-enhancing tumors, indicating its potential to delay disease progression and improve growth control [72].

A clinical trial evaluating the combination of the IDH inhibitor enasidenib and azacitidine versus azacitidine alone in patients with newly diagnosed mutant-IDH2 acute myeloid leukemia (AML) assessed the safety and efficacy of the combination [73]. The results showed that enasidenib combined with azacitidine was well tolerated and significantly improved the overall response rate (74% vs. 36%), demonstrating better efficacy compared to the monotherapy group. Although the combination group experienced more grade 3 or 4 adverse events, no treatment-related deaths were reported. This regimen offers potential for improving treatment outcomes for patients with newly diagnosed mutant-IDH2 acute myeloid leukemia [73].

Various forms of immunotherapy are being explored for the treatment of IDH-mutant glioma patients. Among the most advanced is the IDH-mutant peptide vaccine. IDH1 R132H, a neoantigen expressed universally in all IDH-mutant gliomas but absent in normal tissues, serves as a clonal, tumor-specific vaccine target presented on major histocompatibility complex (MHC) class II molecules [74]. Recently, the results of a phase I trial of the IDH1 R132H vaccine (IDH1-vac) in patients with newly diagnosed WHO grade 3 or 4 IDH-mutant astrocytomas were reported (NCT02454634). The vaccine was well-tolerated and elicited an immune response in 93% of patients [74, 75].

In the combination of IDH inhibitors and immunotherapy, the synergistic treatment of PD-1 inhibitors and IDH1 inhibitors has been shown to reduce tumor volume and prolong survival in mouse glioma models [76]. Recent clinical trials with the anti-PD-1 monoclonal antibody nivolumab have demonstrated good treatment tolerance, with long-lasting responses observed in a subset of patients, supporting further evaluation when combined with IDH inhibitors [77].

Impact of IDH gene mutation on treatment protocols for gliomas of different grades

The evaluation of IDH mutation is primarily applied to diffuse gliomas classified as WHO grade II and above, while WHO grade I gliomas typically do not involve IDH mutations [78, 79]. Based on IDH status, gliomas are categorized into IDH-mutant and IDH-wildtype. Oligodendrogliomas include only IDH-mutant cases with 1p/19q co-deletion as a defining molecular feature. IDH-mutant astrocytomas can be classified as WHO grade II/III or grade IV, with molecular characteristics including ATRX loss, TP53 mutations, and CDKN2A/B deletions, the latter being associated with prognosis in grade II/III cases. IDH-wildtype astrocytomas are typically glioblastomas (WHO grade IV), characterized by molecular features such as chromosome 7 gain/chromosome 10 loss, EGFR amplification, and TERT promoter mutations. This classification, which integrates histopathological and molecular features, facilitates more accurate diagnosis and prediction of glioma biological behavior [78, 79].

Maximal safe microsurgical resection is the standard treatment for IDH-mutant glioma patients, regardless of 1p/19q co-deletion, and has been shown to be associated with improved prognosis [80]. The role of supramaximal resection in IDH-mutant gliomas remains controversial, but a small single-center study on grade 3 IDH-mutant and 1p/19q co-deleted oligodendroglioma patients failed to find an association between the extent of resection and survival [80, 81]. The optimal timing of appropriate targeted therapy in the course of IDH-mutant glioma is crucial, as the importance of IDH mutations in glioma pathogenesis makes them a target for treatment. As mentioned earlier, ivosidenib, in studies involving non-enhancing tumor patients, showed a median progression-free survival (PFS) of 19.4 months for grade II tumors (18 patients) and 23 months for grade 3 gliomas (4 patients; archived data) [80]. These data suggest that some patients with recurrent grade 3 non-enhancing gliomas may benefit from ivosidenib. Another study evaluating the IDH1/2 inhibitor vorasidenib showed, in 29 patients, a median PFS of 3.0 months for grade 2 gliomas (8 patients), 3.7 months for grade 3 gliomas (17 patients), and 1.1 months for grade 4 gliomas (4 patients) [80, 82]. Although these data are limited, they suggest no significant difference in response to vorasidenib between grade II and grade III gliomas.

For the overall treatment regimen, for newly diagnosed IDH-mutant, 1p19q-codeleted adult oligodendrogliomas (WHO grade II and III), radiation therapy (RT) and a combination of procarbazine, lomustine, and vincristine (PCV) should be offered [79, 83]. For newly diagnosed IDH-mutant, 1p19q non-codeleted adult astrocytomas (WHO grade II), RT with adjuvant chemotherapy (TMZ or PCV) should be offered. For IDH-mutant, 1p19q non-codeleted adult astrocytomas (WHO grade III), RT with adjuvant TMZ should be offered [83]. For IDH-mutant adult astrocytomas (WHO grade IV), treatment recommendations may follow those for either IDH-mutant, 1p19q non-codeleted CNS WHO grade III astrocytomas or IDH-wildtype, CNS WHO grade IV glioblastomas. For newly diagnosed IDH-wildtype glioblastoma (WHO grade IV), concurrent TMZ and RT should be offered, followed by 6 months of adjuvant TMZ therapy [79, 83].

Last but not least, several other molecular alterations are known to occur in IDH-mutant gliomas, such as amplifications of CDK4, PDGFRA, MET, and MYCN, homozygous deletions of RB1, deletions of 14q, mutations in PIK3R1 or PIK3CA, and higher global copy number variation burden. Determining the potential individual prognostic impact of these features is complex, as many of these alterations occur concurrently [84, 85]. Their prognostic value remains unclear, and currently, these changes are not associated with WHO grading, requiring further investigation.

IDH-induced gene rearrangement and treatment

Gene rearrangement

In addition to inducing metabolic alterations, numerous clinical studies have demonstrated a close association between IDH mutations and hypermethylation of CpG islands. Glioma G-CIMP has actually been identified as a unique indicator of solid tumors with IDH mutations [86, 87]. Research has indicated that the altered activity of the new form of IDH1 mutation results in extensive methylation of histones and DNA. Intriguingly, the kind of tumor determines the amount and particular targets

of hypermethylation [88]. Exploring the distinctive pattern of methylation specific to gliomas could provide valuable insights into the pathogenesis of IDH mutant gliomas.

Methyltransferases and demethylases both control DNA methylation. During demethylation, TET enzymes play a crucial role. These enzymes act at specific sites, facilitating the conversion of 5-mC to 5-hmC through a process that relies on iron and α-KG. Moreover, TET enzymes promote further demethylation steps by converting 5-hmC into 5-formylcytosine and 5-caC. Ultimately, 5-caC will be repaired and changed into cytosine via mechanisms of base excision repair and thymine DNA glycosylase [89]. Because of its structural similarity to α-KG, D-2HG inhibits TET activity. Furthermore, α-KG is essential for the demethylase activity of TET enzymes [90, 91]. It was demonstrated in 2012 by two different study teams that IDH mutations linked to cancer were sufficient to cause hypermethylation symptoms (**Figure 2**) [92, 93]. While DNA methylation is commonly viewed as a reversible process, subsequent research has revealed that certain DNA methylation sites may persist even after the mutant enzyme is deactivated in IDH-mutated cells. This suggests that IDH mutations play a crucial role in malignant transformation. Once cellular transformation occurs, it may become an irreversible process [94].

In addition to affecting DNA methylation, D-2HG also promotes histone methylation by suppressing histone demethylases like lysine-specific demethylase (KDM) [90, 95]. Histone methyltransferases (including G9a, GLP, SET, and EZH2) and demethylases (such KDM, LSD, and JARID) control the amount of methylation in histones. In addition to TET enzymes, elevated D-2HG levels inhibit histone demethylases, such as KDM4 and KDM5 (**Figure 2**) [95]. Consequently, in IDH-mutated cancers, there is often an accumulation of histone methylation markers such as histone H3 lysine 4 trimethylation (H3K4me3), trimethylation of histone H3 lysine 9 (H3K9me3), and histone H3 lysine 27 trimethylation (H3K27me3). D-2HG impedes histone demethylation, resulting in compromised cell differentiation, which may contribute to the onset of IDH mutant cancers [96, 97].

Targeted therapy strategy of gene rearrangement

Gene rearrangement regulator: IDH mutation induces a variety of hypermethylation, resulting in genetic changes in tumor cells. Moreover, hypermethylation may be associated with oncogene activation. Therefore, correcting gene rearrangement is considered to be a potential therapeutic strategy for cancer expressing IDH mutants [64, 66, 98]. Flavahan et al. identified that G-CIMP spectrum is related to cohesion and hypermethylation of CCCTC binding factor (CTCF) binding site, this reduces the affinity of the protein [99]. The absence of CTCF binding allows enhancers to promote the continuous expression of platelet-derived growth factor receptor A (PDGFRA), a known mitogen associated with glioma. Partially restoring CTCF binding through demethylating agents can decrease the expression of PDGFRA. Another study provided additional evidence for the effectiveness of methylation inhibition, showing that decitabine, an inhibitor of DNA methyltransferase (DNMT1), hinders the growth of IDH mutant glioma cells both in vivo and vitro [100]. Likewise, 5-azacytidine, a cytidine analogue recognized for its ability to interfere with the function of DNA methyltransferase, demonstrates the capacity to shrink patient-derived IDH1 mutant gliomas [1]. However, although gene rearrangement regulators may be sufficient to reverse IDH-related hypermethylation. It is currently unknown how these therapies may affect other cancer characteristics in IDH mutant tumors, such as metabolic changes and DNA repair mechanisms.

Targeted DNA repair enzyme: Compared with wild-type gliomas, gliomas with IDH mutation showed a better trend of disease development. Several studies have indicated that gliomas harboring mutant IDH appear to exhibit heightened sensitivity to treatments such as radiotherapy and chemotherapy [101-103]. Mechanistically, D-2HG interferes with the DNA repair pathway by functioning as an inhibitor of DNA repair enzymes such as AlkB homologue 2 and 3 (ALKBH2/3) [104, 105], and by obstructing the process of homologous recombination (HR) DNA repair (**Figure 2**) [106]. Because of the suppression of the overall DNA repair pathway, directly inhibiting residual DNA repair

enzymes could be harmful to IDH mutant cells, presenting a potential therapeutic method. Recent findings propose that combining small molecule inhibitors targeting poly ADP ribose polymerase (PARP) may serve as an effective treatment strategy for IDH mutant malignant tumors.

Because of the inhibition of the HR pathway, IDH mutant cells display pronounced DNA repair deficiencies, akin to those commonly observed in BRCA mutant cancers - a phenomenon often referred to as "BRCAness" [106-108]. PARP inhibitors can exploit synthetic lethality in the presence of HR defects arising from IDH mutations, leading to elevated apoptosis. Likewise, Tateishi et al. [109] found that the depletion of NAD+ by nicotinamide phosphoribosyltransferase (NAMPT) inhibitors such as FK866 and GMX1778 results in the cessation of PARP DNA repair activity. This is due to the fact that PARP relies on NAD+ during DNA damage repair induced by chemotherapy. Consequently, this disruption triggers various metabolic stress responses to chemotherapy-induced DNA damage, thus prolonging the durability of treatment response. Despite the correlation between the presence of IDH mutations and increased treatment sensitivity in patients, and the apparent efficacy of targeting DNA repair enzymes for IDH-mutated cells, several studies have suggested that IDH-mutated gliomas may experience changes in DNA repair pathways that differ from those observed in IDH wild-type gliomas. For example, RAD51 recombinase, a critical enzyme in the homologous recombination (HR) pathway, confers protection to IDH mutant cells against DNA damage induced by TMZ. Nunez and colleagues highlighted that depleting TP53 or ATRX in the context of IDH mutation results in glioma cells experiencing DNA damage, as evidenced by the upregulation of the ataxia telangiectasia mutant gene (ATM) signal, leading to resistance to radiotherapy.

Redox imbalance caused by IDH mutation and treatment

Redox imbalance

Increased reactive oxygen species (ROS) level is a marker of IDH mutation in malignant tumor [110]. A study using imaging techniques uncovered alterations in the levels of glutamine, glutathione, and glutamate in the tumor region of IDH mutant glioma patients were lower compared to those in the contralateral area [111]. In addition, tumor glutathione levels were negatively correlated with D-2HG levels, indicating that glutathione is essential for maintaining redox homogenization in IDH mutant cells. Elevated glutathione consumption suggests a heightened demand for scavenging ROS in IDH mutant cells [112]. The production of ROS is intricately associated with fundamental parts of cancer biology, such as genomic instability, uncontrolled proliferation, cell motility, and invasiveness. Excessive ROS levels can be detrimental to biomolecules, resulting in oxidative damage to DNA, lipids, and proteins (**Figure 4**) [113, 114].

Cancer cells often hijack signaling pathways that are responsive to ROS levels, allowing them to proliferate uncontrollably. ROS can influence cell signaling pathways related to cytoskeletal dynamics, thereby enhancing the ability of cancer cells to migrate and invade adjacent tissues. The Role of Antioxidants and Scavenging Mechanisms. The increased demand for scavenging ROS in IDH mutant cells is evidenced by elevated consumption of glutathione. His heightened usage underscores how IDH mutant gliomas may be employing antioxidant defense mechanisms to counteract oxidative damage. However, if antioxidants such as glutathione are depleted or ineffective, cells may face increased oxidative stress which could promote cell death or senescence, or alternatively, enhance the acquisition of additional mutations. Hence, the relationship between increased ROS levels and IDH mutations in malignant tumors like gliomas is a critical aspect of tumor biology. The intricate balance between ROS generation, antioxidant defenses, and metabolic alterations can have profound implications for glioma progression, treatment response, and patient outcomes. Understanding these dynamics opens avenues for therapeutic strategies that target metabolic vulnerabilities in IDH mutant tumors, potentially improving the efficacy of interventions aimed at managing this aggressive form of cancer.

Targeted redox homogeneity

It is key to maintain an appropriate level of ROS during tumorigenesis and treatment [113].

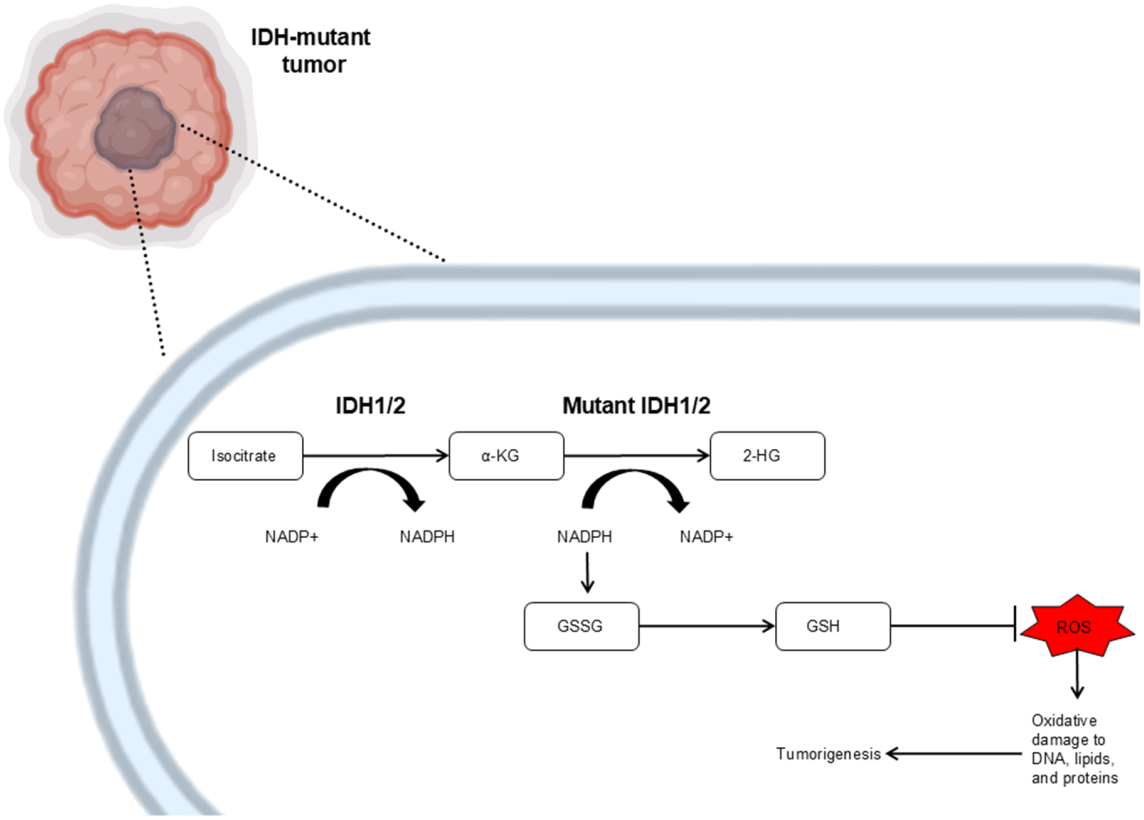

Figure 4. The buildup of oxidative damage stands as a hallmark of IDH mutant cancer biology. Glutathione reductase uses NADPH to reduce oxidized glutathione (GSSG) to glutathione (GSH). Cellular NADPH consumption destroys the reduction equivalent of biosynthesis; thus, these disruptions can interfere with crucial ROS scavenging mechanisms, ultimately resulting in the accumulation of ROS. Excessive ROS levels can be detrimental to biomolecules, resulting in oxidative damage to DNA, lipids, and proteins.

Cancer-related IDH mutations increased NADPH (reduced nicotinamide adenine dinucleotide phosphate) (Km = 0.44 μM) and α-KG (Km = 965 μM). Cellular NADPH consumption destroys the reduction equivalent of biosynthesis, thus these disruptions can interfere with crucial ROS scavenging mechanisms, such as the reduction of glutathione disulfide, ultimately resulting in the accumulation of ROS [114, 115]. Hence, the buildup of oxidative damage stands as a hallmark of IDH mutant cancer biology [115, 116]. These disruptions can impede essential mechanisms for scavenging ROS, such as by impeding ROS clearance through glutathione-derived mechanisms, represents a promising direction for treatment [116]. According to preclinical research conducted on animals, IDH mutant gliomas are more sensitive to radiation therapy because the glutaminase inhibitor CB-839 disturbs the redox equilibrium by preventing glutamine metabolism [117]. In Tang's study, the inhibition of nuclear factor erythrocyte 2 related factors-2 (Nrf2) by the natural compound brustato led to significant tumor suppression and pronounced oxidative damage in IDH1 mutant xenografts [118]. Although in these cases, the destruction of redox homogeneity leads to strong cytotoxicity accompanied by tumor inhibition, most current therapeutic compounds are still in the preclinical phase and exhibit significant systemic toxicity. However, the development of potent and selective next-generation therapeutic compounds will help target the redox imbalance in IDH mutant malignancies.

Due to the activation of the Telomerase Reverse Transcriptase (TERT) promoter by the IDH mutation, c-Myc/Max is recruited to the promoter and histone lysine methylation increases [107]. Numerous investigations have observed a connection between prognosis in gliomas

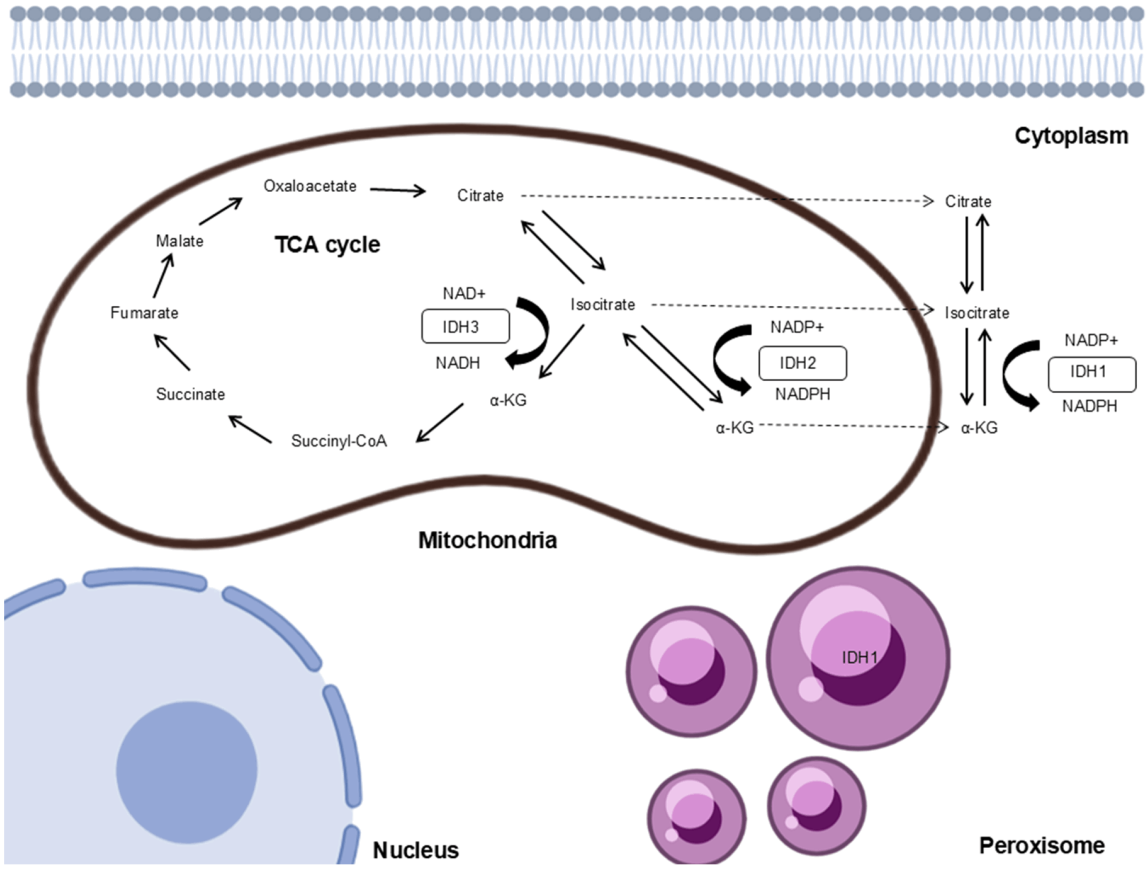

Figure 5. IDH subtypes and functions. IDH includes three subtypes: IDH1, IDH2 and IDH3. IDH1 and IDH2 utilize NADP+ as a cofactor, generating NADPH, while IDH3 uses NAD+ as a cofactor, producing NADH. IDH1 is primarily situated in the cytoplasm and peroxisomes, whereas IDH2 and IDH3 are mainly located in the mitochondria. IDH1 is mainly localized in the cytoplasm and peroxisomes, whereas IDH2 and IDH3 are primarily found in the mitochondria.

and mutations in the TERT promoter [107-109, 119]. Pekmezci et al. demonstrated that out of 291 grade II or III oligodendrogliomas with IDH mutation and 1p/19q codeletion, 94% of patients solely had TERT promoter mutations, 0.69% exhibited only ATRX mutations, 1.7% harbored both TERT promoter and ATRX mutations, and 4% had no mutations in either TERT promoter or ATRX [109]. The overall survival (OS) of the group with TERT promoter mutations was significantly better compared to the group without TERT promoter mutations [109].

2% of the 154 patients with IDH wild-type astrocytoma had mutations in both the TERT promoter and ATRX, whereas 60% of the patients only had mutations in the TERT promoter. In comparison to the TERT promoter wild-type group, the TERT promoter mutation group demonstrated significantly poorer overall survival (OS) [109]. Akyerli et al. classified hemisphere-diffuse gliomas according to the mutation status of IDH and TERT promoters: the promoters for TERT and IDH are both mutants, the promoter for TERT is the only one mutated, or none of the promoters is mutated. There were distinct demographic, anatomical, clinical, and prognostic associations for each group [120]. Over time, the tumor's status regarding the TERT promoter mutation either remained stable or recurred [120].

NADP+ is used as a cofactor by IDH1 and IDH2 to produce NADPH, and by IDH3 to produce NADH. IDH1 is mainly localized in the cytoplasm and peroxisomes, whereas IDH2 and IDH3 are primarily found in the mitochondria. Within glial cells, IDH participates in regulating glutamine and glutamate metabolism, as well as the synthesis of N-acetylated amino acids (**Figure 5**).

Furthermore, IDH enzymes play a crucial role in protecting cells and orchestrating their responses to oxidative and energetic stress.

NADPH is crucial for replenishing the antioxidant glutathione, while α-KG serves as an antioxidant in its own right. A recent study conducted on HT-22 neurons revealed that subjecting them to an energy challenge by substituting glucose with galactose led to heightened expression of IDH enzymes and halted proliferation. Interestingly, inducing oxidative stress via glutathione depletion did not affect the expression of IDH. Collectively, these discoveries propose that under moderate oxidative stress conditions, there's a tendency for increased production of NADPH and α-KG facilitated by IDH. However, during severe oxidative stress, the activity of IDH may remain stable or even diminish, possibly to mitigate the continued generation of oxygen free radicals. This alteration abolishes the "forward" catalytic function of IDH, which involves converting isocitrate into α-KG. Simultaneously, it restricts the "reverse" catalytic function to a partial reaction wherein α-KG is reduced but not carboxylated. As a result, cells with IDH mutations experience a decrease in α-KG and NADPH levels, which disrupts vital cellular functions dependent on these compounds. Mutant IDH1 generates the enantiomer D-2-HG, whereas the tumor-associated IDH2 mutation produces the enantiomer R-2-HG. Presently, it remains uncertain whether this structural disparity influences functionality. Both D-2-HG and R-2-HG are recognized as tumor metabolites in gliomas and leukemia cells.

Conclusion and future prospect

The mutation of IDH is obviously related to the occurrence of human malignant tumor. Several groundbreaking studies have unveiled the impacts of IDH mutants and D-2HG on cell physiology, including metabolic reprogramming, alterations in the epigenome, and homogenization of redox processes. As disease models in vitro and in vivo become increasingly accessible, it is anticipated that further breakthroughs will elucidate the pivotal pathways involved in tumorigenesis, tumor metabolism, and therapeutic vulnerabilities. As disease models become increasingly available both in laboratory settings and in living organisms, it is anticipated that additional breakthroughs will shed light on the crucial pathways implicated in tumorigenesis, tumor metabolism, and therapeutic susceptibilities. IDH is emerging as a significant factor in the development of various human malignant tumors, particularly gliomas and AML. These mutations result in the aberrant production of D-2HG, a metabolite that has profound implications for cellular physiology and tumor dynamics. Firstly, impact of IDH mutations and D-2HG on cell physiology is metabolic reprogramming. IDH mutations lead to altered metabolic pathways, shifting cellular energy production and biosynthetic processes such as inhibiting the branched-chain amino acid aminotransferase which causes the patient's glutamate level was severely reduced. D-2HG acts as an oncometabolite, which means it contributes to cancer progression. Elevated levels of D-2HG can inhibit α-ketoglutarate-dependent dioxygenases, disrupting normal cellular metabolism and promoting tumorigenic adaptations. Secondly, IDH mutations influence histone and DNA methylation patterns. What is more, the accumulation of D-2HG inhibits the activity of key enzymes involved in demethylation processes, resulting in increased levels of histone methylation. This can lead to oncogene activation or tumor suppressor gene silencing, creating an environment conducive to uncontrolled cell growth. Thirdly, the balance of ROS influenced by these metabolic changes can also affect immune responses, evading detection and destruction by the immune system. As research progresses, the development and refinement of more sophisticated in vitro and in vivo disease models are expected to enhance our understanding of the precise mechanisms by which IDH mutations promote tumorigenesis and affect tumor metabolism. By understanding the molecular underpinnings of IDH mutations, there is potential for better stratification of patients for targeted therapies, enhancing the clinical outcomes through personalized medicine approaches. In summary, the connection between IDH mutations and the occurrence of human malignant tumors underscores a complex interplay of metabolic reprogramming, epigenetic modifications, and redox equilibria. Continued advancements in research methodologies and disease modeling will likely unveil new therapeutic strategies and provide deeper insights into the biology of these aggressive cancers, paving the way for improved treatment outcomes for affected patients. The last but not least, this article describes many potential therapeutic targets developed based on the

unique metabolic and epigenetic characteristics of IDH mutant tumors. The role of and D-2HG provides targets for drug development, resulting in new therapeutic strategies that specifically destroy the metabolic advantages given by these mutations.

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Address correspondence to: Maohua Zheng, The First Hospital of Lanzhou University, No. 1, Donggang West Road, Chengguan District, Lanzhou 730000, Gansu, China. E-mail: 620200701891@lzu.edu.cn

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