Bridging Cancer Biology with the Clinic: Comprehending and Exploiting IDH Gene Mutations in Gliomas

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Abstract. Isocitrate dehydrogenases 1 and 2 (IDH1/2) are enzymes that play a major role in the Krebs cycle. Mutations in these enzymes are found in the majority of lower gliomas and secondary glioblastomas, but also in myeloid malignancies and other cancers. IDH1 and IDH2 mutations are restricted to specific arginine residues in the active site of the enzymes and are gain-of-function, i.e. they confer a neomorphic enzyme activity resulting in the accumulation of D-2-hydroxyglutarate (2-HG). 2-HG is an oncometabolite causing profound metabolic dysregulation which, among others, results in methylator phenotypes and in defects in homologous recombination repair. In this review, we summarize current knowledge regarding the function of normal and mutated IDH, explain the possible mechanisms through which these mutations might drive malignant transformation of progenitor cells in the central nervous system, and provide a comprehensive review of potential treatment strategies for IDH-mutated malignancies, focusing on gliomas.

In the past decade, our knowledge regarding the molecular events that drive malignant transformation in diffuse gliomas has increased significantly. This knowledge led to a major revision of the 2007 edition of the World Health Organization Classification of Tumors of the Central Nervous System that was published 2 years ago, the 2016 Classification of Tumors of the Central Nervous System. In the 2016 revision, molecular parameters are integrated with histology in order to clearly define glioma subtypes, providing at the same time, in some cases, prognostic information. IDH mutations are undoubtedly one of the most important molecular parameters in the current glioma classification (1-3).

IDH mutations in gliomas were first reported in 2008. Parsons et al., using next-generation sequencing technology, found IDH1 mutations to be present in 12% of patients with glioblastoma, mainly in younger patients and in patients with secondary glioblastoma. In this initial publication, it was reported for the first time that the presence of IDH1 mutations is also associated with improved prognosis in terms of overall survival, relative to patients with glioblastoma with wild-type IDH1 (4). Following this pivotal study, Yan et al. reported that IDH1 and IDH2 mutations occur in the majority (>70%) of WHO grade II/III astrocytomas, oligodendrogliomas, oligoastrocytomas and secondary glioblastomas, and are associated with improved prognosis (5). Multiple subsequent studies have confirmed these findings (6-13). Interestingly, two studies have shown that the presence of an IDH mutation in patients with astrocytoma/glioblastoma is a stronger predictor for overall survival than the histological type and grade of the tumor (14, 15).

IDH1 and IDH2 mutations have also been found in patients with hematological malignancies and in a number of solid tumor types, including acute myeloid leukemia (AML), myelodysplastic syndromes, myeloproliferative neoplasms, cholangiocarcinoma, melanoma and cartilaginous tumors (16-24). In AML, IDH1/IDH2 mutations have been reported in 16-17% of patients, while the frequencies in all other entities remain much lower (23, 25). Furthermore, IDH mutations have also been observed in intrahepatic...
cholangiocarcinomas (26), chondrosarcomas (16) and sporadically in other tumors as well (Table I).

In this review, we summarize current knowledge regarding the function of normal and mutated IDH, explain the possible mechanisms through which these mutations might drive malignant transformation of progenitor cells in the central nervous system, and provide a comprehensive review of potential treatment strategies for IDH-mutated malignancies, focusing on gliomas.

Biochemistry and Function of Wild-type IDH

In biochemistry, IDH enzymes are known for their role in the Krebs cycle (tricarboxylic or citric acid cycle). The IDH family in humans consists of three IDH isoenzymes, IDH1, IDH2 and IDH3, which all catalyze the oxidative decarboxylation of isocitrate into alpha-ketoglutarate (αKG) and carbon dioxide. IDH1 and IDH2 are homodimeric enzymes with high structural similarity (69%) that are encoded by two distinct genes, IDH1 on 2q33.3 and IDH2 on 15q26.1, respectively. The protein IDH1 is located in the cytoplasm and peroxisomes, while IDH2 is located in the mitochondria. They are both nitotinamide adenine dinucleotide phosphate (NADP⁺)-dependent enzymes that use NADP⁺ as a cofactor, producing NADPH during their enzymatic activity (27, 28). IDH1 and IDH2 are the major sources of NADPH in the cytosol and mitochondria respectively (20).

IDH3 is a heterotetrameric enzyme consisting of two alpha, one beta and one gamma subunit that are encoded by the genes IDH3A on 15q25.1-2, IDH3B on 20p13 and IDH3G on Xq28, respectively. IDH3 is located in the mitochondria and is one of the most critical enzymes in the Krebs cycle. IDH3 uses NAD⁺ as a cofactor and produces NADH, which is necessary for energy production (29, 30). Despite its important role in cellular metabolism, mutations in IDH3 genes have not as yet been linked to tumorigenesis.

IDH1 and IDH2 are necessary for the production of αKG and NADPH. NADPH is an important cofactor in many cellular functions, e.g. lipid metabolism (31), glucose metabolism (32) and oxidative stress defense, by reducing glutathione and thioredoxin, and by activating catalase (33-35). Interestingly, IDH1 is the main source of NADPH in the brain and is also thought to be a main source of NADPH in other tissues (36, 37).

αKG is also an important molecule in diverse cellular processes, by being an essential cofactor for the family of αKG-dependent dioxygenases. This family consists of more than 60 enzymes that require αKG as a cofactor. αKG-dependent dioxygenases are present in all living organisms and affect multiple cellular functions: they catalyze hydroxylation reactions on a diverse set of substrates, including collagen, lipids, proteins, histones, transcription factors, alkylated DNA and RNA, 5-methylcytosine of genomic DNA and 6-methyladenine of RNA, as well as antibiotics. Members of the αKG-dependent dioxygenase family are propyl hydroxylases, jumonji-C domain-containing histone demethylases, ten-eleven translocation (TET) enzymes, 5-methylcytosine hydroxylases, collagen propyl-4-hydroxylases 1, 2 and 3, and many more (37, 38). Many of these enzymes play a pivotal role in regulating histone and DNA demethylation in normal cells (39, 40).

Biochemistry and Function of Mutant IDH

In gliomas, mutations in the IDH1 and IDH2 genes are somatic and invariably heterozygous, missense mutations that result in a single amino acid substitution. Interestingly, these mutations involve specific conserved arginine residues in the active site of the IDH enzymes that play a key role in substrate binding (4).

For the IDH1 gene, mutations are found at the arginine codon 132 (R132) and the most common mutation is the substitution of arginine by histidine (R132H), which occurs in more than 90% of all IDH1 mutants. Far less common are R132C substitutions (arginine→cysteine), R132S (arginine→serine), R132G (arginine→glycine) and R132L mutations (arginine→leucine), which occur in approximately 5% of cases. For the IDH2 gene, the homologous conserved arginine residue is at codon 172 (R172) and the reported mutations are R172K (arginine→lysine), R172M (arginine→methionine), R172G (arginine→glycine) and R172W (arginine→tryptophan) (5, 41), as well as R172S (arginine→serine). All these mutations are

| Gene | Tumor type | Frequency | Reference |
|------|------------|-----------|-----------|
| IDH1 | Astrocytoma | 54-72%    | (6, 9, 41) |
|      | Oligodendroglioma | 65-70% | (6, 9, 41) |
|      | Primary glioblastoma | 3% | (9) |
|      | Secondary glioblastoma | 50-88% | (6, 9) |
|      | AML | 6-16% | (65) |
|      | MDS | 2-3% | (65) |
|      | MPN | <1% | (65) |
|      | Chondrosarcoma | 40% | (16) |
|      | Intrahepatic cholangiocarcinoma | 7-20% | (17) |
| IDH2 | Low-grade gliomas and glioblastoma | <5% | (5, 51) |
|      | AML | 8-19% | (65) |
|      | MDS | 2-7% | (130) |
|      | MPN | 2% | (65) |
|      | Chondrosarcoma | 16% | (16) |
|      | Intrahepatic cholangiocarcinoma | 3% | (17) |

AML, Acute myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms.
registered in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (https://cancer.sanger.ac.uk/cosmic). The incidence of mutations of each IDH gene differs among tumor types, as summarized in Table I.

The fact that IDH1/2 mutations affect the active site of the enzyme led to the initial theory that these mutations cause loss of enzymatic activity of wild-type IDH. Initial in vitro studies had shown that mutant IDH proteins impair normal IDH catalytic action in a dominant-negative fashion by heterodimerizing to the wild-type enzyme and altering its activity, leading to reduced levels of aKG and NADPH (42-44). Reduced levels of NADPH and aKG could then lead to cellular damage and genomic instability, through impairment of the normal cellular detoxification mechanisms, as well as other important cellular processes described above. This theory was supported by biochemical studies suggesting that mutant IDH1/2 was unable to catalyze the oxidative decarboxylation of isocitrate. However, subsequent studies revealed that mutant IDH enzymes were not catalytically inactive, but rather enzymes with a gain-of-function activity [summarized in (45)].

A landmark report by Dang et al. showed that the mutant IDH1 protein is not a non-functional enzyme, but rather an enzyme with a neomorphic activity, which converts aKG to 2-hydroxyglutarate (2-HG) with the simultaneous consumption of NADPH (46). 2-HG is a byproduct in normal mitochondrial metabolism that is normally found at very low levels in the cell and has two enantiomers, D-2HG and L-2HG (or, R-2HG and S-2HG, respectively). IDH1-mutant cells exclusively produce D-2HG at very high levels, up to 100-fold higher than in normal tissues. In the same manner, IDH2 mutations have been found to result in high levels of D-2HG (47). Jin et al. showed that accumulation of high levels of D-2HG takes place in vivo and in vitro only when both wild-type and mutant IDH1 alleles are expressed (48), indicating that the wild-type– mutant IDH1 heterodimer is critical for the rapid conversion of aKG to D-2HG. Indeed, loss of wild-type IDH1 expression in IDH1-mutated glioblastoma cells led to reduced levels of D-2HG. This may explain why loss of heterozygosity is rare in IDH1-mutated gliomas (48, 49). Interestingly, in vitro studies have additionally shown that L-2HG is increased in human neuroblastoma, pediatric glioblastoma, glioblastoma, renal cell carcinoma, and embryonic kidney cell lines in the setting of hypoxia via enzymatic reduction of aKG (50).

It is worth noting that 2-HG accumulation in human cells has also been described in 2-HG acidurias that are rare inherited metabolic disorders characterized by abnormally high levels of hydroxyglutaric acid in almost all organ systems and body fluids (51). 2-HG aciduria is caused by inherited loss-of-function mutations in the genes encoding enantiomer specific flavin adenine dinucleotide-dependent 2-hydroxyglutarate dehydrogenases (D-2HGDH and L-2HGDH for D and L enantiomers, respectively) that normally convert 2-HG to aKG preventing its accumulation in cells (52, 53). D-2HG aciduria has also been reported in association with inherited gain-of-function mutations in IDH2 and is characterized by developmental delay, epilepsy and cardiomyopathy and short life-span, while L-2HG is characterized by a variable clinical course and by increased risk of developing brain tumors in longer survivors (51, 54).

The right-enantiomer, D-2HG, is structurally similar to aKG. The two molecules differ only in the presence of a C2 hydroxyl group in D-2HG instead of the C2 carbonyl group in aKG. D-2HG has been shown to act in vitro as a competitive inhibitor of aKG-dependent enzymes, including jumonji-C domain-containing histone demethylases and TET family of hydroxylases. These enzymes, as mentioned earlier, are key regulators of histone and DNA demethylation in cells and therefore their inhibition through D-2HG results in a profile of cellular hypermethylation (38, 55-57). D-2HG is considered an ‘oncometabolite’ not only because it increases dramatically in cells as a consequence of IDH1/2 mutations (46), but also because it was shown to transform hematopoietic into leukemia cells (58) and promote epithelial–mesenchymal transition in colorectal cancer cells even in the absence of IDH mutation (59); by contrast, L-2HG does not appear to have such phenotype-aggravating properties.

The intracellular accumulation of 2HG in IDH-mutated gliomas has been used as a non-invasive tool for accurate diagnosis using magnetic resonance spectroscopic (MRS) technology (60).

Recently, a more specific technique has been described, Fourier-transform infrared spectroscopy, which seems promising for rapid and intraoperative glioma classification. This technique can provide prognostic information to the surgeon at the time of the surgery for optimal treatment decisions (61), but needs further development for clinical applications. In the same vein, in vivo 3D MRS may be used for patient surveillance in the context of clinical trials for assessing treatment efficiency (62).

Role of Mutant IDH in Oncogenesis

The originally proposed oncogenic effect of IDH mutations through increasing the expression of hypoxia-inducible factor-1 alpha (HIF1α) and its target genes (44) was later rejected since IDH mutations in fact result in increased degradation of HIF1α (63). The exact role of IDH mutations in tumorigenesis is still not fully understood, although much progress has been made in this direction (64).

The described gain-of-function IDH mutations giving rise to gliomas have traditionally been considered as being directly responsible for malignant transformation (13, 30, 65), since these are established in neural progenitors in the
brain (30) before lineage-specific genomic alterations that are described in IDH-mutated gliomas (Figure 1). Corresponding knowledge on the manifestation of IDH mutations in myeloid malignancies is less concise; in leukemia, for example, the biological effects of IDH mutations, including a favorable prognostic impact of IDH2 mutations, seem to depend on coexisting genomic alterations (66); this may support a previous hypothesis that IDH mutations may develop in later steps of malignant transformation in this context (67).

The early establishment of IDH mutation seems to provide the common origin and perturbed metabolic and molecular environment for the development of IDH-mutation-positive gliomas (68-70) that diverge into specific oligodendrocytic and astrocytic lineages based on additional genomic alterations aided by changes in their microenvironment (71). Thus, oligodendrogliomas acquire changes such as 1p/19q co-deletion and mutations or fusions in key genes located in 1p, such as the capicua transcriptional repressor gene (CIC) and far upstream element binding protein 1 gene (FUBP1), but also in the promoter of telomerase reverse transcriptase (TERT), the gene encoding the catalytic subunit of telomerase (72-74). In comparison, astrocytomas are characterized by the addition of mutations in tumor protein 53 (TP53) in 80% of cases and in alpha thalassemia/mental retardation syndrome X-linked gene (ATRX); the latter is involved in alternative lengthening of telomeres (75-77), while ATRX mutations are mutually exclusive from mutations in the TERT promoter. As shown with single-cell RNA sequencing, lineage determination in IDH mutation-positive gliomas is non-overlapping (71), thus justifying the WHO 2016 classification that recommends avoiding use of the histological term ‘mixed oligoastrocytoma’.

Additional genomic changes determine the malignant potential of anaplastic gliomas (Figure 1). It remains obscure however, how IDH mutations and the resulting oncometabolite D-2HG contribute to the acquisition of the changes necessary for the development of each glioma lineage, and whether the same mutations drive the transition of low-into high-grade glioma.

The main global metabolic consequence in IDH-mutated cells seems to be energy deprivation: IDH-mutated tumors have a low-energy requirement, with dozens of metabolites contributing to this pro-survival feature (68, 70). The low-energy requirement of IDH mutation-positive tumors may in fact be related to the methylator phenotype that has been proposed as the oncogenic mechanism of IDH mutations. Noushmehr et al. in 2010 described a specific hypermethylation pattern in CpG islands in a subset of patients with glioma referred to as a glioma CpG island methylator phenotype (G-CIMP). This pattern is associated with altered expression of several genes through transcriptional silencing (78). Furthermore, G-CIMP has been found to be tightly associated with a specific gene-expression profile called the proneural subtype; the latter is always characterized by the presence of IDH mutations (79). Following these studies, Turcan et al. were able to replicate the G-CIMP signature in human astrocytic cells by expressing IDH1 R132H mutations, establishing in this way the attractive theory that IDH mutations constitute the molecular basis of G-CIMP (80). However, not all IDH mutation-positive gliomas exhibit the methylator phenotype (69), while the same phenotype may result from mutations in other genes.

As previously mentioned, aKG-dependent dioxygenases are directly involved in histone and DNA methylation and their inhibition through D-2HG can result in a hypermethylation pattern consistent with the G-CIMP signature. This interesting scenario is supported by multiple preclinical data. DNA demethylation is in part being regulated by TETs, enzymes that catalyze the conversion of 5-methylcytosine to its unmethylated form. It has been shown that in vitro expression of IDH mutations inhibits TET activity, resulting in DNA hypermethylation, and this inhibition can be reversed by the exogenous addition of aKG (38). In patients with AML, IDH1/2 mutations have been found to result in a DNA hypermethylation pattern similar to G-CIMP through impairment of normal TET catalytic activity. Interestingly, a subset of patients with AML harbor TET loss-of-function mutations and have the same epigenetic defects as patients with IDH mutations. It is worth noting that IDH and TET mutations are mutually exclusive (81).

Main implications of the methylator phenotype associated with IDH mutations include the altered expression of genes participating in practically all cellular functions, some of which have been studied in detail. IDH mutations have been shown to inhibit aKG-dependent histone jumonji-C demethylases that regulate histone methylation. Chowdhury et al. showed that IDH mutations inhibit members of the jumonji-C family with different potencies, with the 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid (KDN) family of histone demethylases being the most sensitive to inhibition, leading to an increase in histone methylation marks (55). These findings have been replicated by other investigators (38). Lu et al. showed that this increase in histone methylation leads to a block in cellular differentiation, probably due to hypermethylation of genes associated with differentiation (82). Flavahan et al. showed that the methylator phenotype associated with IDH mutations alters normal chromosomal topology via disruption of CCCTC-binding factor (CTCF) insulator protein binding. This protein is responsible for organizing DNA into chromatin loops and boundaries. Methylation of CTCF-binding sites disrupts normal binding of the CTCF proteins, allowing aberrant gene expression. It has been shown that in IDH-mutant cells, loss of CTCF binding at a specific domain boundary results in...
overexpression of a prominent glioma oncogene, platelet-derived growth factor receptor A (PDGFRA). Moreover, treatment of these cells with a demethylating agent resulted in down-regulation of PDGFRA and partial restoration of the CTCF function (83). Turcan et al. also proposed that histone and chromatin modifications are the main consequences of the metabolic environment in IDH-mutant cells (84). Chesnelong et al. found that in IDH-mutant cells there is silencing of lactate dehydrogenase A gene (LDHA) via methylation of its promoter. LDHA is a subunit of LDH essential for glycolysis and silencing of LDHA in these cells results in a defective glycolytic pathway. This could perhaps explain the slow growth reported for IDH-mutant tumors compared to their wild-type IDH counterparts (85). The methylation-based silencing of genes encoding for immune checkpoint inhibitors, such as programmed cell death protein 1 (PDCD1/PD1) and programmed cell death-ligand 1 (PDL1) (86-88) is also worth mentioning in the context of the above described IDH-related methylator phenotype.

Two consequences directly attributed to the high levels of 2-HG resulting from IDH mutations include endoplasmic reticulum stress in murine glioma progenitors (89) and the stalled DNA-damage repair demonstrated in various IDH mutation-positive tumors, including gliomas (90). Compared to IDH mutation-negative gliomas, IDH mutation-positive gliomas exhibit higher apoptotic death rates that can be further increased with endoplasmic reticulum stress-inducing agents such as tunicamycin and thapsigargin (89) and with inhibition of B-cell lymphoma-extra large protein (BCL-xL) (91). IDH mutations through high 2-HG levels induce homologous recombination repair deficiency, which was accompanied by a high sensitivity of IDH-mutated tumors to poly (ADP-ribose) polymerase (PARP) inhibitors in preclinical models (90, 92). The importance of the above features in IDH mutation-positive tumors lies in the fact that IDH mutations can be exploited with synthetic lethality strategies using existing drugs.

Prognostic and Predictive Role of IDH Mutations

Many studies have shown that patients with IDH mutation-positive gliomas have better survival compared to their wild-type IDH counterparts irrespective of histology and grade, making IDH mutation the most important prognostic factor for survival, followed by age, tumor grade and O6-methylguanine-DNA methyltransferase gene (MGMT) status, as summarized in (20). The favorable prognostic effect of IDH mutations compared to wild-type IDH has been reported in patients with glioblastoma (median overall survival: 31 vs. 15 months) and anaplastic astrocytoma (median overall survival: 65 vs. 38 months) (5, 14, 93, 94) and with anaplastic oligodendroglioma (95). In line with the
The mostly tested strategy in this context is with compounds acting as IDH inhibitors. The fact that IDH mutations occur early in gliomagenesis and that such mutations are tumor specific and are expressed uniformly in all tumor cells (13) resulted in the development of drugs targeting IDH1/2 enzymes. Data from preclinical studies showed that IDH inhibitors can reduce 2-HG production, reverse histone and DNA methylation, and induce cell differentiation (110-112). The clinical trials testing the efficiency of IDH inhibitors in gliomas and hematological malignancies are shown in Table II.

Popovici-Muller et al. in 2012 were the first to develop an IDH1/2 inhibitor that lowered the 2-HG level in a glioblastoma xenograft mouse model (113). Following these findings, Chatuverdi et al. showed that the use of another IDH1 inhibitor in leukemia cells from patients with IDH1 mutations blocked colony formation without affecting normal cells (114). AGI-5198, also an IDH1 inhibitor, was shown in two in vitro studies to inhibit 2-HG production and induce cell differentiation (110, 115). Similarly, AGI-6780, an IDH2 inhibitor, was shown to induce differentiation of IDH2-mutated erythroleukemia and primary human AML cell lines (111).

IDH inhibitors were first studied in patients in 2013. The first agent to be tested was AG-221 (enasidenib), a selective IDH2 inhibitor. Yen et al. showed in vitro that enasidenib suppressed 2-HG production in and induced cellular differentiation of primary human IDH2 mutation-positive AML cells ex vivo and in xenograft mouse models (116). On this basis, enasidenib was initially tested in a phase I/II clinical trials in patients with advanced hematological malignancies and a known IDH2 mutation (NCT01915498). Results from this trial were encouraging. The drug was well tolerated and resulted in 98% reduction of 2-HG levels. The objective response rate among 181 patients with relapsed or refractory AML was 41%, with 28% of patients achieving complete response and a median response duration of 5.8 months. Grade 3 or 4 drug-related side-effects were observed in 21% of patients and included indirect hyperbilirubinemia (12%) and IDH-inhibitor differentiation syndrome (7%) (117-119). Subsequent translational studies from the trial population have shown that cellular differentiation is the main mechanism of action of enasidenib (120). Interestingly, in the trial population, 23% of patients taking enasidenib at a dose of 100 mg once daily had a complete response lasting a median of 8.2 months (121).

These results led to the approval of enasidenib by the Food and Drug Administration (FDA) (August 2017) for use in patients with refractory or relapsed AML along with a companion diagnostic, the RealTime IDH2 assay to detect IDH2 mutation (USFDA Approved Drugs—FDA Granted Regular Approval to Enasidenib for the Treatment of Relapsed or Refractory AML; https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm569482.htm).
which is also being tested in many clinical trials. A phase III trial evaluating enasidenib versus best supportive care in elderly patients with AML harboring IDH2 mutation is currently recruiting (NCT02577406). Enasidenib has also been evaluated in a phase I/II trial in patients with advanced solid tumors harboring an IDH2 mutation (NCT02273739).

Similarly, AG 120, an IDH1 inhibitor, has been tested in patients with advanced hematologic malignancies (NCT02074839) and solid tumors harboring IDH1 mutations (NCT02073994). Preliminary results have been presented and AG 120 has been reported to have a clinical benefit rate of 37% among all patients and 25% among those with glioma (122).

Furthermore, additional IDH inhibitors have been designed and have entered clinical trials, including IDH-305, DS-1001b and BAY-1436032, which are all IDH1-mutant inhibitors (122, 123), and AG-881 (vorasidenib), a pan inhibitor of mutant IDH1 and IDH2 enzymes, which has been shown to fully penetrate the blood–brain barrier (NCT02381886, NCT03030066, NCT02746081). AG-881 is currently being tested in two clinical trials, NCT02481154 and NCT02492737, involving patients with advanced solid tumors including gliomas with IDH1/IDH2 mutations and advanced hematological malignancies, respectively (20, 49).
A different treatment approach, synthetic lethality for IDH-mutant solid tumors, was recently suggested by Sulkowski et al. (90) based on the observation that 2-HG results in homologous recombination repair deficiency, rendering such cells highly sensitive to PARP inhibition. Importantly, they also observed that this sensitivity is reversed by IDH inhibitors. In the same context, Lu et al. (92) reported on synergistic effects between temozolomide and the PARP inhibitor olaparib, in patients with IDH mutation, providing the possibility to achieve improved cytotoxic effects with minimal use of alkylating agents in order to reduce bone marrow cytotoxicity (109). Based on these results, a phase I trial with the above combination in patients with relapsed glioblastoma recently completed accrual and results are awaited (NCT01390571) (124).

Another potential pathway to be targeted in IDH-mutant gliomas was identified based on the specific hypermethylation patterns associated with such tumors. As previously described, histone and DNA hypermethylation reported in IDH-mutant tumors leads to an arrest of cellular differentiation and malignant transformation. The use of decitabine and azacytidine, both DNA-demethylating agents approved by the FDA for myelodysplastic syndromes, has been shown in preclinical models to reverse the hypermethylation phenotype, induce cellular differentiation and delay tumor growth in IDH1-mutated xenograft models (125, 126).

As immunotherapy constantly gains ground in the battle against cancer, many researchers have tried to use different immunotherapy approaches against IDH-mutant tumors. The fact that IDH mutations are events that occur early and...
steadily through time in gliomagenesis, in combination with the fact that mutant IDH enzymes are expressed only in glioma cells, have made them intriguing antigens for activating the immune system. A mutation-specific anti-IDH1(R132H)-specific peptide vaccine has been produced and been shown to generate an immune reaction in preclinical studies and to reduce tumor growth in a mouse model (127, 128). Currently there are three IDH1 peptide and dendritic vaccines targeting the IDH1 R132H mutation that are being evaluated in phase I clinical trials (NCT02193347, NCT02454634 and NCT02771301). Since PD1 and PDL1 genes were found to be methylated and underexpressed in IDH-mutant tumors (86-88), inhibitors of PD1 (pembrolizumab) and PDL1 (avelumab) are currently being evaluated in pretreated patients with gliomas, either alone in patients with glioma grade II-IV that harbor hypermutator phenotype, or in combination with radiotherapy in secondary glioblastoma (NCT02658279 and NCT02968940, respectively). Pretreatment with irradiation with/without temozolomide may interfere with the
methylator phenotype and hence alter the expression of targets of pembrolizumab and avelumab, while temozolomide may induce a mutator phenotype in gliomas, through inactivation of DNA mismatch repair genes (129).

In conclusion, several therapeutic approaches are being tested in patients with IDH mutant tumors based on preclinical evidence (summarized in Figure 4). The first approach involves IDH inhibitors, which target the effect of IDH mutations, i.e., the oncometabolite 2-HG, and reduce its levels. The second tries to exploit the effects of the oncometabolite, i.e. deficient DNA strand breaks and apoptosis. The third is in the context of immunotherapy. Because IDH inhibitors do not kill cells but induce them to differentiate or drive them into a reversible autophagic state, these inherently conferant existing treatment modalities, such as radiotherapy, cytotoxic chemotherapeutics, as well as most molecularly targeted agents. Thus, despite approval, this class of molecules is not expected to be effectively integrated into clinical practice, for gliomas at least. In comparison, approaches of synthetic lethality appear more promising based on the rationale of combination possibilities and repurposing of existing drugs. IDH-mutant tumors are progressively being understood as an individual class of malignancies across tumors of different origins, the reason being the oncometabolite (D-)2-HG. Deepening our knowledge on how this metabolite is influenced by currently applied treatments in patients with IDH mutation-positive tumors is warranted for the efficient design of clinical trials targeting its consequences directly or after initial treatment failure, particularly in patients with glioma.

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