Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ31787

Biochemical Roles of IDH Arginine Residue Mutations in Onco-metabolism and Their Clinical Implications

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Abstract. IDH1 and IDH2, two metabolic enzymes that have exhibited a high mutation frequency in wide ranges of cancers, especially in intrahepatic cholangiocarcinoma, acute myeloid leukemia, and gliomas, make for a tangible target in cancer therapeutics. Upon mutation, both enzymes gain an aberrant function which causes them to produce an oncometabolite, that being 2-hydroxyglutarate. However, the biology of IDH-mutant cancers makes them hard to drug like a typical oncogene, this compounded with the fact that IDH1/2 mutations are still a minority across all cancers makes research dedicated towards it limited. The main objective of this qualitative study was to explore the full pathway behind how a mutation in a seemingly "non-proto-oncogenic" can eventually lead to the formation of cancer, so that a coherent treatment proposal can be made. Secondary data were obtained through written literature concerning this topic, and reviewing was done to come to a proper conclusion. Due to its similarity in structure to α-ketoglutarate, 2-hydroxyglutarate is able to lead to downstream hindrance of intended chromatin modifications by binding competitively against α-ketoglutarate to TET demethylases, enzymes that "turn" genes on by using α-ketoglutarate as a cofactor. This oncometabolite has potential serve as a relevant biomarker in targeted therapeutics against the oncogenic pathway. Specifically, Ivosidenib, Vorasidenib, and Enasidenib inhibitors of IDH1 and IDH2 are discovered to have the greatest efficacy as treatment against tumorigenesis via this pathway.

Keywords: 2-hydroxyglutarate, isocitrate, TET, ivosidenib, vorasidenib

1. Introduction

IDH1, located in the peroxisomes and cytoplasm, and IDH2, located in the mitochondrial matrix, are both homo-dimeric isocitrate dehydrogenases that catalyze the reduction of NADP+ to NADPH through the conversion of isocitrate to α-ketoglutarate, releasing CO2 as a byproduct. In contrast to IDH3, the Krebs Cycle enzyme that produces the NADH required for oxidative phosphorylation; the physiological roles of IDH1 and IDH2 are less well defined but are hypothesized to contribute to the metabolism of glucose, fatty acids, and glutamine. NADPH, while not an electron carrier eventually fed to oxidative phosphorylation, serves as a powerful reducing agent, such as reducing glutathione to combat reactive oxidative species, and hydrogenating ketones in carbon chains to synthesize fatty acids. IDH1/IDH2 are significant in cancer therapeutics because certain IDH1/IDH2 mutations create a druggable, mutation-dependent metabolic pathway that can be tracked and targeted.

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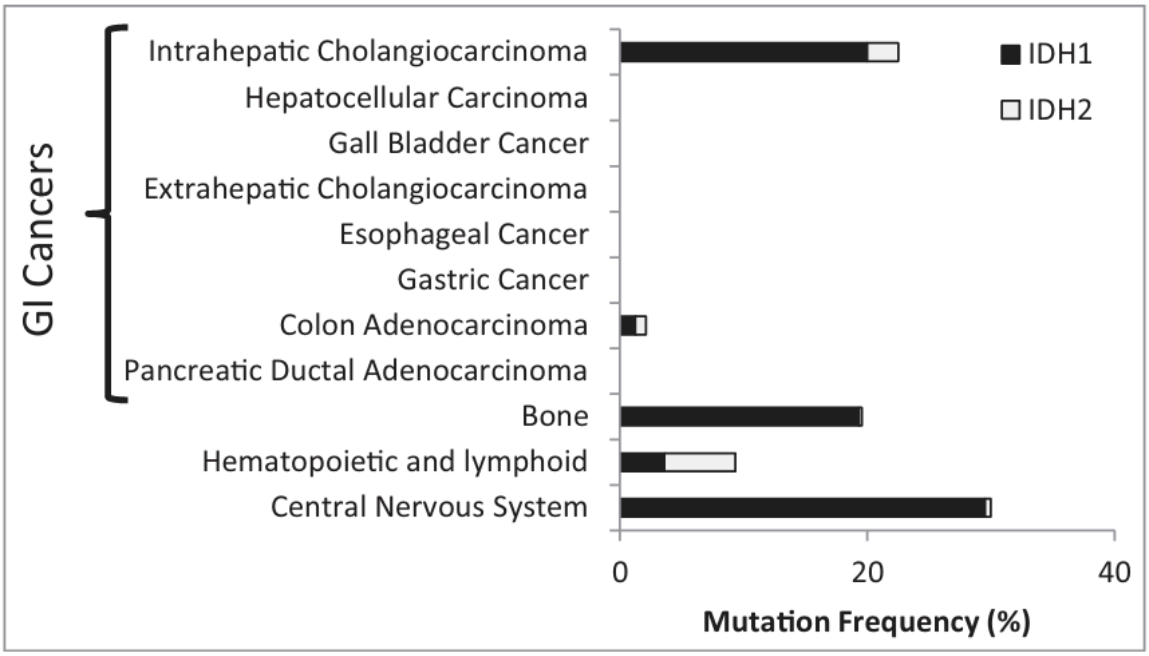


Figure 1. The frequency in which IDH1 and IDH2 mutations can be found in different types of documented cancers

Indeed, as shown in Figure 1, the frequency of IDH mutations, specifically IDH1 mutations, is noticeably high in Intrahepatic Cholangiocarcinoma, Acute Myeloid Leukemia (bone marrow cancer) and Gliomas (CNS cancer). Additionally, it has been discovered through cancer genome sequencing projects that mutually exclusive mutations (i.e., Not coexisting together) in IDH1 and IDH2 can be identified in cases of glioblastoma multiforme - a type of brain cancer [1]. Similarly, they were also identified in cases of acute myeloid leukemia - a cancer occurring from the displacement of functioning blood cells with rapidly dividing myeloid blasts [1]. Both of the mutations were point mutations, with the former undergoing R132C or R132H substitutions in the vast majority of cases, and the latter prominently undergoing R172K and additional R140Q substitutions [1]. Accordingly, both driver mutations involve a change in an arginine residue that can be found in the active site of the dehydrogenase enzymes. Arginine residues, deposits of positively charged amino acids, are typically found at anion-binding sites in proteins, specifically forming hydrogen bonds with the α-carboxyl and β-carboxyl groups of isocitrate. The mutated dehydrogenases gain a neomorphic ability that further converts α-ketoglutarate into D-2-hydroxyglutarate, as shown in Figure 2 below; this process would utilize one molecule of NADPH, restoring it back to NADP+. D2HG can inhibit a class of α-KG–dependent enzymes involved in epigenetic regulation and cell signaling, potentially leading to mis-regulation of cell division [1]. Epigenetics is regulatory processes that aim to control gene expression which involves chemical modification of histone proteins and of the DNA strand itself. Examples of epigenetics include methylation of cytosine bases in DNA and acetylation of lysine residues in histone proteins, both of which are controlled by α-ketoglutarate. Buildup of hydroxyglutarate can lead to inhibition of these enzymes, acting as a means by which IDH mutations could contribute to tumorigenesis. This paper aims to investigate the biochemical mechanisms of IDH mutations, influence on epigenetics, and finally, its medical implications.

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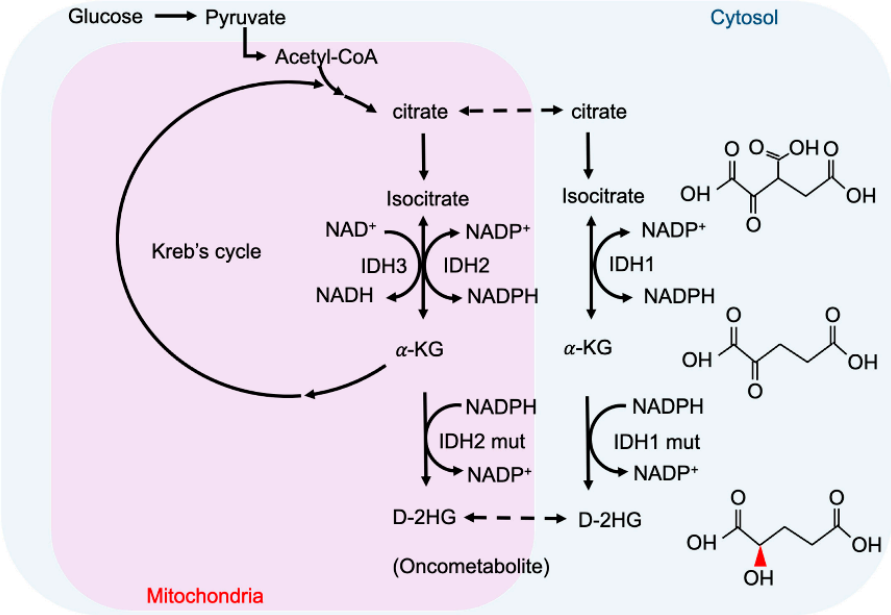


Figure 2. Description of the pathways taken to form the oncometabolite, 2-hydroxyglutarate

2. Biochemical mechanisms of arginine mutations

The R132H IDH1 active-site point mutation is not just a loss-of-function, but a gain-of-function neomorphic enzymatic activity that causes mutated IDH-1 to consume NADPH to reduce α-ketoglutarate into R-2-hydroxyglutarate. Glioblastoma cell lines engineered to express mutant IDH1 were analyzed using untargeted and targeted liquid chromatography-mass spectrometry metabolomics, revealing that the most prominent metabolic effect was massive R-2-hydroxyglutarate accumulation [2]. Isotope tracing further demonstrated that the carbon backbone of 2-HG was derived largely from glutamine through glutamate to α-ketoglutarate, the direct substrate of the neomorphic reaction [2].

2.1. IDH1: R132C vs R132H

In Intrahepatic cholangiocarcinoma: overwhelmingly IDH1 R132C In matched expression experiments in liver progenitor cells, IDH1 R132C produced 5x more 2-HG than IDH1 R132H at comparable Doxycycline concentrations when both IDH alleles were expressed under a doxycycline-inducible promoter [3]. This indicates that ICC may "select" alleles like R132C because they generate more 2-HG, which seems more effective at consolidating the differentiation block of oval cells in the liver (the liver is the locational origin of ICC).

2.2. IDH2: R172K vs R140Q

In ICC: IDH2 R172K is relatively more common in the same kind of liver progenitor system, IDH2 R172K produced ~2x more 2-HG than IDH2 R140Q and was more effective at preventing differentiation of oval cells [3].

It is worthy to note that both IDH1 R132H and R132C both arise from similar CpG to TpG deamination type events (as shown in Figure 3 below), so the different patterns across tissues likely

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aren't only about how the mutations happen, but also about which mutant proteins give a selective advantage in the context of cancerous cells in a mechanism similar to natural selection [3].

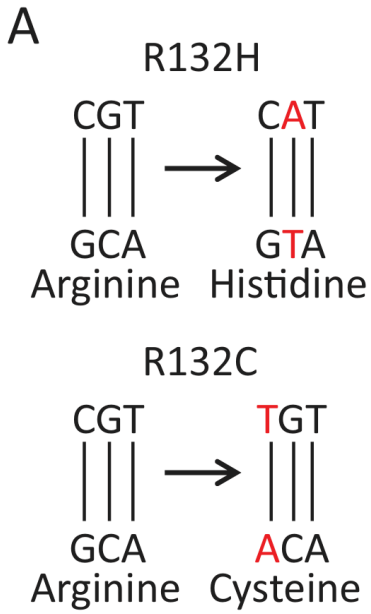


Figure 3. Mutations that occur in IDH1 R132H and R132C [3]

In the wild type IDH1 active site, Arg132 projects into the substrate pocket and makes a salt bridge to the β-carboxylate of bound isocitrate [4]. This positively charged guanidinium is critical for pulling ICT into the catalytic site. When Arg132 is mutated to His (R132H) or Cys (R132C), the shorter imidazole cannot reach the substrate and the uncharged sulfhydryl is unable to form favorable interactions, explaining the loss of oxidative activity [4]. Strikingly, crystallography of IDH1 R132H bound to α-KG shows the enzyme in a fully closed conformation with α-KG in the catalytic site, even though His132 is ~5.5 Å away and makes no direct contact with α-KG [4]. In this mutant structure, other active-site residues (e.g., Arg100, Ser94, Thr77, Asn96) and the NADPH cofactor adopt positions very similar to the wild-type ICT-bound state [4]. Importantly, Tyr139 (on the flexible catalytic loop) reorients toward α-KG and donates a hydrogen bond to its C2 keto group, thereby compensating for the missing Arg132 charge [5]. In short, R132H IDH1 remodels its H-bonding network: loss of Arg132–substrate contacts are offset by new Tyr139–αKG interactions and a locked closed pocket that tightly accommodates α-KG [4].

The mitochondrial IDH2 enzyme follows analogous principles. In WT IDH2, the homologous residues Arg140 and Arg172 together stabilize isocitrate. Structural modeling suggests a two-step binding of ICT: Arg140 guides ICT from a peripheral site into the catalytic cleft [6]. In the closed, ICT-bound state both Arg140 and Arg172 form salt bridges with the –3 charge of isocitrate [6]. Mutation R140Q (glutamine) removes one positive charge and one salt bridge, and R172K (lysine) retains a positive charge but with a shorter sidechain. Because the wild-type IDH2 active site has net +3 charge (optimized for ICT tri-anion) while αKG is –2, loss of a positive charge (as in R140Q or R172M) adjusts the pocket to favor αKG [6]. Thus IDH2-R140Q/K and R172K mutants reshape the electrostatic landscape: the reduced positive potential better complements αKG's dianion, and flexible loop residues (like Tyr179, the IDH2 equivalent of Tyr139) can reorient to interact with αKG.

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There are plausible inferences for effective differences between the two enzymes. IDH1 is cytosolic and peroxisomal, potentially impacting cytosolic NADPH and pathways like lipogenesis. IDH2 is mitochondrial, potentially impacting mitochondrial redox balance.

3. Epigenetics and downstream impacts

3.1. TET demethylases

Dioxygenases are enzymes that incorporate both atoms from a molecule of oxygen (O_2) into a substrate, facilitating the breakdown of complex compounds such as aromatic hydrocarbons. They often use iron, which can be either heme or non-heme, and α-ketoglutarate as cofactors. TETs are specialized dioxygenases that use non-heme Fe (II) and alpha-ketoglutarate to oxidize 5-methylcytosine (5mC) in DNA, initiating epigenetic demethylation as shown in Figure 4, a key process in gene regulation and development [7]. The mechanisms are as follows: TET binds Fe (II) in its active site, then α-ketoglutarate binds in another site next to the iron. When O_2 binds, α-KG undergoes oxidative decarboxylation (α-KG -> Succinate + CO_2) and donates electrons that help activate oxygen. The enzyme generates a highly reactive Fe (IV)=O intermediate, which abstracts a hydrogen atom from the methyl group of 5mC, creating a substrate radical and subsequently undergoes hydroxyl rebound to generate 5hmC. For clarity, O_2 has two oxygen atoms, one oxygen ends up in succinate and the other oxygen becomes the Fe=O that ultimately supplies the -OH that goes onto the substrate. The TET then oxidizes the newly formed hydroxyl group into a carboxylate, which can act as a leaving group in the form of CO_2.

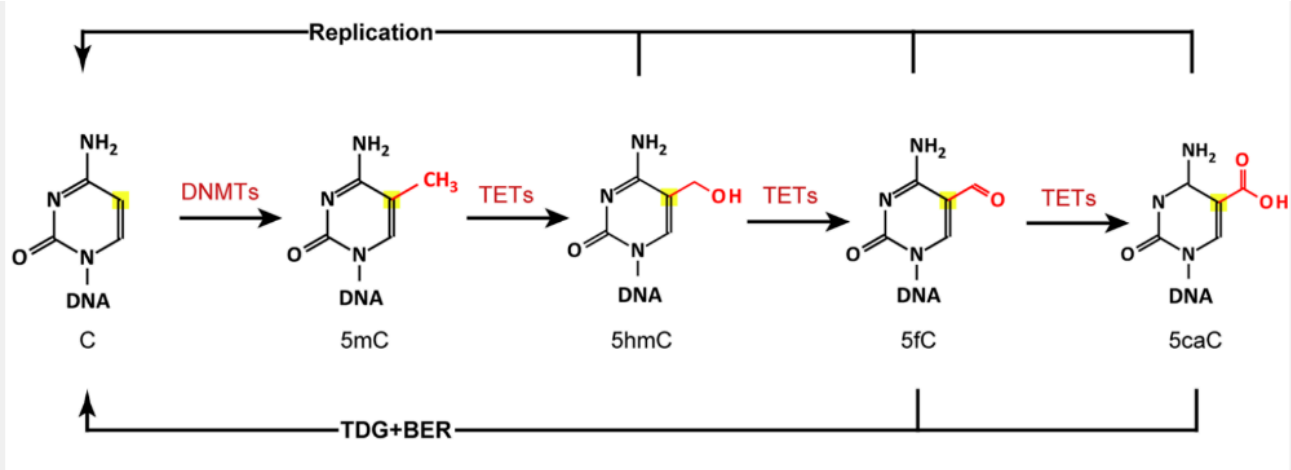


Figure 4. The reaction pathway taken by TETs to remove methyl groups from cytosine bases

TET enzymes belong to the Fe (II)/α-ketoglutarate-dependent dioxygenase family, which uses Fe (II) to activate O_2 during catalysis. Their active site adopts a double-stranded β-helix domain [7]. As shown in Figure 5, The Fe (II) ion is coordinated by conserved protein residues that do not form a porphyrin ring, typically a 2-His-1-carboxylate triad, in which the carboxylate can originate from either aspartate or glutamate, allowing the metal ion to be tightly but not permanently bound [7]. The remaining coordination sites are initially occupied by water molecules and are subsequently displaced by substrates, including α-ketoglutarate and O_2.

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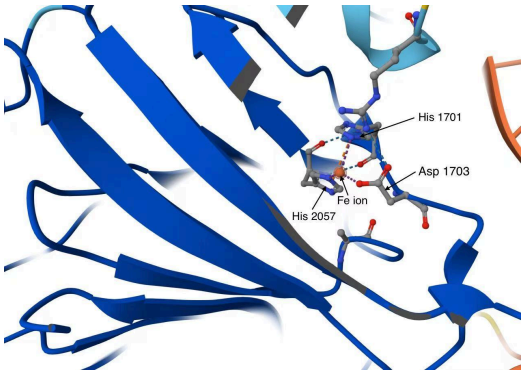


Figure 5. The active site of a general TET protein, with the 2-His-1-Aspartate motif and the double-stranded β-helix domain present, building the catalytic pocket, as predicted by AlphaFold

3.2. Detailed mechanisms

The Fe (II) ion can be easily oxidized into Fe (III) and participate in electron transfer processes. When α-ketoglutarate binds, it chelates Fe (II) in a bidentate manner (through its keto oxygen and one carboxylate oxygen), thereby positioning it adjacent to the oxygen-binding site [7]. An arginine side chain helps stabilize α-ketoglutarate via a salt bridge. Once Fe (II) and α-KG are properly coordinated, O_2 binds at the iron center, as shown in Figure 6.

Shown below from Figure 6 to Figure 9 is a step-by-step prediction of the biochemical mechanisms in which TET catalyzes the removal of a methyl group from a cytosine base and why this catalysis is impossible to conduct with 2-HG. The mechanisms are denoted in conventional organic chemistry notations.

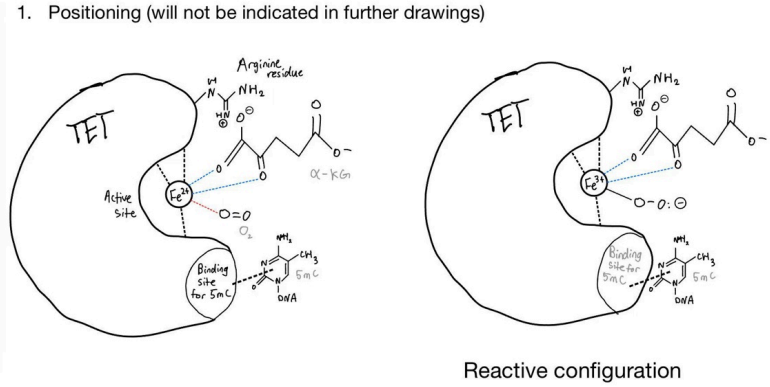


Figure 6. The docking of all the participating entities within the reaction

For clarification, there are three types of TET enzymes: TET1, TET2, and TET3. TET1 and TET3. TET3 is expressed immediately after fertilization and regulates early embryonic development, whereas TET1 is expressed in later-stage embryonic stem cells and contributes to the differentiation of stem cells. TET2 is mainly expressed in later-formed multipotent stem cells, such as hematopoietic stem cells. Both TET1 and TET3 contain N-terminal CXXC DNA-binding domains, which facilitate targeting of unmethylated CpG-rich DNA and enable a rapid response if methylation appears [8]. TET2 on the other hand, lacks that CXXC domain and instead, a related CXXC protein acts as a partner for TET2 targeting [8].

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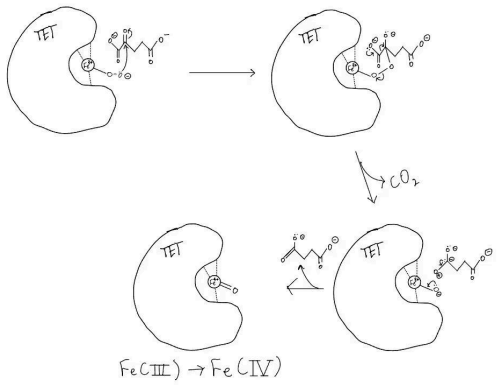


Figure 7. The step-by-step mechanism of the formation of the reactive Fe (IV)=O intermediate that will eventually attack 5mC

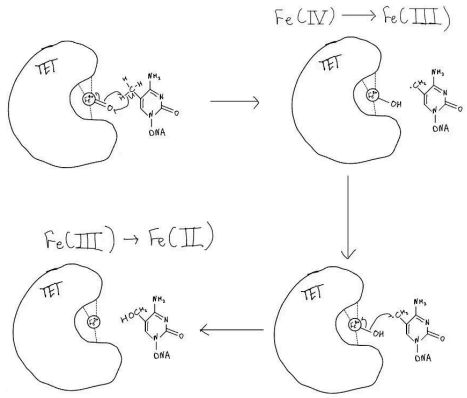


Figure 8. The step-by-step mechanism of the formation of 5hmC from 5mC

The 5hmC will undergo the same repeated process again, with hydroxy groups being added to its methyl group after every cycle until it is fully oxidized into a carboxyl group, which can leave as a CO2 molecule.

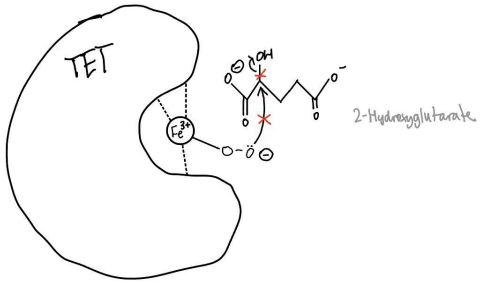


Figure 9. How 2-hydroxyglutarate fails to initiate the reaction

The first step is impossible to occur if α-ketoglutarate was replaced with 2-hydroxyglutarate. This is because: The OH is a poor leaving group, and the α-KG binding site of TET is not configured to protonate OH into a stable H2O leaving group. Hence, the oxygen atom cannot bond with the C2 of 2-hydroxyglutarate like it did with α-ketoglutarate. The 2-hydroxyglutarate is orientated differently

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because the C2 carbonyl is replaced by an alcohol, making the binding orientation unsuitable for reaction progression. 2-HG is too "reduced" to fully oxidize the Fe (II) ion into Fe (IV).

However, 2-hydroxyglutarate can still occupy the α-KG binding site and bind antagonistically, thereby blocking α-KG and inhibiting TET activity. 2-hydroxyglutarate, especially the D-2-HG that accumulates in IDH1/IDH2-mutant tumors, can act as a competitive inhibitor of α-ketoglutarate-dependent dioxygenases, including histone demethylases and TET DNA hydroxylases, thereby producing histone/DNA methylation changes. In vitro enzyme assays show that both enantiomers, D-2-HG and L-2-HG, can inhibit JmjC histone demethylases, and that increasing α-ketoglutarate counters this inhibition, creating competition between the two metabolites [9].

It was explicitly shown that the addition of cell-permeable 2-HG to cells increases the concentration of methyl groups on histone proteins, whereas adding cell-permeable α-KG produces the opposite effect, supporting competitive inhibition in vivo [9]. It is worth noting that 2-HG is a relatively weak antagonist, requiring a large excess over α-kG for strong inhibition [10]. However, this inhibition becomes relevant because IDH-mutant tumors accumulate very high levels of 2-HG. It is estimated that in IDH1-mutant gliomas, 2-HG: α-KG ratios can average approximately 373-fold, supporting the physiological plausibility of competitive inhibition in tumors [10].

4. Clinical implications

IDH being a metabolic-epigenetic driver rather than a simple growth-switch proto-oncogene makes medical responses towards it slower, more context-dependent, and more prone to resistance, often demanding more complicated procedures. Currently, the efficacy of conventional therapies is inconsistent in the context of IDH mutations; conventional chemotherapy and hypomethylating agents have shown inconclusive results as clinical evidence to address this is still confined to small sample sizes [11]. One study evaluating elderly patients with AML found no correlation between IDH1/2 mutations and response to hypomethylation treatment, and others have found that TET2 or IDH1/2 mutations did not predict treatment response [11]. The same can be said for chemotherapy - On one hand, in glioma, clinical data has suggested that patients with IDH1-mutated grade 3 gliomas have a better response to chemotherapy than wild-type tumors; on the other hand, in AML studies, the presence of IDH1/2 mutations did not appear to impact treatment response in patients less than 60 years old receiving induction chemotherapy or in patients of any age receiving prominently conventional chemotherapy or hypomethylating agents [11].

Fortunately, preclinical studies have shown that inhibitors of mutant IDH1/2 enzymes delayed aberrant growth and promoted normal differentiation in both IDH-mutated glioma cells and IDH-mutated AML cells treated ex-vivo [11]. In addition, in vitro subjection of erythroleukemia cells with IDH2 R140Q mutations to an inhibitor of mutated IDH2 resulted in decreases in intracellular 2-HG concentration and stagnated hypermethylation [11].

Indeed, in the entire pathway, the binding/inhibition step of 2-HG competitively occupying α-KG dependent dioxygenases is typically fast and reversible, once 2-HG is high enough relative to α-KG, those enzymes get "crowded out", so the rate determining step is usually getting 2-HG above the threshold needed to inhibit the key dioxygenases. Hence, to control 2-HG flux, the two main factors are mutant enzyme activity and availability of α-KG and NADPH. In pharmaceutical firms, understanding the mechanisms foundational to this oncogenic pathway will be a crucial step towards informing optimal approaches for deploying IDH1/2 inhibitors as effective drugs.

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4.1. Mechanism of allosteric IDH inhibitors

Small molecule inhibitors bind to allosteric pockets on the mutant IDH enzymes to suppress this neomorphic 2-HG production. Structural studies show that these inhibitors do not compete with the substrate (isocitrate or α-KG) at the active site, but rather bind at a site created by the conformational change of the mutated enzyme (at the dimer interface near the mutated residue) [12]. Binding induces a configuration resembling the inactive state of the enzyme, thereby preventing it from reducing α-KG to 2-HG [12]. The inhibitors effectively brake on the enzyme's aberrant activity [12]. Notably, one molecule of Ivosidenib binds per IDH1 mutant dimer, whereas newer inhibitors like Olutasidenib can bind two per dimer (one on each monomer), fully occupying the interface. Covalent inhibitors add an irreversible lock on the enzyme by forming a bond with a cysteine in the pocket [12].

4.2. Ivosidenib

Ivosidenib is a first-in-class oral inhibitor targeting the mutant IDH1 enzyme (generally the R132 mutations). It binds allosterically to the mutant IDH1 dimer, stabilizing an inactive conformation and thereby blocking the enzyme's neomorphic conversion of α-ketoglutarate (α-KG) to the oncometabolite 2-hydroxyglutarate (2-HG) [13]. In preclinical models, ivosidenib can reduce 2-HG levels by ~96% at sub-micromolar concentrations [13]. By lowering 2-HG, ivosidenib releases the block on cellular differentiation that 2-HG imposes, allowing malignant cells to mature.

Currently, Ivosidenib is a very promising inhibitor of IDH1 due to its efficacy and safe usage. The latter is supported by a clinical trial conducted on 50 patients who received Ivosidenib at 500 mg – A relatively large dose - per day, which showed that only 14% of patients experienced grade ≥3 adverse effects, and headache (39.4%), nausea (22.7%), and fatigue (22.7%) are the most common types of adverse effects [14]. At the orally administered dose of Ivosidenib 500 mg per day, only 8 patients had a dose interruption due to adverse effects, and no patients required dose reduction due to adverse effects [14]. This validates Ivosidenib's safety. As for its efficacy, in AML, single-agent Ivosidenib yielded a Complete Remission CR/CRh (A measure of the disappearance of all signs of cancer in response to treatment) rate around 30% (with ~24% CR) and 8 months of median response duration [15]. Many responding AML patients exhibit differentiation of blasts into mature myeloid cells rather than immediate cytoreduction, and a known toxicity is differentiation syndrome resulting from this rapid leukemic maturation. In IDH1-mutant cholangiocarcinoma, Ivosidenib improved median overall survival to ~10.8 months vs 9.7 months on placebo (12-month OS 48% vs 38%) [15].

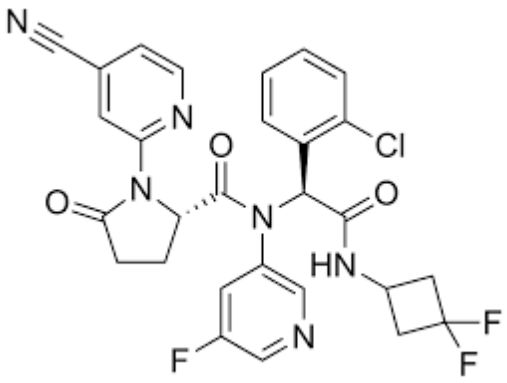


Figure 10. Structure of Ivosidenib

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As shown in Figure 10, Ivosidenib is a relatively large molecule featuring multiple aromatic rings and polar functional groups. Notably, it contains a chiral pyrrolidine-2-carboxamide core with appended chlorophenyl, difluorocyclobutyl, cyanopyridyl, and fluoropyridyl moieties. This complexity contributes to its molecular weight and physicochemical properties (e.g., polar surface area and H-bonding capacity) that influence its pharmacokinetics.

A noticeable weakness in Ivosidenib is its inability to target gliomas due to having a very high polar surface area and hence being blocked by the blood-brain barrier, and it being exclusive to IDH1 without any documented trials on successful activity against IDH2. Another choice of an inhibitor would be Vorasidenib as it has shown more potent inhibitory effects against 2-HG and better blood-brain barrier penetration abilities, allowing targeting of gliomas as well as other types of cancers.

4.3. Vorasidenib

Vorasidenib is an oral inhibitor that targets both mutant IDH1 and IDH2 enzymes [16]. It was designed to be a brain-penetrant derivative of earlier IDH inhibitors, intended for treating IDH-mutant gliomas. Chemically, Vorasidenib is a modified diaminotriazine scaffold that symmetrically binds the allosteric pocket of IDH1^R132 and IDH2^R140 homodimers [16]. It interacts with residues conserved in both isoforms (e.g., forming hydrogen bonds to the catalytic pocket on each monomer), effectively "locking" the mutant dimer in an inactive state [16]. Vorasidenib potently inhibits 2-HG production and in preclinical models lowers 2-HG levels and partially restores cellular differentiation in IDH-mutant tumors [16].

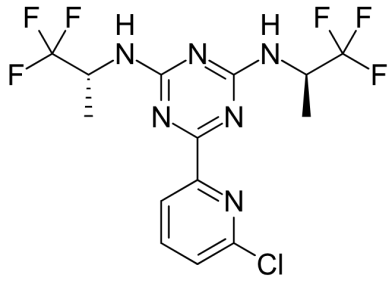


Figure 11. Structure of Vorasidenib

As shown in Figure 11, Vorasidenib is a smaller, symmetric inhibitor built on a 1,3,5-triazine core, the symmetry allows for the dipole moments to offset one another, allowing for reduced hydrophilicity. It carries two identical (R)-2-(trifluoropropyl) substituents (one on each of two N-atoms of the triazine) and a chloropyridyl group on the third position of the triazine ring. This design (fewer ring systems, high fluorine content, and reduced polar surface area) was intentionally optimized for cell permeability and CNS penetration, distinguishing it from the bulkier ivosidenib.

Both ivosidenib and vorasidenib are allosteric inhibitors that bind within a shallow pocket at the interface of the IDH homodimer, rather than the active site. By occupying this interface, the inhibitors lock the enzyme in an open, inactive conformation, preventing the normal active-site loop closure and halting the mutant enzyme's production of the oncometabolite 2-HG. In mutant IDH1-R132H, for example, inhibitor binding displaces key metal-binding residues (Asp275, Asp279, etc.), which in turn disrupts isocitrate/α-KG binding at the catalytic site. The resultant effect is steric hindrance and conformational trapping of the mutant IDH in an inactive state.

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4.4. Ivosidenib vs Vorasidenib

4.4.1. Potential resistance mechanism: isoform selectivity

Tumors can sometimes evade isoform-specific inhibitors by activating the alternate IDH isoform. In one reported mechanism, an IDH1-mutant cancer under ivosidenib pressure acquired a new IDH2 mutation, restoring 2-HG production through the parallel enzyme [17]. Conversely, an IDH2-mutant malignancy might develop an IDH1 mutation upon inhibitor exposure [17]. Such isoform switching effectively bypasses the drug, since the drug only targets the original isoform. Dual inhibitors like vorasidenib provide a countermeasure to this: they would continue to suppress 2-HG even if the tumor began relying on the other isoform [17]. While isoform switching is not exceedingly common, it has been documented as a cause of relapse, especially in solid tumors like cholangiocarcinoma. Therefore, vorasidenib's breadth could translate to a lower risk of this specific resistance pathway. In long-term glioma treatment, this might be especially relevant

4.4.2. Blood brain barrier penetrability

Vorasidenib was purpose-built to be brain-penetrant. Medicinal chemistry efforts minimized its polar surface area, maximized its symmetry and kept hydrogen-bond donors less than 2, characteristics favorable for CNS drugs. In animal studies, Vorasidenib showed high brain levels: brain: blood-plasma ratios around 1 or greater across multiple species [18]. For example, in a mouse orthotopic glioma model, Vorasidenib reached approximately equal concentrations in brain tumor and plasma while suppressing 2-HG by >97% in the tumor [18]. Clinically, vorasidenib's CNS penetration is reflected in its efficacy in glioma (discussed below) and a human trial confirmed that vorasidenib achieves therapeutic concentrations in cerebrospinal fluid and tumor tissue [18]. In summary, ivosidenib's CNS activity is limited by poor BBB permeability, whereas vorasidenib readily crosses into the brain. This difference in design (larger polar ivosidenib vs. smaller lipophilic vorasidenib) underlies their divergent utility: ivosidenib is suitable for systemic cancers, whereas vorasidenib can target IDH-mutant tumors in the CNS.

4.4.3. Efficacy

AML: In IDH1-mutated AML, ivosidenib has shown clear clinical benefit. In relapsed/refractory AML, it produces an overall response rate of ~30–42%, including CR rates around 20–22% [17]. By contrast, vorasidenib has not been studied in AML, there is no evidence to suggest it would outperform ivosidenib in that disease (and it is not currently used for AML).

Cholangiocarcinoma: In cholangiocarcinoma, ivosidenib provided an improvement in progression-free survival (~2.7 months vs 1.4 months on placebo) in a Phase 3 trial and is now approved for IDH1-mutant advanced cholangiocarcinoma [19]. Vorasidenib was not developed for cholangiocarcinoma, so ivosidenib is uniquely positioned for that indication.

Glioma: In IDH-mutant gliomas, vorasidenib has demonstrated unprecedented activity in a largely untapped patient population. Ivosidenib, in contrast, has only minor activity in gliomas.

4.4.4. Enasidenib

An IDH-2 specific inhibitor would be Enasidenib and can be used in AML/Cholangiocarcinoma cases where the mutation occurs in IDH-2 rather than IDH-1, its profile is very similar to Ivosidenib aside from the fact that it's exclusive towards IDH-2 rather than IDH-1. This article focused more on

DOI: 10.54254/2753-8818/2026.PJ31787

Ivosidenib rather than this Enasidenib counterpart due to IDH-1's larger dominance in the three main types of IDH mutant cancers.

Furthermore, progress has been made in the definition of relevant biomarkers. An in vivo H-NMR study found elevated baseline 2-HG levels in patients with IDH1/2 mutated gliomas, which decreased following conventional treatment [11]. This highlights 2-HG's use as a suitable biomarker in targeted treatments towards cancers involving IDH1/2 mutations due to 2-HG levels being directly correlated to tumor burden, a thesis further consolidated by trials conducted with IDH1/2 mutant cholangiocarcinoma patients.

5. Conclusion

Due to the repressed catalytic ability of TET demethylase enzymes, unintended extra methyl groups act like gene silencers, they prevent certain genes from turning on when they should. Importantly, genes involved in cell differentiation (the process by which a young, immature cell matures into a specialized cell) are kept off by abnormal methylation patterns. The downstream effect of these epigenetic changes is a block in cell differentiation, cells remain stuck in an immature, undifferentiated state, supported studies that found that introducing mutant IDH into cells impaired their ability to differentiate properly. This is a hallmark of cancers like acute myeloid leukemia (AML): a flood of immature cells that don't function as normal cells but continue to proliferate. Both ivosidenib and vorasidenib are groundbreaking therapies targeting mutant IDH enzymes, but each has clear strengths suited to different clinical contexts. For IDH1-mutant AML, ivosidenib remains the superior choice: it has proven ability to induce complete remissions and improve survival in AML, and its lack of brain penetration is irrelevant in this systemic disease. Vorasidenib, while theoretically active against IDH1, offers no advantage in AML and lacks clinical data in that arena. Moreover, Ivosidenib's long track record in AML means physicians are experienced with managing its differentiation syndrome and integrating it into therapy (including combinations with chemo or hypomethylating agents). In IDH1/2-mutant solid tumors outside the CNS (like cholangiocarcinoma and AML), ivosidenib (or enasidenib for IDH2) is again the appropriate agent, as vorasidenib's specialty – BBB penetration – is not needed, and ivosidenib has the regulatory approval and evidence in those diseases. Conversely, for IDH-mutant brain tumors (diffuse gliomas), vorasidenib is unequivocally superior. Its ability to cross the BBB and robustly suppress 2-HG in the brain translates into tangible clinical benefit – significantly delaying tumor progression and the need for radiation in low-grade glioma. Further research can be done on enasidenib and expand more than it just being an "IDH-2 counterpart" to ivosidenib, this would allow for a greater understanding of inhibition pathways and create more templates for further improvements in inhibitors, allowing for a new generation of IDH-inhibitors to spring. An unavoidable adverse effect of all inhibitors is off-target inhibition, where liver cells – cells highly active in metabolism, and therefore have high concentrations of both IDH enzymes – may be unintentionally inhibited by IDH inhibitors upon treatment. Further study can be conducted into genome editing techniques, like CRISPR, a novel emergence in the field of medical sciences as an alternative treatment to inhibitors.

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