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DNA damage in IDH-mutant gliomas: mechanisms and clinical implications

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Abstract

Purpose—Since the discovery of *IDH* mutations in glioma over a decade ago, significant progress has been made in determining how these mutations affect epigenetic, transcriptomic, and metabolic programs in brain tumor cells. In this article, we summarize current understanding of how *IDH* mutations influence DNA damage in glioma and discuss clinical implications of these findings.

Methods—We performed a thorough review of peer-reviewed publications and provide an overview of key mechanisms by which *IDH* mutations impact response to DNA damage in gliomas, with an emphasis on clinical implications.

Results—The effects of mutant IDH on DNA damage largely fall into four overarching categories: Gene Expression, Sensitivity to Alkylating Agents, Homologous Recombination, and Oxidative Stress. From a mechanistic standpoint, we discuss how mutant IDH and the oncometabolite (*R*)-2HG affect each of these categories of DNA damage. We also contextualize these mechanisms with respect to ongoing clinical trials. Studies are underway that incorporate current standard-of-care therapies, including radiation and alkylating agents, in addition to novel therapeutic agents that exert genotoxic stress specifically in IDH-mutant gliomas. Lastly, we

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discuss key unanswered questions and emerging data in this field that have important implications for our understanding of glioma biology and for the development of new brain tumor therapies.

Conclusion—Mounting preclinical and clinical data suggest that *IDH* mutations alter DNA damage sensing and repair pathways through distinct mechanisms. Future studies are needed to deepen our understanding of these processes and provide additional mechanistic insights that can be leveraged for therapeutic benefit.

Keywords

DNA damage; IDH; Isocitrate dehydrogenase

Introduction

Mutations in *IDH1* or *IDH2* genes, which encode isocitrate dehydrogenase (IDH) enzymes, define diagnostic subsets of gliomas [1, 2]. The 2021 WHO classification now formally incorporates *IDH* mutation status as a component of glioma diagnoses, with the three primary adult-type diffuse gliomas being (1) astrocytoma, IDH-mutant, (2) oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, and (3) glioblastoma, IDH-wildtype [3]. IDH-mutant gliomas are more often lower-grade (grade 2–3) and diagnosed in young adults. Wild-type IDH1/2 enzymes reversibly convert isocitrate to 2-oxoglutarate (2OG). In contrast, glioma-associated IDH mutants (the most common of which is $IDH1^{R132H}$) are neomorphs that convert 2OG to (*R*)-2-hydroxyglutarate [(*R*)-2HG]. (*R*)-2HG accumulates to millimolar levels in IDH-mutant gliomas, constituting one of the most abundant metabolites in these tumors. Due to structural similarity between (*R*)-2HG and 2OG, (*R*)-2HG competitively inhibits 2OG-dependent enzymes [4–6] to promote tumorigenesis and is thus termed an “oncometabolite.”

In addition to oncogenic effects of (*R*)-2HG, (*R*)-2HG also confers bystander effects that may be therapeutically exploited. One of the most well-described of these so-called “collateral vulnerabilities” is an altered response to DNA damage. In this review, we discuss preclinical and clinical studies that illustrate mechanisms by which mutant IDH affects response to DNA damage. We describe molecular mechanisms underlying these effects, including gene expression changes, sensitivity to alkylating agents, homologous recombination defects, and response to oxidative stress. Lastly, we discuss key unanswered questions that inform translation of these findings to the clinic.

Gene expression

IDH mutations influence gene expression by regulating chromatin modifying enzymes. (*R*)-2HG competitively inhibits 2OG-dependent DNA and histone demethylases. One of the most well-established signatures of these epigenetic changes is the glioma CpG island methylator phenotype (G-CIMP) [7, 8]. Most promoter sites in the human genome are preceded by CpG islands, which are CG-rich regions that can be methylated by DNA methyltransferases to alter expression of downstream genes. Methylation of these CpG island sites leads to transcriptional repression and gene silencing (Fig. 1A). A glioma-specific G-CIMP phenotype was first discovered through profiling of mutations [8].

Mechanistically, this likely reflects (*R*)-2HG-mediated inhibition of the 2OG-dependent ten-eleven translocation (TET) family of DNA-modifying enzymes, in addition to other 2OG-dependent histone and DNA demethylases.

Epigenetic changes caused by mutant IDH have multiple functional effects, including maintenance of a stem-like state [8] and increased expression of glioma oncogenes [9]. However, much remains unknown regarding how mutant IDH functionally reprograms the glioma epigenome. Epigenetic-driven changes in gene expression by mutant IDH have been implicated as the cause of multiple "collateral vulnerabilities" that may be exploited therapeutically. One such example is highlighted in recent data from Liu and colleagues demonstrating increased expression of NRF2 pathway genes and reliance on this pathway for reactive oxygen species (ROS) homeostasis [10] (see "Oxidative Stress" below for further discussion). Importantly, the kinetics of these changes mirrored that of the long-term time course observed in mutant IDH-associated epigenetic reprogramming [8]

Mutant IDH-mediated epigenetic changes have also been implicated in directly controlling expression of genes that mediate DNA damage responses (DDR), with data supporting different mechanisms. Recent work from our group [11] revealed that mutant IDH sensitizes gliomas to inhibition of the de novo pyrimidine nucleotide synthesis pathway. Drugs that inhibit this pathway caused nucleotide pool imbalance, replication stress-dependent DNA damage, and cell death in multiple in vitro and in vivo models of IDH-mutant glioma. Mechanistically, these data support a model in which mutant IDH causes epigenetic and transcriptomic changes that silence DDR genes necessary to maintain genome integrity during nucleotide pool imbalance. In support of this hypothesis, an analysis of TCGA data demonstrated decreased expression of DDR-related genes in IDH-mutant as compared to IDH-WT gliomas. Similar findings of mutant IDH-driven DDR defects due to epigenetic changes have been made in IDH-mutant leukemia [12]. Additional data also suggest that mutant IDH increases replication stress by promoting heterochromatin formation, providing another mechanistic link between these mutations and susceptibility to DNA damage [13].

In contrast to these findings, data from Nuñez et al. [14] support an alternative hypothesis, in which mutant IDH acts as a tumor suppressor and increases DNA damage repair via epigenetic reprogramming. In the context of a genetically engineered mouse model harboring *Trp53* loss, *Atrx* loss, and an *Nras* G12V mutation, mutant IDH1 enhanced histone H3K4 methylation and was associated with increased expression of DDR genes. These molecular changes were associated with radioresistance of IDH-mutant versus IDH-WT murine gliomas. These data raise interesting mechanistic questions regarding how genetic context may determine the impact of mutant IDH on expression of DDR genes.

Ongoing clinical trials will help clarify how *IDH* mutations impact DDR. An early-phase trial testing the de novo pyrimidine synthesis inhibitor BAY 2402234 in IDH-mutant glioma patients is forthcoming (Table 1). In addition, early data from the CODEL trial demonstrated a significant progression-free survival benefit in the radiation arms compared to temozolomide alone in IDH-mutant, 1p/19q codeleted patients [15], providing preliminary clinical evidence that IDH-mutant gliomas respond to radiation therapy. Given

these early results, the CODEL trial is now undergoing redesign to omit the temozolomide-alone arm and will test radiation with either concurrent temozolomide or PCV.

Sensitivity to alkylating agents

Alkylating agents are part of standard-of-care treatment for gliomas. These include temozolomide, CCNU, and procarbazine, the latter two of which comprise the three-agent regimen PCV along with vincristine. Given that alkylating agents are the primary systemic therapy class used for glioma treatment, multiple studies have deepened our understanding of how mutant IDH affects efficacy of alkylating chemotherapies.

Work from Wang et al. [16] and Chen et al. [17] explore the effect of (*R*)-2HG on the AlkB family of proteins, which are 2OG-dependent enzymes that repair alkylated DNA lesions [18, 19]. Wang et al. used engineered glioma and fibrosarcoma cell lines with or without mutant IDH1 to show that (*R*)-2HG inhibits the ALKBH2 and ALKBH3 enzymes, causing decreased repair of chemotherapy-induced DNA alkylation (Fig. 1B). Loss of function of ALKBH2 and ALKBH3 was due to inhibition of the catalytic activity of these enzymes as opposed to a decrease in expression. Furthermore, the catalytic activity of mutant IDH was necessary for mutant IDH-mediated sensitivity to alkylating agents, as demonstrated through experiments in which catalytically dead IDH1 double-mutants rescued the increased cell death observed in $IDH1^{R132H}$ single-mutant expressing cells. While response to temozolomide was not reported, mutant IDH expression sensitized cells to the alkylating agents CCNU and procarbazine, which was partially mitigated by exogenous expression of ALKBH2/3. These data suggest that inhibition of 2OG-dependent ALKBH dioxygenases by (*R*)-2HG may be functionally linked to sensitivity to alkylating agents. Additional characterization of the kinetics of inhibition under physiologic conditions has been described in work by Chen et al. [17].

In addition to ALKBH inhibition, mutant IDH confers metabolic vulnerabilities that may sensitize IDH-mutant glioma cells to alkylating agents. Work from Tateishi et al. demonstrate that mutant IDH1 decreases NAD + levels in glioma cells and increases susceptibility to therapeutics that deplete NAD + pools, such as NAMPT inhibitors [20]. This finding has important implications, as temozolomide-induced DNA damage can be repaired by the NAD+-dependent enzyme poly(ADP-ribose) polymerase (PARP). In follow-up work aiming to further exploit this dependency, they identified that temozolomide decreased NAD + levels, and that combination treatment with temozolomide and a NAMPT inhibitor enhanced efficacy of either treatment alone [21]. Similarly, NAD + depletion can also be exploited by use of temozolomide and inhibition of poly(ADP-ribose) glycohydrolase (PARG), the latter of which sequesters NAD + pools that are normally released following break-down of PAR chains after temozolomide-induced DNA damage [22]. These synergistic combinations may allow for use of reduced dose in patients, potentially mitigating dose-limiting toxicities encountered when using either treatment alone.

Clinically, temozolomide is part of standard-of-care treatment for gliomas as concurrent, adjuvant, or monotherapy treatment dependent on clinical scenario. Nevertheless, the

CATNON trial in IDH-mutant, 1p/19q non-codeleted tumors suggest a benefit to adjuvant (but not concurrent) temozolomide [1], and the redesigned CODEL trial (enrolling IDH-mutant, 1p/19q codeleted patients) will test different alkylating chemotherapy regimens as concurrent treatment with radiotherapy [15]. Collectively, these data will help further clarify the role of *IDH* mutations in mediating sensitivity to alkylating agents and whether treatment timing impacts efficacy. Importantly, response to alkylating agents is not only affected by mutant IDH status, but also by known biomarkers such as O^6-methylguanine methyltransferase (MGMT) promoter methylation in CpG islands [23]. While *IDH* mutations have been causally linked to CpG island hypermethylation (discussed above (in "Gene Expression") [8]), not all IDH-mutant gliomas display MGMT promoter methylation [24, 25]. It thus remains unclear how the mechanisms of mutant IDH-driven response to alkylating agents highlighted above intersect with MGMT methylation status to control response to these therapies.

Homologous recombination

DNA damage can cause breaks that increase the potential for new mutations, thus representing an essential player in the development and progression of cancers. Homologous recombination (HR) is a high-fidelity mechanism that repairs various forms of DNA damage. HR promotes DNA repair through exchange of nucleotide sequences between similar or identical DNA strands, such as in double-strand break repair. Impairments in HR function can thus lead to genomic instability, which may render cancer cells sensitive to chemotherapies and radiation.

Tumor cells with *IDH* mutations have been shown to display HR defects driven by (*R*)-2HG accumulation. (*R*)-2HG inhibits 2OG-dependent dioxygenases [8, 26], including some enzymes that play important roles in the HR pathway. Work from Sulkowski et al. showed that (*R*)-2HG inhibits the 2OG-dependent dioxygenase KDM4B, leading to hypermethylation of histone 3 lysine 9 (H3K9). H3K9 methylation normally marks areas of DNA breaks and facilitates recruitment of HR machinery. In IDH-mutant tumor cells with high (*R*)-2HG and consequent H3K9 hypermethylation, H3K9 methylation-dependent activation of the Tip60 acetyltransferase-ATM kinase axis is impaired, and DNA double-strand break recognition is compromised. This prevents recruitment of downstream DNA repair factors like RPA, BRCA1, and RAD51 [27]. Thus, IDH-mutant tumor cells may display a "BRCAness" phenotype that confers sensitivity to PARP inhibitors [28] (Fig. 1C), though recent work has suggested an alternative mechanism that may contribute to this effect [13]. In addition to H3K9 hypermethylation, PARP inhibitor sensitivity is also driven by impaired NAD + metabolism in IDH-mutant glioma cells, as shown by Lu et al. [29]. Their work demonstrated that NAD + depletion in IDH-mutant glioma cells is associated with reduced PARP activity and hypersensitivity to combined PARP inhibitor and temozolomide treatment. This research builds on work from Tateishi et al. [20] and corroborates the mechanistic link between mutant IDH and perturbed NAD + homeostasis.

Like the variable impact of *IDH* mutations on DDR gene expression, there appear to be context-specific effects of *IDH* oncogenes on HR function. Contrasting the findings above, Ohba et al. found that *IDH* mutations increase HR-mediated DNA repair that is

dependent on the recombinase RAD51. These findings were made in isogenic immortalized astrocyte cell lines harboring or lacking the *IDH1-R132H* oncogene, suggesting that *IDH* mutations increase HR activity when introduced in non-malignant cells. These findings are in agreement with those reported by Nuñez et al. [14], who found enhanced RAD51 expression in IDH-mutant glioma cells relative to IDH wild-type controls. Ohba and colleagues reported that increased HR efficiency driven by *IDH* mutations thus enhances resistance to temozolomide in their model systems.

Against the backdrop of an apparent complex relationship between *IDH* mutations and HR-dependent DNA damage repair, clinical trials testing PARP inhibitors in glioma patients are ongoing (Table 1). Olaparib as a monotherapy was investigated in the phase 2 OLAGLI clinical trial, which enrolled patients with recurrent IDH-mutant high-grade glioma. Olaparib was well tolerated, and median progression-free survival was 2.3 months [30]. Another phase 2 clinical trial reported that combination treatment with olaparib and the PD-L1 inhibitor durvalumab can be safely administered but displays limited efficacy [31]. Exploiting synthetic lethality between deficient HR DNA repair and *IDH* mutations through PARP inhibition may be enhanced by concurrent radiotherapy, as has been shown in preclinical models of glioma [32], and is being tested in ongoing clinical trials [33].

Oxidative stress

Oxidative stress can initiate cancers or prompt progression by chemically modifying DNA bases and causing mutations. IDH enzymes catalyze the conversion of isocitrate to 2OG while generating nicotinamide adenine dinucleotide phosphate (NADPH), a cofactor critical for maintaining cellular redox balance. IDH-mutant enzymes, in contrast, produce (*R*)-2HG through a catalytic mechanism that consumes NADPH [34]. *IDH* mutations have been demonstrated to reduce NADPH pools, which can inhibit recycling of oxidized glutathione to reduced glutathione and elevate ROS levels [35] (Fig. 1D). Reduced glutathione promotes elimination of free radicals, peroxides, lipid peroxides, and metals that may be harmful to DNA [36]. Moreover, reduced glutathione prevents oxidative DNA damage during radiotherapy [37].

In addition to consuming NADPH, IDH-mutant enzymes have also been shown to cause (*R*)-2HG-dependent inhibition of the 2OG-dependent transaminases BCAT1/2 [38]. Reduced BCAT activity decreases steady-state levels of glutamate and reduced glutathione, which is partly composed of glutamate. BCAT inhibition also increases reliance on the enzyme glutaminase (GLS) for glutamate and glutathione biosynthesis. These findings offer a potential mechanistic explanation for GLS hyperdependence displayed by IDH-mutant cells [39]. Notably, GLS inhibition is synthetic lethal with *IDH* mutations under conditions of oxidative stress or radiotherapy.

IDH-mutant glioma cells have been shown to display and respond to increased ROS levels by upregulating the Nrf2 antioxidant pathway [10]. Nrf2 is a transcription factor that regulates antioxidant gene expression and promotes redox homeostasis. In IDH1-mutant cells, elevated ROS leads to Nrf2 activation, which increases transcription of antioxidant genes, such as the gene encoding a key enzyme in the de novo glutathione biosynthesis

pathway, glutamate-cysteine ligase (*GCLC*) [10]. The antioxidant response stimulated by Nrf2 can thus be seen as a compensatory response to the oxidative stress induced by IDH1-mutated cancer cells. Targeting the Nrf2 antioxidant pathway could prove to be a novel approach to the treatment of IDH1-mutant cancers.

Notably, work by Molenaar et al. demonstrated that the $IDH1^{R132H}$ inhibitor AGI-5198 protects IDH-mutant tumor cells from radiotherapy [40], consistent with its ability to restore NADPH, glutamate, and glutathione homeostasis. After exposure to radiation, higher levels of ROS, DNA double-strand breaks, and cell death were found in $IDH1^{R132H}$-mutants as compared to IDH1 wild-type cells. Therefore, clinical trials of mutant IDH inhibitors are currently underway and, to date, do not involve combination with radiotherapy [41]. To exploit the radiosensitizing effects of *IDH* mutations, a trial is ongoing to test the addition of a GLS inhibitor, CB-839 (Telaglenastat), to standard-of-care radiation and temozolomide therapies for IDH-mutant glioma [42].

Discussion

IDH mutations induce profound metabolic, epigenomic, and transcriptomic reprogramming in glioma. Prior research has revealed multiple mechanisms through which the effects of *IDH* mutations converge on DNA damage repair pathways, leading to a number of clinical trials seeking to exploit these interactions for therapy (Table 1). Results from these ongoing studies will help resolve areas where data remain incomplete or conflicting, such as the role of mutant IDH in regulating radiosensitivity. Despite significant progress in understanding these mechanisms, important unanswered questions remain.

Given the multiple mechanisms through which *IDH* mutations impact DNA damage repair, disentangling the effects of any single mechanism in response to therapy remains challenging. However, this is an important goal in the field, considering that insights into these processes may inform rational design of combination therapy. For example, strategies that exploit DNA damage vulnerabilities caused by (*R*)-2HG would not be amenable to combination strategies involving a mutant IDH inhibitor. In contrast, therapies that exploit durable DNA damage repair deficits that are not altered by acute changes in (*R*)-2HG may permit use of concurrent mutant IDH inhibitors. The multiple downstream effectors of (*R*)-2HG can pose challenges for designing treatment strategies. For example, some data suggest that IDH-mutant gliomas develop alkylating agent-induced hypermutated phenotypes [43–45], possibly due to mutant-IDH driven DNA damage deficits. Exploiting this DNA damage deficit may therefore leverage increased tumor mutational burden and render these tumors susceptible to therapies such as immune checkpoint blockade. This is also supported by data suggesting that DNA damage can trigger an anti-tumor immune response [46]. However, other data suggest that (*R*)-2HG also suppresses the immune response and creates an immunosuppressive microenvironment [47–54] arguing for a mutant IDH inhibitor strategy to bolster immunotherapy response. Thus, it remains to be seen how to best optimize treatments that may exploit DNA damage (caused by mutant IDH and/or therapies such as alkylating agents or direct DDR inhibitors) in combination with mutant IDH inhibitors. Given the ongoing clinical testing of the efficacy of mutant IDH inhibitors

in lower-grade gliomas [55], this question will likely have heightened relevance as outcomes are reported from this study in the future.

In addition to the therapeutic implications of mechanisms linking *IDH* mutations with DNA damage, emerging data suggest these mechanisms may also help define the genomic landscape of gliomas. For example, recent clinical data show that among IDH-mutant astrocytomas and oligodendrogliomas, increased glioma grade is correlated with increased copy number variation (CNV), increased chromothripsis, and gene expression signatures of chromosomal instability (CIN) [56–58]. These genomic features and processes are intimately linked to DNA damage. Importantly, IDH-mutant astrocytomas with high expression signatures of CIN display worse progression-free and overall survival, suggesting that this signature may have prognostic significance. Further work is needed to determine whether CNV and CIN alterations themselves cause DDR deficits in IDH-mutant glioma or whether these effects are the result of upstream DNA damaging processes driven by mutant IDH. Nevertheless, these findings may reveal additional mechanisms of interplay between DNA damage and *IDH* mutations distinct from those highlighted in this article. Presence of CNV/CIN may also serve as a biomarker to identify subsets of mutant IDH glioma patients who may benefit most from treatments targeting DDR deficits.

Significant progress has been made in our understanding of the complex interplay between DDR and *IDH* mutations in gliomas, with promising new data providing a foundation for additional investigation. Results from ongoing clinical trials, as well as future preclinical studies of this topic, will establish deeper mechanistic insights that may ultimately be leveraged to develop new treatment strategies for IDH-mutant glioma patients.

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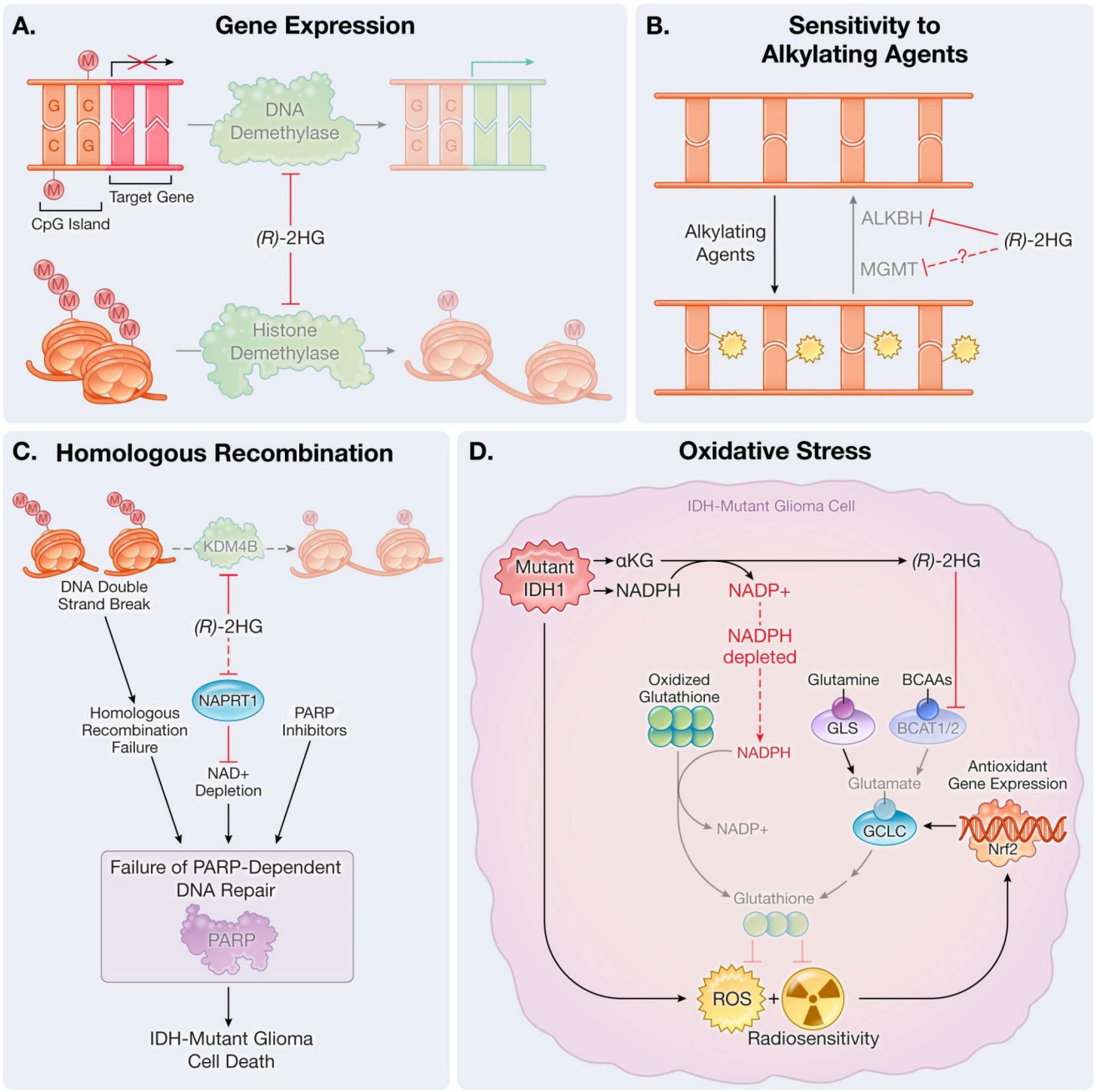

Fig. 1.

Altered responses to DNA damage in IDH-mutant gliomas. Examples of mechanisms related to (A) gene expression, (B) sensitivity to alkylating agents, (C) homologous recombination, and (D) oxidative stress. Dashed lines indicate indirect effects. BCAAs: branched-chain amino acids; ROS: reactive oxygen species

Table 1

Select completed and ongoing clinical trials related to DNA damage in IDH-mutant gliomas

Patient population	Therapy	Phase	Status	Outcome	Reference / NCT
Grade 3, 1p/19q codeleted oligodendroglioma	Radiation, TMZ	III	Undergoing redesign	Improved PFS with RT	NCT00887146;[15]
Anaplastic gliomas, 1p/19q non-codeleted	Radiation, TMZ	III	Completed	Improved OS with adjuvant TMZ	NCT00626990; [1]
Recurrent grade 4 IDH-mutant glioma	BAY 2402234 (pyrimidine synthesis inhibitor)	0	In development	N/A	N/A
Grade 2–3 IDH-mutant glioma	Telaglenastat (glutaminase inhibitor)	I	Not accruing	N/A	NCT03528642
Recurrent IDH-mutant glioma	Olaparib (PARP inhibitor)	II	Completed	Median PFS 2.3 months	NCT03561870; [30]
Recurrent grade 2–4 IDH-mutant astrocytoma	Niraparib (PARP inhibitor)	0	Accruing	N/A	NCT05076513
Recurrent grade 2–4 IDH-mutant glioma	Pamiparib (PARP inhibitor) and metronomic TMZ	I/II	Not accruing	N/A	NCT03914742
Recurrent IDH-mutant glioma	Olaparib and durvalumab	II	Accruing	N/A	NCT03991832

TMZ: Temozolomide

PFS: Progression-free survival

RT: Radiation therapy

OS: Overall survival