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REVIEW ARTICLE

# Molecular mechanisms involved in gliomagenesis

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**Abstract** The application of molecular parameters in the World Health Organization classification of central nervous system tumors has advanced remarkably in this field. Large-scale genomic DNA analyses, including gene expression profiling, genome-wide association studies, and single-nucleotide polymorphism analysis, have revealed differences between tumors with the same pathological features. Because mutated genes and their signaling pathways can be targets for therapy, categorizing tumors by molecular parameters facilitates the selection of optimal therapeutic methods. Many genes are either oncogenes or tumor suppressor genes, and many of them are also involved in normal development, such as neural stem cell maintenance and neural differentiation. Moreover, genetic engineering has enabled the generation of tumors that phenocopy human tumors in mice. Here, I will discuss key molecular parameters, mechanisms of neural differentiation, isocitrate dehydrogenases, 1p36/19q13, and p53 in gliomagenesis. Because future therapeutic methods will be determined by the molecular mechanisms of tumors, identification of new parameters is still needed for further classification of glioma.

**Keywords** Glial development · Glioma · IDHs · 1p36/19q13 · P53

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## Introduction

The main change in the 2016 World Health Organization (WHO) classification of central nervous system (CNS) tumors is the use of molecular parameters for diagnosis [1]. This change is a significant advance, because genome-wide gene expression analyses of CNS tumors have revealed that tumors diagnosed in the same group (e.g., glioblastoma; GBM) have different gene expression profiles, which were recently categorized as classical, neural, pro-neural, and mesenchymal types [2]. In addition, therapeutic targets are largely dependent on the molecular mechanisms of tumors. Therefore, classification of CNS tumors by molecular parameters is appropriate.

The development of glioma involves many factors. Three signaling pathways, namely, p53, retinoblastoma (RB), and receptor tyrosine kinase (RTK), play crucial roles in GBM development [3, 4]. Mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2), which reduce their enzymatic activities, have been the center of attention in gliomagenesis, because patients with IDH mutations have a better outcome than those with wild-type IDHs [5, 6]. Chromosomes 1p36 and 19q13 are frequently deleted in oligodendroglioma, although the genes encoded in these chromosomes have not been identified yet [7–9]. It has been further demonstrated that factors, which regulate stem cell maintenance and inhibit differentiation, are aberrantly activated in glioma [10–14]. These factors are not only diagnostic markers and therapeutic targets, but can also be used to establish glioma models with the pathological features of human tumors [2–15].

Based on these findings, I will summarize how these factors are involved in gliomagenesis and discuss future insights for glioma therapy.

## Molecular mechanisms of glial differentiation

Neural stem cells (NSCs) self-renew and give rise to neurons, astrocytes, and oligodendrocytes [10, 11]. Many extrinsic and intrinsic factors have been demonstrated to regulate NSC self-renewal and differentiation in rodent systems (Fig. 1). Basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF) are used to maintain NSCs in culture [16, 17]. Sox2, Bmi1, Hairy-and-enhancer-split (Hes), and Inhibitor-of-differentiation (Id) are involved in NSC maintenance by preventing the functions of basic helix-loop-helix (bHLH)-type differentiation inducers, such as Mash1 and neurogenin, and the cell cycle inhibitor Ink4a/ARF [18–21].

Bone morphogenic proteins (BMPs) and leukemia inhibitory factor (LIF)/ciliary neurotrophic factor (CNTF) induce astrocytic differentiation through activation of Smads and STAT3 transcription factors, respectively [22, 23], whereas BMPs block neuronal and oligodendrocyte differentiation by induction of Ids [24, 25]. Many other factors also play dual functions in a similar manner. Notch signaling maintains NSCs and induces astrocytiv differentiation, but it blocks neuronal and oligodendrocyte differentiation by induction of Hes transcription factors. Oligodendrocyte lineage transcription factor (Olig) 2, which is induced by hedgehog (Hh)-Gli signaling, is not only involved in oligodendrocyte differentiation by forming a heterodimer with the homeobox transcription factor Nkx2.2, but also prevents astrocytic differentiation by blocking STAT3-p300 histone acetyltransferase association [26]. In addition, both Wnt and Hh promote oligodendrocyte differentiation and NSC self-renewal. Oligodendrocyte differentiation is also regulated by platelet-derived growth factor AA (PDGFAA), thyroid hormone (TH), and retinoic acid (RA) [27–34]. Fyn kinase regulates oligodendrocyte morphology through activation of the integrin α6/β1 complex [35]. Although many factors have been identified to exclusively regulate NSC maintenance and glial differentiation, it remains to evaluate whether the same factors regulate human NSC maintenance and their differentiation.

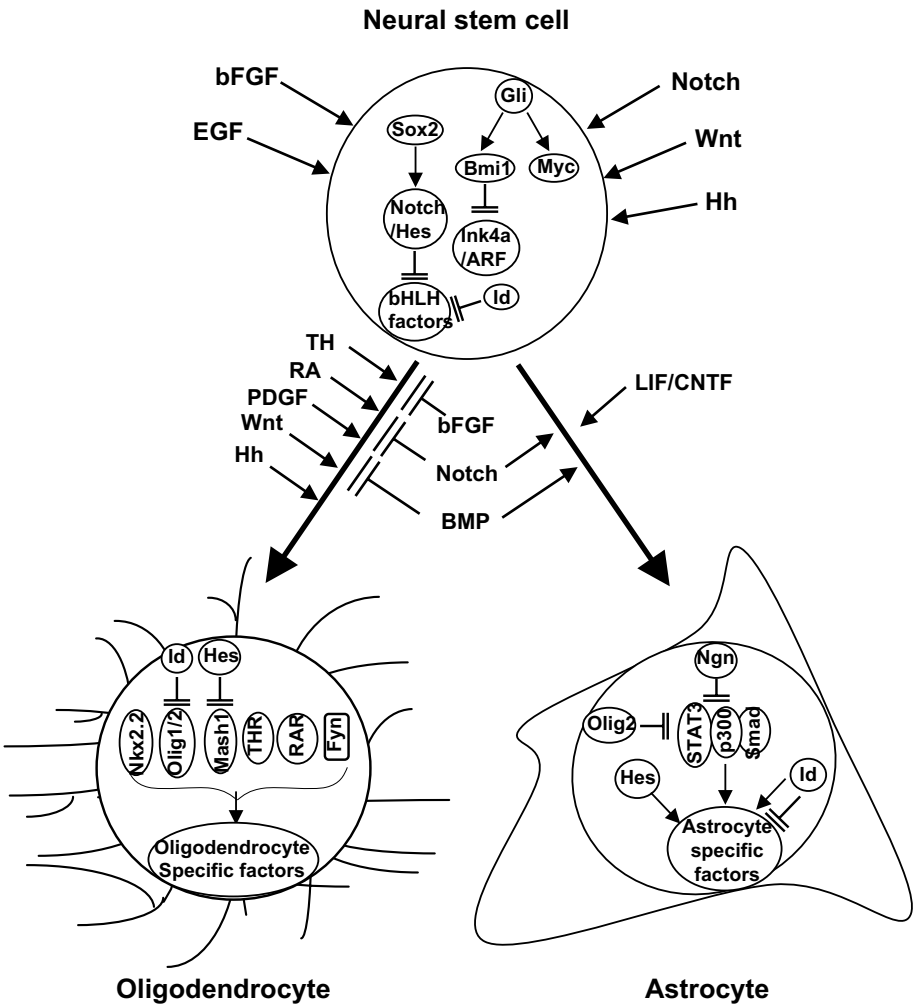



**Fig. 1** Intrinsic and extracellular factors involved in glial differentiation. Extracellular and intrinsic factors regulate maintenance of neural stem cells and their differentiation into oligodendrocytes and astrocytes

## Functions of IDHs and their mutants

Whole genome sequences of human GBMs have revealed IDH1 and IDH2 mutations at amino acid residues 132 (mainly arginine to histidine) and 172 (arginine to lysine, methionine, or glycine), respectively [5, 6]. Surprisingly, IDH1 mutations have been found in more than 70% of low-grade astrocytoma and oligodendroglioma [6]. Over 80% of secondary GBMs also contain the same mutation, whereas less than 5% of primary GBMs contain the mutation [5]. In addition, the Cancer Genome Atlas has shown that the average ages of GBM patients with wild-type or mutant IDH1 are 53.3 and 33.2 years, respectively [6]. Taken together, these data suggest that IDH1 is primarily mutated in gliomagenesis.

Wild-type IDH1 converts isocitrate to α-ketoglutarate (α-KG) by oxidation of nicotinamide adenine dinucleotide phosphate (NADP+) to NADPH, whereas mutant IDH1 catalyzes reduction of α-KG to 2-hydroxyglutarate (2-HG), which is called an oncometabolite, with production of NADP+ from NADPH (Fig. 2) [36]. Moreover, 2-HG promotes tumorigenesis through multiple mechanisms. First, 2-HG competitively inhibits the activity of α-KG-dependent Jumonji C domain containing histone demethylases (JHDMs), thereby maintaining the repressive histone methylation of certain chromosomal domains, such as trimethylation of H3K9 and H3K27, and blocking cell differentiation [37]. Second, 2-HG blocks α-KG-dependent prolyl hydroxylase (PHD) activity, which induces degradation of hypoxia-inducible factor 1α (HIF1α) through the proteasome pathway, and promotes activation of HIF1α downstream factors including nuclear factor-κB (NF-κB) [38]. Third, 2-HG blocks mature collagen formation by α-KG-dependent PHD activity [39]. Because precise collagen formation is essential for the proper function of various types of tissues and cytoplasmic apparatus, abnormal collagen, such as misfolding, might contribute to tumorigenesis by induction of necrosis and tumor angiogenesis. Finally, decreased levels of NADPH by mutant IDHs prevent the conversion of glutathione disulfide to glutathione, a major antioxidant, causing an increase of reactive oxygen species that induce DNA damage and genetic instability [40]. Thus, mutant IDH1 likely prepares tumorigenesis in multiple manners.

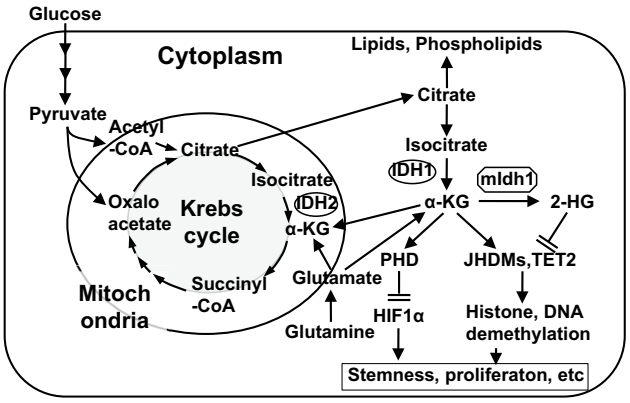


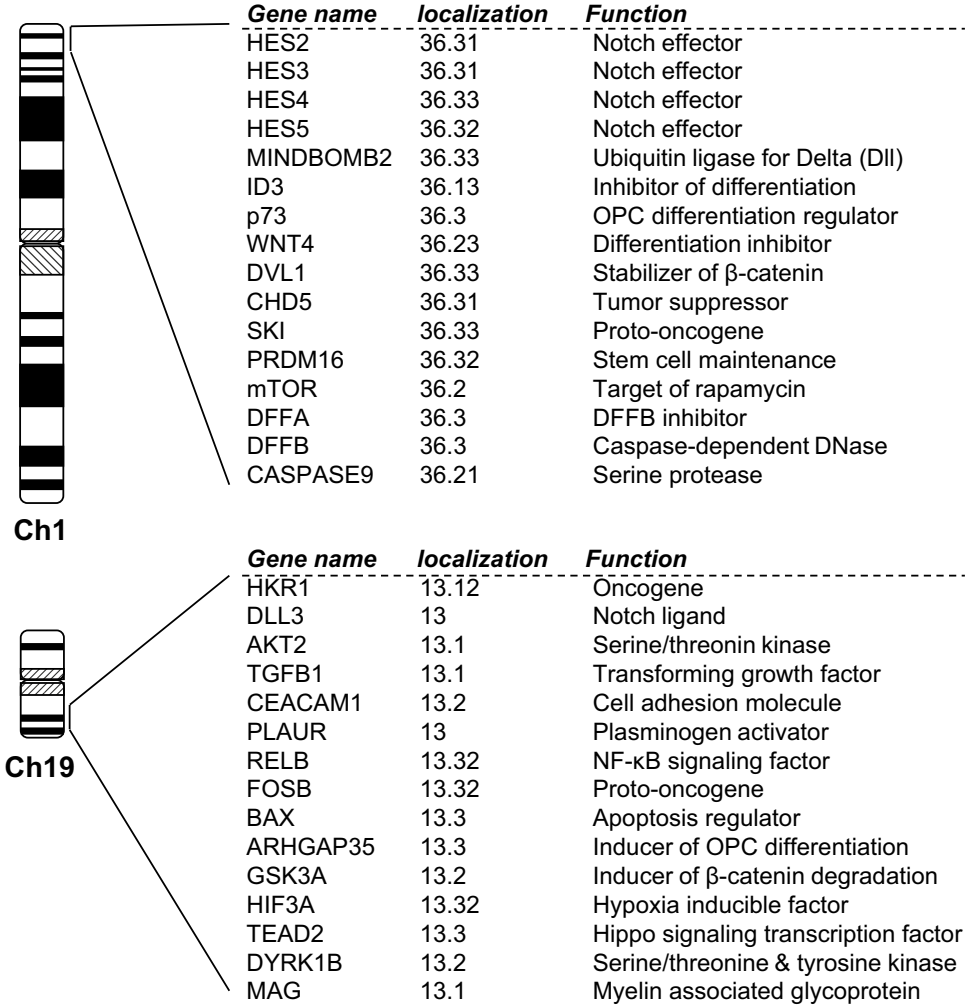

**Fig. 2** Metabolic regulation in mutant IDH-bearing cancer cells. Mutant IDH1 converts α-ketoglutarate (α-KG), which activates Jumonji-C domain histone demethylases (JHDMs) and TET DNA demethylase 2 (TET2), to 2-hydroxyglutarate (2-HG). In turn, 2-HG not only competes with α-KG for JHDM binding, but also inhibits demethylases. Reduction of α-KG suppresses the Krebs cycle and increases HIF1α expression. Eventually, these events induce the expression of stemness- and cancer-related genes

## Genes encoded on human 1p36 and 19q13

Chromosomes 1p36 and 19q13 are frequently deleted in oligodendroglioma, thereby making this co-deletion a surrogate marker. Whole genome sequence analysis has revealed that these chromosomal regions contain many important genes involved in tumorigenesis and oligodendrocyte differentiation, including Notch-related factors (HES2-5, MINDBOMB2, and DLL3), WNT factors (WNT4, DVL1, and GSK3A), oncogenes/proto-oncogenes/tumor suppressors (p73, CHD5, SKI, HKR1, AKT2, TGFB1, ARHGAP35, and FOSB), apoptosis-related factors (DFFA, DFFB, CASPASE9, and BAX), and cancer-related factors [mTOR (mammalian target of Rapamycin), CEACAM1, PLAUR, RELB, and DYRK1B] (Fig. 3). The fact that 1p36 encodes important apoptosis regulators DFFA, DFFB, and CASPASE 9 suggests that oligodendroglioma cells with 1p36 loss may not exhibit typical apoptotic phenotypes in their death.

Among these genes, p73 and Arhgap35 (also known as p190RhoGAP) are involved in oligodendrocyte differentiation. Overexpression of a dominant negative form of p73 inhibits differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes in culture [41]. Phosphorylated Arhgap35 by Fyn kinase induces morphological changes in differentiating oligodendrocytes [42], whereas its overexpression induces cell cycle arrest and enhances process extension [43]. In addition, Arhgap35 is involved in cell motility and metastasis [44]. These findings suggest that co-deletion of 1p36 and 19q13 might maintain OPCs in the undifferentiated state, although it is unknown why co-deletion is specific to oligodendroglioma.

Bagchi et al. identified chromodomain helicase DNA binding domain 5 (CHD5) encoded on 1p36 and demonstrated that CHD5 controls cell proliferation, apoptosis, and senescence through the cyclin-dependent kinase inhibitor (CDKI) p14ARF-p53 pathway, thereby identifying CHD5 as a new tumor suppressor gene [45]. This finding indicates that p53 functions should decrease in oligodendroglioma




| Gene name | localization | Function |
|---|---|---|
| HES2 | 36.31 | Notch effector |
| HES3 | 36.31 | Notch effector |
| HES4 | 36.33 | Notch effector |
| HES5 | 36.32 | Notch effector |
| MINDBOMB2 | 36.33 | Ubiquitin ligase for Delta (Dll) |
| ID3 | 36.13 | Inhibitor of differentiation |
| p73 | 36.3 | OPC differentiation regulator |
| WNT4 | 36.23 | Differentiation inhibitor |
| DVL1 | 36.33 | Stabilizer of β-catenin |
| CHD5 | 36.31 | Tumor suppressor |
| SKI | 36.33 | Proto-oncogene |
| PRDM16 | 36.32 | Stem cell maintenance |
| mTOR | 36.2 | Target of rapamycin |
| DFFA | 36.3 | DFFB inhibitor |
| DFFB | 36.3 | Caspase-dependent DNase |
| CASPASE9 | 36.21 | Serine protease |

| Gene name | localization | Function |
|---|---|---|
| HKR1 | 13.12 | Oncogene |
| DLL3 | 13 | Notch ligand |
| AKT2 | 13.1 | Serine/threonin kinase |
| TGFB1 | 13.1 | Transforming growth factor |
| CEACAM1 | 13.2 | Cell adhesion molecule |
| PLAUR | 13 | Plasminogen activator |
| RELB | 13.32 | NF-κB signaling factor |
| FOSB | 13.32 | Proto-oncogene |
| BAX | 13.3 | Apoptosis regulator |
| ARHGAP35 | 13.3 | Inducer of OPC differentiation |
| GSK3A | 13.2 | Inducer of β-catenin degradation |
| HIF3A | 13.32 | Hypoxia inducible factor |
| TEAD2 | 13.3 | Hippo signaling transcription factor |
| DYRK1B | 13.2 | Serine/threonine & tyrosine kinase |
| MAG | 13.1 | Myelin associated glycoprotein |

**Fig. 3** Characteristic genes encoded on human 1p and 19q chromosome loci. Both 1p36 and 19q13 loci encode many differentiation inhibitors, oncogenes/proto-oncogenes, and apoptosis-related genes. Of note, tumor suppressor CHD5, which activates p53 through ARF, is mapped on 1p36.31

with 1p36 loss, although 1p36 loss and p53 mutation are exclusive in glioma.

It is notable that 1p36 and 19q13 encode many differentiation inhibitors and oncogenes/proto-oncogenes. Among them, both AKT2 and mTOR are key effectors in gliomagenesis in multiple mechanisms [46, 47]. CEACAM1, the plasminogen activator system, and non-canonical NF-κB pathway also play crucial roles in GBM-initiating cells [48–50]. These findings might explain the reason why 1p36 and 19q13-co-deleted oligodendrogliomas are susceptible to therapy.

## p53 regulates multiple functions

p53 was originally found as an essential tumor suppressor preventing cell cycle progression and inducing apoptosis [51]. External and internal stress signals, including DNA damage, oncogene activation, hypoxia, and nutrient stress, induce p53 expression at transcriptional and post-transcriptional levels and regulate its activation through various kinds of modification, including phosphorylation, ubiquitination, acetylation, methylation, glycosylation, sumoylation, and ADP ribosylation (Fig. 4) [52, 53]. It is well known that ubiquitination of p53 by mouse double minute gene 2 (Mdm2) induces its degradation via a proteasome pathway, whereas phosphorylation at the N-terminal blocks the interaction of p53 with Mdm2 and induces cell cycle arrest and senescence by increasing Cdki p21/Cip1 and plasminogen activator inhibitor 1 (Pai1) [54]. Acetylation of p53 at lysine 120 activates p21/Cip1 expression by binding with monocytic and promyelocytic leukemia zinc finger proteins or triggers cell death by inducing p53-upregulated modulator of apoptosis (Puma) and cofactors in a cell context-dependent manner [55]. In addition, p53 induces the expression of other apoptosis-related factors, such as Bcl2-associated X protein (Bax), Noxa, Fas, death receptor (DR) 4 and DR5.

It is evident that p53 supports the oxidative phosphorylation pathway and blocks glycolysis at multiple steps. For example, p53 inhibits expression of glucose transporters Glut1 and 4, glycolytic enzyme phosphoglycerate mutase

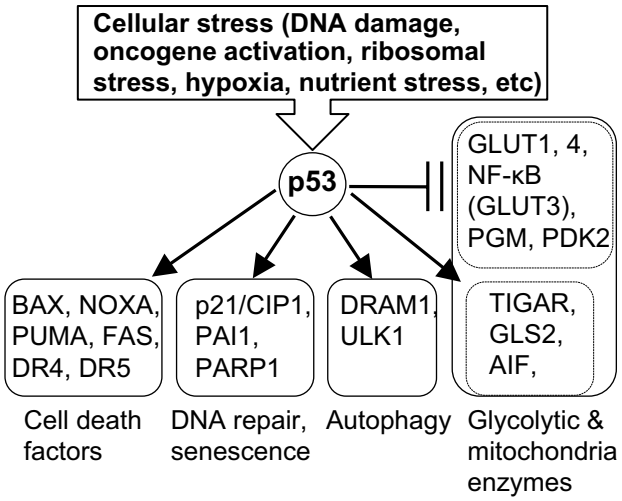



**Fig. 4** p53 has multiple functions as a stress sensor. p53 activated by cellular stress regulates cell fates, survival, death, and senescence in a cell context-dependent manner. The detailed mechanisms of how p53 regulates these cellular behaviors precisely remain to be elucidated

(Pgm), and pyruvate dehydrogenase kinase 2 (Pdk2) that prevent acetyl-CoA production from pyruvate. Moreover, p53 induces expression of Tiger, which reduces glycolysis indirectly, glutaminase 2 (Gls2) that produces glutamate from glutamine, another source of α-KG (Fig. 2), and apoptosis-inducing factor (Aif) that is essential for both the electron transport chain in mitochondria and DNA fragmentation in apoptosis.

There is increasing evidence that p53 induces the expression of autophagy-related genes, including DNA-damaged-regulated autophagy-modulator 1 (Dram1) and UNC51-like autophagy-activating kinase 1 (Ulk1). Conversely, autophagy reduces various types of stress, such as DNA damage and damaged organelles, which activate p53. Furthermore, p53 binds to autophagy-related factors, such as autophagy protein 7 (ATG7) and RB1 inducible coiled-coil 1 (RB1CC1), and inhibits cell cycle progression and autophagy [56]. It would be of interest to further analyze the relationship between p53 and autophagy in tumorigenesis.

Taken together, these findings indicate that p53 blocks tumorigenesis by regulating multiple pathways, DNA repair, senescence, cell death, glycolysis, mitochondrial functions, and autophagy.

## Conclusion and future perspective

There is no doubt that the molecular parameters introduced in the new WHO classification of CNS tumors will facilitate diagnosis of certain tumors with difficult pathological classification. Simultaneously, this raises the interesting question of why some tumors with different molecular parameters, such as GBM with wild-type or mutant IDH, show the same characteristics pathologically. Diagnostic parameters and other mutations in p53, RB, and RTK pathways may share targets or complement essential oncogenic signals [3, 4]. For example, HIF1α is activated by mutant IDH-dependent reduction of α-KG, while activation of RTKs indicues HIF1α, indicating that HIF1α is commonly activated in GBM with wild-type or mutant IDH in different manners [57]. The shared regulators are likely primary therapeutic targets. Furthermore, such parameter-specific factors can be useful as selective targets.

1p36/19q13 loss and p53 mutation are exclusive markers for oligodendroglioma and astrocytoma, respectively. Nonetheless, the evidence that CHD5, a functional activator of p53, is encoded on 1p36, indicates that p53 functions may decrease in 1p36-deleted oligodendroglioma as well as p53-mutated astrocytoma. Billon et al. have shown that p53 is also involved in oligodendrocyte differentiation, suggesting that p53 mutations found in astrocytoma may prevent oligodendrocyte differentiation [41]. Thus, it is essential to identify factors regulating glioma phenotypes, oligodendroglioma, and astrocytoma on 1p36/19q13. In summary, further investigations of molecular mechanisms involved in glioma may be applied to diagnosis, new molecular classification, and therapy in the future.

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