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Therapeutic strategies for downregulating isocitrate dehydrogenase in the treatment of glioblastoma multiforme

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Abstract

IDH-wildtype glioma (Glioblastoma) is the most lethal primary brain tumor in adults, with a median survival of 12–15 months despite optimal treatment. The isocitrate dehydrogenase (IDH) enzyme family, particularly IDH1, plays a central role in Glioblastoma Multiforme (GBM) pathobiology by regulating cellular redox homeostasis, NADPH production, and metabolic adaptation. In IDH-wildtype GBM, which constitutes the majority of primary cases, IDH1 significantly contributes to antioxidant defenses, thereby conferring resistance to radiotherapy, temozolomide (TMZ), and other chemotherapeutic agents. In contrast, IDH-mutant lower-grade gliomas and secondary GBMs harbor gain-of-function mutations that induce CpG island hypermethylation through the production of the oncometabolite 2-hydroxyglutarate (2-HG), resulting in epigenetic dysregulation. The dual mechanistic roles of IDH in GBM biology present distinct therapeutic vulnerabilities. This review evaluates three principal therapeutic strategies to modulate IDH in GBM: (1) small molecule inhibitors targeting IDH-mutants, including FDA-approved agents ivosidenib and vorasidenib, while noting the absence of FDA-approved agents for IDH-wildtype GBM and the ongoing preclinical investigation of IDH1-wildtype targeting; (2) gene manipulation techniques, such as RNA interference (RNAi) and CRISPR-Cas9-mediated knockout; and (3) nanomedicine-based delivery systems, including lipid nanoparticles (LNPs) and exosomes, designed to traverse the blood-brain barrier (BBB) and enable tumor-targeted delivery of therapeutic agents. The review aims to establish a framework for combination therapies directed at IDH in GBM, with a focus on improving clinical outcomes.

Introduction

Epidemiology and Clinical Burden of GBM

Glioblastoma (GBM) is the most prevalent and deadly primary malignant brain tumor in adults and is classified as a WHO Grade 4 IDH-wildtype tumor [1, 2]. In the United States, the GBM incidence rate is 3.2 cases per 100,000 people, and similar incidence rates exist in Western populations, accounting for approximately 14.5% of all primary brain tumors and approximately 49% of all primary malignant brain tumors, respectively [3, 4]. Despite decades of intensive research, patient outcomes remain dismal: median overall survival following diagnosis ranges from 12 to 15 months, and the five-year survival rate is approximately 5–7% [3, 5].

The standard treatment for newly diagnosed GBM is the Stupp protocol, which consists of maximal safe surgical resection, concurrent radiation therapy (60 Gy over 6 weeks), and adjuvant temozolomide chemotherapy. Developed in 2005, this protocol has seen only minor modifications since its introduction [6]. While modest improvements in overall survival have been observed with the addition of agents such as bevacizumab and tumor-treating fields (TTFields), these interventions have not produced significant survival benefits [7, 8]. The continued lack of success with novel agents in late-phase trials highlights the need to better understand and address the underlying biology of GBM treatment resistance.

The epidemiological profile of GBM has important prognostic implications. GBM more frequently affects adult males (male-to-female ratio of 1.6:1), is more prevalent among Caucasian populations, and is most commonly diagnosed in individuals over 50 years of age [3]. In contrast, IDH-mutant central nervous system (CNS) World Health Organization (WHO) grade 4 astrocytoma, classified as a high-grade glioma, is typically observed in younger patients and is associated with a more favorable prognosis due to the presence of IDH mutations. This molecular distinction has significantly influenced recent advances in GBM classification and treatment stratification [9-12].

Molecular Classification and Pathological Features

The WHO 2021 Classification of Tumors of the Central Nervous System represents a paradigm shift in glioma taxonomy, embedding molecular biomarkers, particularly IDH-mutation status, TERT promoter mutations, EGFR amplification, and chromosome 7/10 copy number changes, alongside histological features [13-16]. This reclassifies the GBM into IDH-wildtype (Primary GBM) and IDH-mutant, CNS WHO grade 4 astrocytoma, which was previously known as Secondary GBM (resulting from lower-grade precursor lesions) [11, 17].

IDH-wildtype GBM presented aggressively with a de novo onset, tends to occur in older patients, and is associated with a variety of other mutations, including EGFR (Epidermal Growth Factor Receptor) amplification (35.4%), CDKN2A/B loss (62%), PTEN gene (Phosphatase and tensin homolog) deletion, TP53 mutation (31.4% each), TERT promoter mutation (86.2%) and RB1(Retinoblastoma 1) loss (10.5%) [1, 15, 17-19]. In contrast, IDH-mutant gliomas share their molecular profile with diffuse astrocytomas and oligodendrogliomas, have CpG island methylator phenotype (CIMP), global DNA hypermethylation, and an excellent clinical prognosis [11, 12, 20].

Histopathologically, GBM is defined by microvascular proliferation, pseudopalisading necrosis, high mitotic activity, and marked nuclear pleomorphism [17, 21]. The features mirror the high level of intratumoral diversity and variability in GBM, which is directly linked to the failure of therapy, including the presence of cells with different genetic profiles, stem-like properties, and metabolic phenotypes [22, 23]. At least four distinct cellular states of GBM have been identified by single-cell RNA sequencing: neural progenitor-like (NPC-like), oligodendrocyte progenitor-like (OPC-like), astrocyte-like (AC-like), and mesenchymal-like (MES-like); each has unique vulnerabilities and resistance mechanisms. [24, 25].

The Blood-Brain Barrier as a Therapeutic Obstacle

One of the most challenging obstacles in GBM pharmacotherapy is the blood-brain barrier (BBB), a highly selective interface between the bloodstream and the brain consisting of brain capillary endothelial cells with tight junctions, pericytes, astrocytic endfeet, and associated basement membrane [26-29]. BBB allows for limited paracellular transport of hydrophilic compounds and large molecules, and many drug molecules that enter the BBB are actively extruded via active efflux transporters such as P-glycoprotein (P-

gp/ABCB1) and BCRP (ABCG2) [23, 28]. It is estimated that over 98% of all small molecule drugs and essentially all large molecule biologics cannot gain access to the intact BBB in therapeutic concentrations [30, 31].

The blood-brain barrier (BBB) is disrupted in regions of active tumor growth, as demonstrated by contrast-enhanced MRI; however, the infiltrative margins of GBM retain a largely intact BBB [32]. Tumor cells residing in these infiltrative regions are primarily responsible for recurrence and are largely inaccessible to conventional systemically administered therapies. Consequently, the development of BBB-penetrant therapeutics, including those utilizing receptor-mediated transcytosis, nanoparticle encapsulation, and active transport mechanisms, is a critical focus in GBM drug development.

Metabolic Reprogramming in GBM

Metabolic reprogramming is now a known feature of cancer, with GBM showing especially marked metabolic changes that drive its ability to proliferate quickly, survive in hypoxic niches, and resist therapy [33-35]. Despite oxygen availability, GBM cells exhibit activation of oxidative phosphorylation, glutamine-dependent anaplerosis, lipid biosynthesis, and one-carbon metabolism based on nutrient availability and microenvironment conditions [34, 36].

A critical aspect of GBM biology is the role of reactive oxygen species (ROS). Although ROS are inherently toxic, GBM cells exhibit highly upregulated antioxidant systems, including the glutathione (GSH) pathway, thioredoxin system, and NADPH-generating enzymes. These systems maintain ROS at concentrations that support proliferation, treatment resistance, and signaling, while preventing cell death [37-40]. Targeting this redox balance through metabolic interventions represents a promising strategy to sensitize GBM cells to chemotherapy. Isocitrate dehydrogenase (IDH) enzymes, particularly IDH1, are central regulators of cellular NADPH production, α-ketoglutarate (α-KG) generation, and the epigenetic landscape, thereby playing a pivotal role in GBM redox homeostasis [11, 12, 18, 20, 41]. A comprehensive understanding of both the physiological and pathological functions of IDH in GBM is essential for leveraging its therapeutic potential.

Isocitrate Dehydrogenase: Normal Physiological Roles

Structure and Subcellular Localization

In mammals, the isocitrate dehydrogenase family contains three distinct isozymes, which have different functions of subcellular localization, cofactor specificity, and physiological homeostasis. IDH1 is a homodimer enzyme found in cytoplasm and peroxisomes. IDH2 is a homodimer, located in the mitochondrial matrix. IDH3 is a heterotrimeric enzyme comprising three subunits, α, β, and γ, which is exclusive to the mitochondria and acts as the rate-limiting and irreversible enzyme in the TCA cycle [12, 20, 42, 43] (**Fig. 1**).

IDH1 and IDH2 are NADP+ dependent enzymes that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) and CO_2 [20, 43]. They share about 70% sequence homology and are very different in terms of regulation and metabolic context. IDH1 has a large domain, a small domain, and a clasp domain that collectively form the active site at the dimer interface, residues that are important to coordinate isocitrate and cofactor, Mg2+/Mn2+: Arg132 (the most common mutation hotspot), Arg100, Asp279, and Thr77 [10, 11, 20, 43].

Physiologically, both IDH1 and IDH2 can operate in the oxidative direction (isocitrate to α-KG) as well as in the reductive carboxylation direction (α-KG back to isocitrate) when NADPH levels are high, which is important for lipid biosynthesis and HIF-1α-independent hypoxic adaptation [44, 45]. This bidirectionality is reflected in the wide range of metabolic functions these enzymes play, apart from their involvement in the TCA cycle.

Cytoplasmic NADPH Homeostasis

IDH1 is primarily known for its physiological role in generating cytoplasmic NADPH by the oxidative decarboxylation of isocitrate. The NADPH supplies electrons for reductive biosynthesis and antioxidant defense systems in the cell [46, 47]. NADP+ is the oxidized form of NADPH and is the cofactor for the enzyme glutathione reductase that converts oxidized glutathione (GSSG) to reduced glutathione (GSH), and for thioredoxin reductase, which converts oxidized thioredoxin into its reduced form. GSH and thioredoxin play an important role in cellular

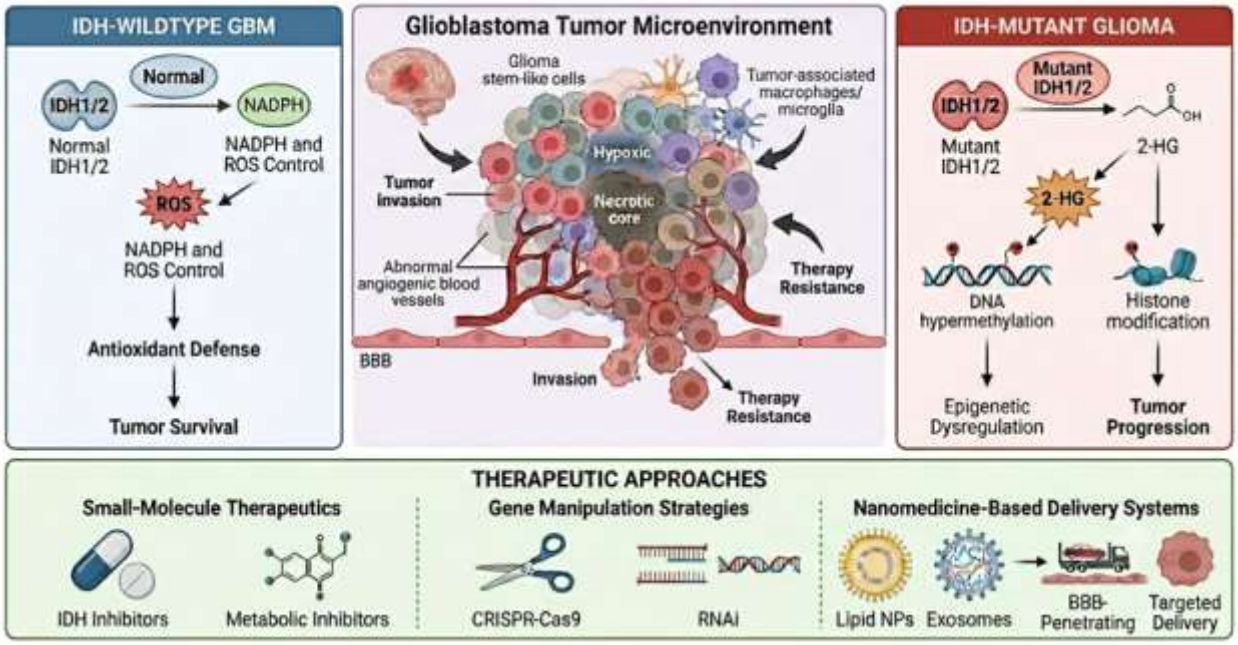

Fig. 1: Overview of GBM Pathobiology and IDH-Directed Therapeutic Strategies. A schematic representation illustrating the molecular landscape of IDH-wildtype and IDH-mutant glioma, key metabolic alterations, including NADPH/ROS balance and 2-HG accumulation, and the therapeutic approaches reviewed: small-molecule inhibitors, gene manipulation (CRISPR/RNAi), and nanomedicine-based delivery systems.

peroxide-scavenging systems that detoxify hydrogen peroxide and lipid peroxides produced in normal metabolic processes, as well as in response to oxidative stress [47].

Studies have shown that IDH1 deficiency in mammalian cells results in decreased GSH/GSSG ratio, elevated ROS production, dysfunction of mitochondria, and increased sensitivity towards ROS-inducing agents [47-49]. In tissues with high oxidative metabolic activity, such as the brain, liver, and adipose tissue, IDH1-generated NADPH is also a quantitatively important source of overall cellular NADPH production in addition to the pentose phosphate pathway (PPP) and malic enzyme [47, 50].

Lipid Biosynthesis and Reductive Carboxylation

The IDH1 also plays a role in *de novo* lipid biosynthesis beyond the antioxidant effect, by providing acetyl-CoA to the cytoplasm. In mitochondrial dysfunction or hypoxia, IDH1 functions in reductive carboxylation; NADPH is used to reduce α-KG to isocitrate, and then isocitrate is converted to citrate by aconitase working in reverse. This citrate can arise via two distinct routes: mitochondrial reductive carboxylation (primarily IDH2-mediated), in which citrate generated in the matrix is exported to the cytosol via the mitochondrial citrate carrier (SLC25A1). The second one is via direct cytosolic reductive carboxylation (IDH1-mediated), which generates citrate locally without requiring export. In the cytosol, this citrate is cleaved by ATP-citrate lyase (ACLY) into acetyl-CoA and oxaloacetate. Acetyl-CoA serves as the direct precursor for both fatty acid synthesis and cholesterol (mevalonate pathway) synthesis, while oxaloacetate is not a lipogenic precursor and is instead reduced to malate for further metabolism [44, 45]. This reductive carboxylation pathway is an essential metabolic adaptation of hypoxic tumor cells, including GBM. Under hypoxia and glutamine-enriched conditions, IDH1 and IDH2 can catalyze citrate in reverse, allowing tumor cells to sustain lipid biosynthesis for membrane biosynthesis and signaling even in the absence of normal mitochondrial citrate synthesis. The fact that IDH1 can be an antioxidant enzyme or a player in lipid biosynthesis [45, 51, 52] suggests its multifaceted metabolic function, which explains why its loss or mutation in GBM can lead to many metabolic changes.

Mitochondrial Metabolism

IDH2 is a mitochondrial NADP+-dependent isoform that functions complementary to IDH1 for maintaining mitochondrial NADPH pools essential for mitochondrial antioxidant defense, primarily via the glutathione peroxidase and peroxiredoxin system in the mitochondrial matrix [10, 12]. The IDH2-generated NADPH is required for mitochondrial ROS clearance, and IDH2 knockdown models have shown enhanced oxidative damage to their mitochondria, diminished efficiency of fatty acid oxidation, and age-related mitochondrial dysfunctions [12, 53].

IDH3 is the NAD+-dependent, mitochondrial isoform that catalyzes the essentially irreversible decarboxylation of isocitrate to generate NADH for the electron transport chain in the TCA cycle. IDH3 is allosterically regulated by ADP (activator) and ATP/NADH (inhibitors), contrary to IDH1 and IDH2. In contrast to IDH1 and IDH2, IDH3 is allosterically regulated by ADP (activator) and ATP/NADH (inhibitors), which link TCA cycle flux to cell energy status. IDH3 is not mutated in the gain-of-function manner in gliomas and has not been found as a direct driver of cancer, but alterations in its expression levels influence overall TCA flux and the ratio of NADH/NAD+ in GBM [12].

IDH in Glioblastoma: Oncogenic Roles and Metabolic Consequences

IDH-Mutations in Gliomas: Epidemiology and Molecular Mechanism

In 2008, genome-wide sequencing of GBMs revealed IDH-mutations as one of the largest discoveries in the field of neuro-oncology in the last 20 years [54, 55]. IDH1 and IDH2 mutations are found in around 70-80% of WHO grade II-III diffuse gliomas, and in astrocytoma IDH-mutant, CNS grade 4 from these lesions, while GBM is wildtype for these [11, 12].

Most IDH-mutations (including ~90% of all IDH-mutations in glioma) are missense point mutations to either the IDH1 gene at codon 132 (typically IDH1 R132H) or the analogous codon 172 of IDH2 [12, 54, 55]. Such mutations are found at the enzymatic active site and have a new enzymatic activity: the IDH1/2-mutant catalyzes the reduction of α-KG to (R)-2-hydroxyglutarate (2-HG) instead of the oxidative decarboxylation of isocitrate, and the resulting product (2-HG) is an oncometabolite that inhibits the tumor suppressor enzyme, the mutant enzyme acts on an NADPH-consuming reaction [11, 43, 46, 54].

Unlike a loss-of-function mutation, mutant IDH is not simply a loss of IDH activity, but it actively shifts cellular metabolic pathways toward the production of 2-HG, an oncometabolite that causes epigenetic changes to promote the growth of the tumor [12, 55].

3.2 2-Hydroxyglutarate as an oncometabolite and its epigenetic effects

The pathogenic significance of 2-HG stems from its structural similarity with α-KG, which enables it to inhibit several α-KG-dependent dioxygenases [12, 54, 55]. The ten-eleven translocation (TET) family of DNA demethylases and the Jumonji C domain-containing (JMJC) histone demethylases are the most impactful targets [11, 43]. Inhibition of TET2 and related enzymes by 2-HG also disrupts the active DNA demethylation process, resulting in genome-wide progressive hypermethylation of CpG islands—a pattern known as CpG island methylator phenotype (CIMP) in IDH-mutant gliomas [18, 55].

A wide range of tumor suppressor genes, differentiation-promoting transcription factors, and DNA repair genes are silenced by CIMP-mediated hypermethylation. Importantly, hypermethylation of the MGMT promoter in IDH-mutant gliomas renders tumors more sensitive to temozolomide by blocking the action of the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT), and this is likely to play an important role in the improved clinical outcomes seen in this molecular subtype [11]. The histone demethylases JMJC are inhibited by 2-HG, resulting in higher levels of H3K9me3 and H3K27me3, which decreases the transcriptional flexibility of the chromatin. In addition to the epigenetic functions, 2-HG is known to inhibit the ATP synthase and cytochrome C oxidase, resulting in mitochondrial dysfunction, to promote HIF-1α stability under normoxia by inhibiting PHD prolyl hydroxylases, and to activate the mTOR pathway by inhibiting LKB1[12, 20, 41]. These pleiotropic effects all contribute to the process of oncogenic transformation that leads to the initiation of gliomagenesis in IDH-mutant cells. However, paradoxically, they can also make IDH-mutant tumor cells more susceptible to certain targeted therapies.

IDH-Wildtype GBM: Retained IDH1 Function as a Metabolic Vulnerability

The IDH-wildtype is the most prevalent form of primary GBM, and IDH1 remains enzymatically active in the cytoplasm and is an important source of NADPH for antioxidant defenses [38, 44]. These tumors often have higher expression of IDH1 than normal brain cells, just as metabolically active cancer cells require more NADPH. In the same way, increased IDH1 expression has been linked with higher resistance to oxidative stress-inducing treatments such as radiotherapy and TMZ in preclinical models [37, 47]. Studies have shown that knockdown of wild-type IDH1 depletes NADPH and glutathione, thereby increasing oxidative stress and sensitizing glioblastoma cells to radiation-induced cytotoxicity.[56] In addition, there is growing evidence that when the production of NADPH by wild-type IDH1 is disrupted, tumor cells adopt alternative metabolic pathways to achieve redox balance and survival during metabolic stress, such as the pentose phosphate pathway and malic enzyme-mediated NADPH production [38, 57].

The mechanism underlying this therapeutic resistance is that GBM cells exposed to a radiotherapy-generated ROS or TMZ-induced mitochondrial stress are dependent on the IDH1 activity, maintaining the GSH/GSSG ratio and NADPH/NADP+ balance [37, 38]. In a GBM setting, IDH1 inhibition or IDH1 knockdown significantly lowered NADPH levels, diminished glutathione pools, and made cells vulnerable to cell death when irradiated, making IDH1 a legitimate mediator of radioresistance in this context [37, 38]. Likewise, it was found that IDH1–deficient mouse embryonic fibroblasts and IDH1–knockdown glioma cells were extremely vulnerable to hydrogen peroxide and other oxidative stress agents [47].

In addition, IDH1 is involved in reductive carboxylation-driven lipid synthesis in GBM cells under hypoxic conditions, especially in the GBM core [37, 44]. IDH-wildtype GBM cells can grow rapidly, synthesize new membranes, and survive in the presence of low levels of oxygen because of this metabolic flexibility, which is reduced by depletion of the activity of IDH1. The dual role as an antioxidant agent and a biosynthetic enzyme makes it a promising metabolic target with the potential to inhibit the viability of GBM cells through multiple mechanisms [37, 48].

IDH1 in Therapeutic Resistance to Temozolomide and Radiotherapy

The backbone of GBM chemotherapy is an alkylating agent, temozolomide (TMZ), which primarily targets guanine residues at the O6 position, resulting in futile mismatching repair cycling and ultimately causing a DNA double-strand break.[58]. In addition to this canonical action, TMZ can cause mitochondrial stress, disrupt the electron transport chain, and produce mitochondrial ROS, further driving its cytotoxic effect [59, 60].

Cells from GBMs that produce more NADPH via IDH1 activity can better combat ROS generated by TMZ. They increase glutathione recycling, reduce oxidative DNA damage, and activate the downstream apoptotic signaling. Several studies have shown that IDH1 expression levels are inversely correlated with TMZ sensitivity in GBM cell lines, and the knockdown of IDH1 has been shown to consistently improve the sensitivity of IDH-wildtype GBM models to TMZ-induced apoptosis [59, 61].

The production of ROS in irradiated water plays a vital role in radiotherapy-induced cytotoxicity, with the hydroxyl radicals generated in water following the radiolysis of water having a particular and significant impact on DNA, lipids, and proteins [37, 38]. The anti-radiation effect of IDH1 in GBM is similar to its role in TMZ resistance, as it helps to preserve NADPH pools and lower ROS. IDH1 regulates the extent of oxidative damage caused by radiation. GBM preclinical studies have revealed that a combination of IDH1 inhibition and radiotherapy shows synergistic cytotoxicity, indicating that strategies targeting IDH1 might be most clinically relevant as radiosensitizers [37, 59] (**Fig. 2**).

Collectively, these findings demonstrate that IDH-mutant and IDH-wildtype enzymes fulfill distinct roles in glioma biology. Consequently, therapeutic strategies targeting IDH are being developed along three principal avenues: pharmacological inhibition, genetic manipulation, and innovative delivery technologies capable of crossing the blood-brain barrier (BBB).

Therapeutic Approaches Targeting IDH1/2-mutation

Small Molecule Inhibitors

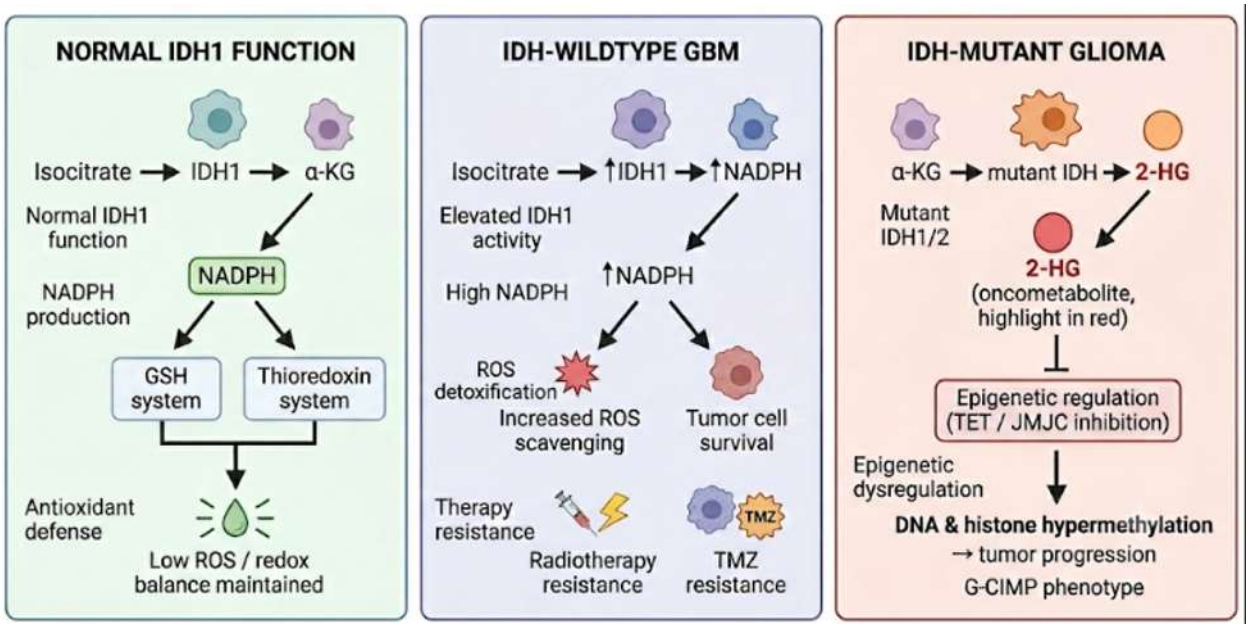

Fig. 2: IDH1 Metabolic Functions in Normal Brain, IDH-wildtype GBM and IDH-mutant Gliomas. Left panel: Normal IDH1 function showing isocitrate → α-KG + NADPH + CO2 reaction, NADPH feeding into GSH/Trx antioxidant systems, and reductive carboxylation pathway. **Right panel**: In IDH-mutant Gliomas, mutant IDH1/2 produces 2-HG from α-KG, with downstream TET and JMJC inhibition causing CIMP hypermethylation. In IDH-wildtype GBM (**center**), elevated wildtype IDH1 drives heightened NADPH production, enhanced ROS scavenging, and radiotherapy/TMZ resistance.

Table 1a: IDH-mutant Inhibitors (2-HG Suppression Mechanism)

Agent	Target	Mutation Relevance	BBB Penetrance	Key Metabolic Endpoint	Reference
Ivosidenib (AG-120)	IDH1 R132X	IDH1-mutant glioma,	Low	Suppresses 2-HG via blockade of neomorphic mutant IDH1 activity	[62]
Vorasidenib (AG-881)	IDH1/2	IDH1/2-mutant Grade 2 glioma	High	Pan-mutant IDH1/2 inhibition → 2-HG suppression	[63]
Enasidenib (AG-221)	IDH2 R172X	IDH2-mutant glioma	Low	Suppresses 2-HG via mutant IDH2 blockade	[64]
Olutasidenib (FT-2102)	IDH1 R132X	IDH1-mutant glioma	Demonstrated CSF penetrance	Suppresses 2-HG	[65]
IDH305	IDH1 R132H	IDH1-mutant glioma, AML, MDS	CNS-penetrant	Suppresses 2-HG via mutant IDH1 blockade	[66, 67]
GSK321 (GSK864)	IDH1-mutant Higher doses can also inhibit the IDH-wildtype IDH	IDH-mutant	CNS-penetrant	Suppresses 2-HG via mutant IDH1 blockade	[57, 68]

AML = acute myeloid. MSD = myelodysplastic syndrome. leukemia; GSH = glutathione; GCL = glutamate-cysteine ligase

Table 1b: IDH-Wildtype GBM Redox-Targeting Agents

Agents	Target	Mutation Relevance	BBB Penetrance	Key Metabolic Endpoints	References

BSO (buthionine sulfoximine)	GCL (GSH synthesis)	IDH-wildtype GBM	Moderate CNS	Depletes glutathione (GSH) pool by blocking the rate-limiting step of GSH synthesis, increasing susceptibility to oxidative stress	[69]
Auranofin	Thioredoxin reductase	IDH-wildtype GBM	CNS-penetrant	Inhibits thioredoxin reductase, collapsing the thioredoxin/NADPH antioxidant axis and driving ROS accumulation	[40]

IDH-Mutant-Specific Inhibitors: Ivosidenib and Enasidenib

Once the IDH-mutations were identified as drivers of cancer, the small-molecule inhibitors of the mutated enzyme pocket were developed in a short time. The FDA approved Ivosidenib (AG-120), an orally bioavailable allosteric inhibitor selective for mutations on IDH1 R132H/C/S/G/L in relapsed/refractory acute myeloid leukemia (AML) in 2018 [70, 71]. It binds to the allosteric site of IDH1and stabilizes the enzyme to carry out the reductive reaction that converts α-KG to 2-HG, resulting in a dramatic decrease in the levels of 2-HG in tumor cells [63, 72, 73].

The pivotal INDIGO trial is a multicenter, randomized, double-blinded Phase 3 study that demonstrated that vorasidenib (AG-881) is a key optimization parameter to inhibit theIDH1/2, with excellent BBB traversing ability. IDH1/2 can significantly extend progression-free survival in patients with residual or recurrent Grade 2 IDH-mutant gliomas [63, 73].

Enasidenib (AG-221) is an IDH2 selective inhibitor, and its potential has been evaluated in the IDH2-mutant gliomas during multiple clinical trials. The incidence rate of this mutation is limited to around 4% of IDH-mutant gliomas [11]. Despite these epidemiological limitations, enasidenib has been demonstrated to have biochemical proof-of-concept in lowering 2-HG and inducing differentiation in IDH2-mutant glioma models [12]. However, it is important to reiterate that all the above-mentioned small inhibitors have been specifically approved against IDH-mutant cancers, and that no clinically approved drugs targeting the IDH-wildtype exist at present. Therefore, targeting IDH-wildtype GBM remains an active area of research. Tables 1a and 1b have enlisted IDH-mutant and IDH-Wild type small molecular inhibitors.

Gene Manipulation Strategies

RNA Interference: siRNA and shRNA Approaches

RNA interference (RNAi) is a method that takes advantage of the endogenous RNA-induced silencing complex (RISC) pathway to silence target genes at the post-transcriptional level by degradation of target mRNA through a sequence-specific process. Small interfering RNA (siRNA) molecules are 19-23 nucleotide-long duplexes of RNA that are double-stranded and have 2-nucleotide 3' overhangs that bind to the RNA-induced silencing complex (RISC), which is a protein complex containing the Argonaute 2 (AGO2) endonuclease that cleaves complementary mRNA with sequence-specificity [74, 75]. Transient siRNA silencing (usually occurs in rapidly dividing cells within 3-7 days) can be beneficial with respect to safety, but it is not so useful for a therapeutic duration. Short hairpin RNA (shRNA) constructs are delivered using viral vectors (lentivirus, AAV), which results in their sustained knockdown through continuous transcription of hairpin precursors that Drosha and Dicer process into functional siRNA-like molecules that incorporate into the RISC (RNA-induced silencing complex) for ongoing mRNA silencing [76-79]. Several studies have used shRNA-induced IDH1 knockdown to validate IDH1 as a therapeutic target in patient-derived GBM xenografts and GBM cell lines (U87MG, U251, and T98G) and have consistently shown that IDH1 silencing leads to decreased NADPH levels, depleted glutathione, elevated ROS, and compromised cell proliferation and colony formation [37, 47, 79, 80].

Several *in vitro* studies have shown that the silencing of IDH1 by siRNA increases the sensitivity of IDH-wildtype GBM cells to TMZ. Two studies have shown that siRNA knockdown of IDH1 in U87MG cells and xenograft models is associated with a decrease in cell viability when combined with therapeutic TMZ, but not when administered alone [81, 82]. One of the key challenges in *in vivo* delivery of siRNA to GBM is the lower permeability of the BBB. Herein, the role of nanomedicine approaches becomes pivotal in facilitating the efficient targeted delivery of therapeutic agents to GBM in the brain milieu across the BBB.

CRISPR-Cas9-Mediated Gene Editing in GBM

The CRISPR-Cas9 system is a revolutionary technology in functional genomics and has opened up new cancer gene therapeutic avenues based on *Streptococcus pyogenes* and related bacteria's adaptive immune system [83-85].

CRISPR-Cas9 has been widely used in GBM research to confirm oncogenic drivers, metabolic dependencies, and identify new therapeutic targets. [86-88]. Multiple enzymes and genes related to cell proliferation and signaling have been knocked out using the CRISPR system in GBM cells. [86, 89-93]. Importantly, IDH1 knockout in IDH-wildtype metastatic colon adenocarcinoma cells (SW620) has led to a decrease in NADPH, an increase in ROS, and inhibition of proliferation of the aggressive colon cancer cell line [48].

In IDH-mutant gliomas, CRISPR-Cas9 is an alternative approach to small molecule inhibitors, namely, to correct the IDH1 R132H mutation to wildtype by Homology-Directed Repair (HDR). Allele-specific correction of patient-derived glioma cells has been successfully demonstrated in single-cell patient-derived glioma using Cas9, partial demethylation of CIMP, and restoration of the differentiation capacity [89, 90, 94]. Although HDR efficiency in post-mitotic or slowly dividing cells makes this therapeutic approach challenging, these results provide support for the concept of precision gene editing as a metabolic therapy for IDH-wildtype GBM and IDH-mutant gliomas (**Fig. 3**).

Nanomedicine-based Approach

Nanomedicine utilizes the physicochemical properties of materials at the 1-1000 nm scale to design the delivery vehicles that control drug loading, drug release kinetics, surface chemistry, and target specificity [95]. The BBB is a major hurdle in GBM therapy, with nanoparticles either taking advantage of the disrupted BBB in the tumor core (i.e., enhanced permeability and retention, EPR effect), binding to receptor-mediated transcytosis pathways (Transferrin receptor, LRP1, LDLR), or being locally injected into the brain via convection-enhanced delivery (CED) to attain therapeutic concentrations in the brain parenchyma [96-98].

The main design considerations for nanoparticles to cross BBB are: size of 50 -150 nm, as this range is optimal for passive EPR-mediated accumulation and transcytosis, surface charge or zeta potential from neutral to slightly negative, assist in minimizing non-specific protein adsorption and extends circulation half-life, PEGylation is the coating of nanoparticles with a polymer molecule named polyethylene glycol, to reduce the potential of opsonization and clearance by the mononuclear phagocyte system, and finally, surface ligand density for active targeting [96, 99, 100]. Cargo can be in the form of small molecules, nucleic acids (siRNA, CRISPR components, mRNA), or protein complexes that need to be encapsulated and stabilized in different ways (**Fig. 4**).

Lipid Nanoparticles (LNPs)

Lipid nanoparticles (LNPs) are the most clinically advanced nano delivery platform. They have been successfully used to deliver siRNA for the treatment of hereditary transthyretin amyloidosis (HTTA) by the approval of patisiran (Onpattro), and the COVID-19 mRNA vaccines (Moderna, Pfizer-BioNTech) [101, 102]. LNPs are structurally composed of an ionizable lipid core, phospholipid shell, cholesterol, and PEG-lipid, in an optimized molar ratio to facilitate endosomal escape and protect payloads [103-106].

Application of LNPs in GBM therapy has involved the functionalization of their polymeric surface with transferrin, folic acid, glucose transporter ligands, or anti-EGFR antibody fragments for receptor-mediated BBB transcytosis and targeting of tumor cells [107, 108].

In orthotopic U87MG xenograft models, TMZ-loaded LNPs demonstrated significantly higher intratumoral accumulation of TMZ while allowing for less systemic toxicity [109, 110]. Nanoparticles loaded with different cargoes have been used in treating gliomas. For instance, knocking out miRNA-21, EGFR, and PLK1 from the U87 cell line inhibits cell growth [90, 111].

CRISPR-Cas9 delivery can be achieved with Cas9 mRNA + sgRNA (two RNA components) or with pre-assembled Cas9 Ribonucleoprotein (RNP) complexes [111, 112]. The RNP delivery approach has the advantage of shortening the lifetime of the Cas9 protein in the cell to reduce the risk of off-target editing. However, it is more difficult to formulate the

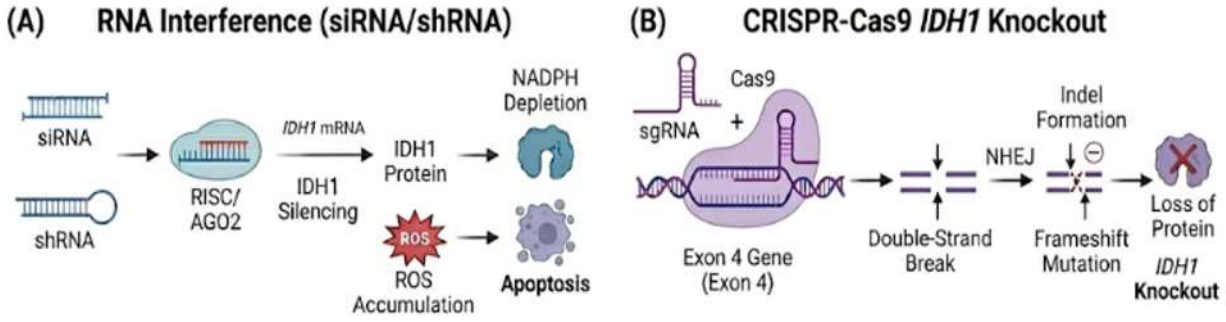

Fig. 3: **Gene Manipulation Strategies Targeting IDH1 in GBM.** (**A**) siRNA/shRNA mechanism, RISC loading, AGO2-mediated mRNA cleavage, and downstream NADPH depletion cascade with increased ROS and apoptosis; (**B**) CRISPR-Cas9 IDH1 knockout mechanism, sgRNA design targeting IDH1 exon 4, Cas9 DSB induction, NHEJ-mediated indel formation, and frameshift leading to nonfunctional protein.

RNP complex because of the high size and charge heterogeneity of the RNP complex [112, 113].

The same platform architecture can be directly applied to metabolic gene ablation, as is the case with the LNP applications listed above, which are targeting resistance-associated or oncogenic targets. The CRISPR-Cas9 plasmid or mRNA/sgRNA-LNP is shown to induce functional gene editing of the metabolic gene LDHA and alter the downstream metabolic flux in tumor cells [114]. LNP-delivered CRISPR-Cas9 against a GBM-relevant target was confirmed to have an on-target editing efficiency by next-generation sequencing and prolonged survival of tumor-bearing mice in the orthotopic GBM model [115], demonstrating that LNP-CRISPR delivery is effective at not only ablating the target at the molecular level, but also imparting a measurable survival benefit in the orthotopic GBM setting relevant to the IDH1 knockout strategy.

Exosomes and Extracellular Vesicles

The extracellular vesicles (EVs) or exosomes are naturally secreted extracellular vesicles with a diameter of 30-150 nm that are produced by all cell types via the endosomal pathway (fusion of multivesicular bodies with plasma membrane) [116]. They have intrinsic cell-to-cell communication properties mediated by their lipid bilayer membrane, which is enriched in sphingomyelin, cholesterol, and phosphatidylserine, and surface tetraspanin proteins (CD63, CD81, CD9) and intercellular adhesion molecules (ICAM-1) that are being utilized for therapeutic agent delivery [116-119].

Exosomes possess a significant therapeutic potential for the delivery of GBM. Exosomes are low immunogenic, less readily cleared by the mononuclear phagocyte system than synthetic nanoparticles and have natural tropism for brain tissue based on their cellular origin [119, 120]. In the preclinical sphere, exosomes obtained from MSCs, macrophages, and dendritic cells have all been shown to pass the BBB, potentially via exosome fusion with brain endothelial cells and the exosomal surface receptor-mediated pathway [120, 121].

Therapeutic cargo can be loaded into exosomes by one of the two methods: endogenous loading – by co-culture or transfection of the producer cells; or exogenous loading – by electroporation, sonication, saponin permeabilization, or incubation with hydrophobic compounds [122]. The most studied loading method for nucleic acid cargo is electroporation, with siRNA loading efficiencies exceeding those of traditional conditions; however, optimized electroporation protocols with low voltage, high capacitance conditions have yielded higher loading efficiencies [123-125]. Delivery of CRISPR-Cas9 RNP has been achieved by electroporation loading of exosomes in both U87MG *in vitro* and *in vivo* models that resulted in functional editing of recipient GBM cells [92, 121].

Targeted delivery of exosomes to tumor cells has been achieved through two methods: genetic fusion of targeting ligands to exosomal surface proteins (such as LAMP2B and CD63 fusions) and chemical conjugation of targeting ligands to the surface of

isolated exosomes [126, 127]. Intravenous injection of anti-EGFR (GE11 peptide), anti-RGD (RGD motifs), and GBM-homing peptides exosomes resulted in significantly higher intratumoral accumulation than for untargeted exosomes in orthotopic GBM models, with 4–6-fold higher tumor-associated fluorescence [120, 126, 128]. Translationally, delivery of siRNA targeting the STAT3 gene using surface-functionalized exosomes has been shown to suppress STAT3 protein by 50.9% and 86.6% in GBM cells *in vitro* and to mediate a decrease in tumor growth *in vivo* in xenograft models [129]. In addition to siRNA delivery, CRISPR-Cas9-based direct gene editing in GBM has been accomplished by exosome-based platforms. A genome-wide CRISPR-Cas9 library screen coupled to the exosome delivery system identified functionally relevant genes in U87-derived and patient-derived GBM cells and reduced in vivo tumor burden in a GBM system sharing a U87 background with the cells used in this study [130], highlighting the feasibility of exosome-mediated functional gene modulation in this model system.

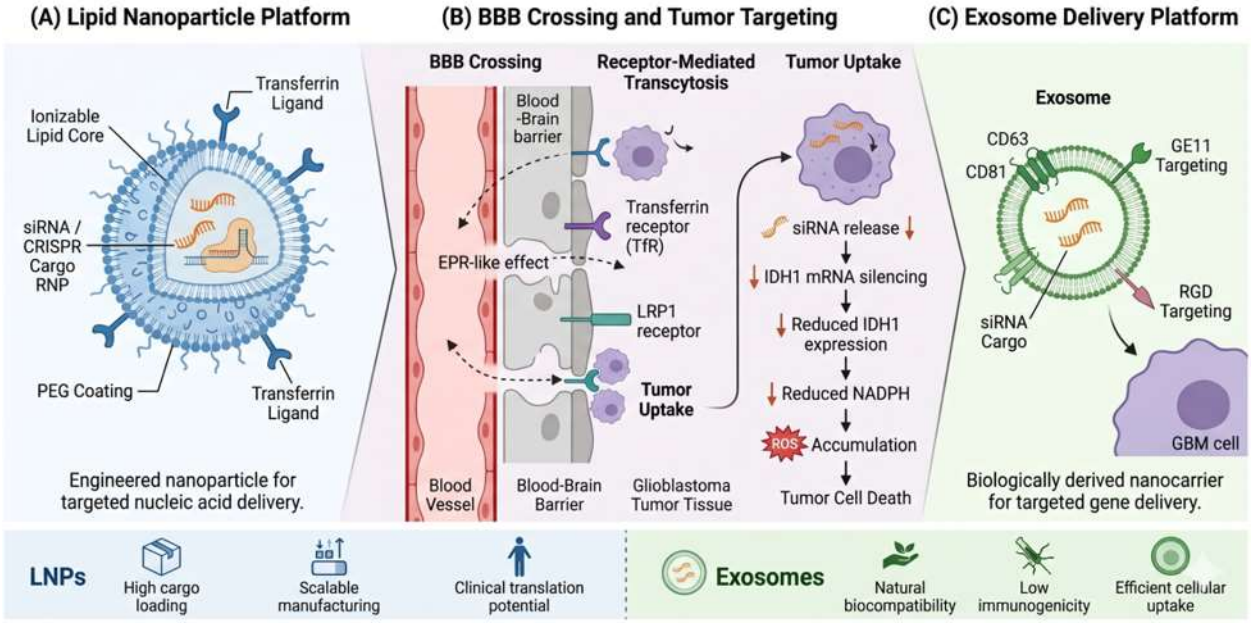

Fig. 4: Nanoparticle-Based Delivery Systems for IDH1 Targeting in GBM. (**A**) Lipid Nanoparticle (LNP) cross-sectional diagram showing ionizable lipid core, siRNA/Cas9 RNP cargo, PEG-lipid corona, and transferrin receptor targeting ligand; (**B**) Exosome — membrane bilayer with tetraspanin markers (CD63, CD81), loaded siRNA, and GE11/RGD surface functionalization; (**C**). The central panel illustrates BBB crossing mechanisms: passive EPR effect through disrupted BBB, receptor-mediated transcytosis (transferrin receptor, LRP1), and intratumoral release with IDH1 siRNA silencing cascade.

Integrated Therapeutic Strategies and Future Perspectives

Rationale for Combination Approaches

The multifactorial nature of GBM resistance, including intratumoral heterogeneity, glioma stem-like cell (GSC) mediated repopulation, adaptive signaling rewiring, and blood-brain barrier (BBB) pharmacokinetic limitations—supports the adoption of rationally designed combination regimens rather than single-agent therapeutic strategies [131-133]. IDH-directed therapies are best conceptualized as metabolic sensitization approaches that augment the efficacy of established cytotoxic modalities, such as radiotherapy and temozolomide (TMZ), as well as emerging targeted agents.

Several preclinical proof-of-concept combinations have demonstrated particular promise. PARP1 and epigenetic silencing induced cell death upon giving TMZ, showing a consistent synergetic effect [81, 134]. IDH inhibitor plus radiotherapy combinations have similarly demonstrated enhanced cell kill, particularly in glioma stem cell-enriched populations

[18, 37]. Nanoparticle co-delivery of TMZ and STAT3 siRNA represents a particularly attractive strategy, enabling simultaneous pharmacological and genetic downregulation of MGMT, thus making the cells sensitive to TMZ [121].

Nanoparticle-Mediated Co-delivery of CRISPR and Chemotherapy

Combining the power of the CRISPR-based gene editing platform with delivery technologies such as nanomedicine is a new frontier in precision medicine for GBM. In a preclinical setting, lipid nanoparticle (LNP)-mediated delivery of Cas9 mRNA and sgRNA have been successfully employed for therapeutic gene editing in glioblastoma models. Studies targeting genes such as PLK1 and miR-10b demonstrated efficient *in vivo* genome editing, suppression of tumor growth, reduced glioma stem cell viability, and prolonged survival in orthotopic GBM models, highlighting the feasibility of RNA-based CRISPR-Cas9 delivery for GBM therapy [135, 136]. However, the application of LNP delivered CRISPR-Cas9 specifically targeting IDH1, either alone or in combination with TMZ, remains an area to be explored in GBM therapeutics. Another translational avenue for delivery of CRISPR components in GBM is to use naturally occurring cellular communication properties of exosomes to convey genome editing machinery with minimal immunogenicity [92, 121]. Proof-of-concept studies have demonstrated that exosomes can be engineered to encapsulate and deliver Cas9-sgRNA ribonucleoprotein (RNP) complexes to recipient cells, resulting in detectable genome editing [137-139]. Although exosome-mediated CRISPR delivery has not yet been extensively evaluated for IDH1 targeting in GBM, the intrinsic biocompatibility, BBB crossing potential, and tumor tropism of engineered exosomes make them promising candidates for future GBM gene editing therapies.

Recent advances in surface engineering, active targeting, and co-loading of chemotherapeutic agents are converging to create a new class of nanoplatforms capable of simultaneously delivering IDH1-targeting payloads and chemotherapeutic agents at the single-cell level within tumors, thereby facilitating pharmacological synergy. IDH-directed combination therapy is poised to become a major component of next-generation GBM treatment. The integration of molecular biology, genomic medicine, and nanotechnology is enabling the identification of genetic targets that may yield therapeutic strategies without the limitations of conventional chemotherapy.

Emerging Targets and Future Directions

In addition to IDH1, several other IDH downstream and parallel targets in the IDH-NADPH-ROS regulatory axis may be considered as complements to IDH-targeted approaches. NRF2 (NFE2L2) is a master regulator of antioxidant response element (ARE) driven gene expression, and it has been demonstrated to transcriptionally upregulate IDH1, G6PD, and other NADPH-generating enzymes in response to therapeutic stress [140-142]. A new concept known as metabolic synthetic lethality suggests that two metabolic pathways simultaneously inhibited would be toxic to cancer cells but not normal cells because of metabolic rewiring of cancer, providing a methodology for selecting the best partners of IDH1 in GBM [143]. Synthetic lethal interaction mapping via high-throughput metabolic flux screens and CRISPR-based combinatorial knockout libraries are still emerging for GBM, and preliminary results show synthetic lethal partners of IDH1, such as PHGDH (serine biosynthesis), FASN (fatty acid synthase), and SLC7A11 (cystine transporter) [52, 144, 145]. The role of the immune system in therapeutic responses to GBM is increasingly understood to be a central one, and this could be relevant to IDH targeting strategies. IDH-mutant gliomas have an immunosuppressive tumor microenvironment, in part caused by 2-HG, which suppresses the function of T-cells by inhibiting HIF-1α-dependent glycolysis and disrupting chemokine signaling that regulates T-cell recruitment [146-148]. This immunosuppressive tumor microenvironment can be partially reversed by IDH inhibition, which reduces the oncometabolite R-2-hydroxyglutarate (2-HG) and is associated with restoration of immune cell recruitment and antigen presentation. This mechanistic rationale has led to ongoing clinical evaluation of combining IDH-targeted therapies with immune checkpoint blockade (ICBs), including anti-PD-1 and anti-PD-L1 strategies. In this context, early-phase clinical trials such as the AMPLIFY-NEOVAC study are investigating an IDH1R132H peptide vaccine in combination with the anti-PD-L1 antibody avelumab to enhance anti-tumor T-cell responses in IDH-mutant gliomas (Bunse et al., 2022; NCT03893903) [149]. In addition, perioperative combination strategies involving the IDH1 inhibitor vorasidenib with immune checkpoint blockade (e.g., pembrolizumab) are currently under investigation in

IDH-mutant glioma, aiming to exploit metabolic reprogramming of the tumor microenvironment to improve responsiveness to immunotherapy (UCSF/early-phase clinical trial platform, ongoing NCT ID: NCT05484622). Collectively, these studies support the emerging concept that metabolic targeting of IDH-mutations may sensitize gliomas to immune checkpoint inhibition.

Outlook

Despite decades of intensive research, overall survival for patients with GBM has shown minimal improvement and remains a significant challenge in oncology. The isocitrate dehydrogenase enzyme family is central to GBM biology, functioning as an epigenetic oncogenic driver in IDH-mutant GBM through 2-HG production, and as a key redox protector in IDH-wildtype GBM via NADPH-dependent antioxidant maintenance, which confers therapeutic resistance. These distinct roles present separate therapeutic opportunities. Targeting IDH has led to notable advances in GBM treatment. The FDA approval of vorasidenib for IDH-mutant Grade 2 glioma established a precedent for molecularly targeted neuro-oncology therapies and validated IDH inhibition as a clinically relevant strategy. In IDH-wildtype GBM, compelling preclinical evidence indicates that inhibition of IDH1 by small molecules or RNAi sensitizes tumor cells to cytotoxic agents such as TMZ and radiotherapy. Given the challenges of achieving acceptable systemic toxicity when targeting IDH1-wildtype, nanomedicine platforms offer a means for precise delivery. Lipid nanoparticles (LNPs) and exosomes each provide unique advantages for delivering nucleic acids and genome editing components across the BBB in GBM. LNPs offer clinical-grade manufacturing and proven siRNA/mRNA delivery capabilities, while exosomes possess natural BBB crossing ability, low immunogenicity, and biocompatibility. Additionally, surface engineering enables specific targeting of tumor cells.

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Conflict of interest

The authors declare no conflict of interest.

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