Review Article

Isocitrate Dehydrogenase Mutations in Human Cancers: Physiopathologic Mechanisms and Therapeutic Targeting

Elvira Pelosi, Germana Castelli and Ugo Testa*

Department of Hematology, Oncology and Molecular Medicine, Viale Regina Elena 299, 00161, Rome, Italy

Abstract

Isocitrate dehydrogenase (IDH) is a metabolic enzyme responsible for the enzymatic conversion of isocitrate to α-ketoglutarate (α-KG). Mutations in the *IDH* gene result in a novel gain-of-function, with development of neomorphic enzymatic activity determining the pathological reduction of α-KG to (R)-2-hydroxyglutarate. The accumulation of this pathological metabolite (onco-metabolite) in cancer cells is, to a large extent, responsible for the development of several cancers, including acute myeloid leukemia (AML), low-grade gliomas (LGGs) or chondrocytic tumors. Furthermore, various experimental studies have shown that *IDH* mutations represent an early, driver event, conserved during tumor progression in neoplasias such AML and LGG. Given all these observations, potent and selective IDH inhibitors have been developed and are currently under investigation in phase I/II clinical studies. In particular, AG-221, a first-in-class inhibitor of mutant IDH2, was tested in hematological patients with refractory/relapsing AML or myelodysplasia and showed an overall response rate of 59/159 (37%), as well as a good safety profile. Similarly, AG-120, an inhibitor of mutant IDH1, was tested in 66 relapsing/refractory AML patients and showed an overall response rate of 36%, with a complete response rate of 16%. A new IDH inhibitor, AG-811 displayed the capacity to inhibit both mutants IDH1/2 and to penetrate the blood: brain barrier, a property that would be suitable for treatment of glioma patients. On the other hand, additional observations have suggested that IDH-mutant AMLs are sensitive to treatment with BCL-2 inhibitors and to the differentiative induction with all-trans retinoic acid. In conclusion, the collective studies carried out in recent years on the characterization of IDH-mutant tumors highlight an admirable paradigm of the virtuosic transfer from basic research (with improvements in our understanding of the physio-pathological role played by IDH mutations in the development of some tumors) to clinical studies (with the development of selective, potent and clinically-active IDH inhibitors).

Introduction

The human genome has five isocitrate dehydrogenase (IDH; EC 1.1.1.42) genes, coding for three distinct IDH enzymes, the activities of which are dependent on either nicotinamide adenine dinucleotide phosphate (NADP; $NADP^+$-dependent IDH1 and IDH2) or nicotinamide adenine dinucleotide (NAD; NAD^+-dependent IDH3). Both IDH2 and IDH3 are localized in the mitochondria and participate in the citric acid cycle for energy production, whereas IDH1 is localized in the cytoplasm and peroxisomes. IDH3 catalyzes the third step of the citric acid cycle, wherein NAD^+ is converted to NADH in the mitochondria. IDH enzymes catalyze the oxidative decarboxylation of isocitrate to produce α-ketoglurate (α-KG, also known as 2-oxoglutarate) and concomitantly produce NADPH from $NADP^+$. IDH enzymes also catalyze the reductive carboxylation of α-KG to form isocitrate and concomitantly produce $NADP^+$ from NADPH. IDH is dependent on $NADP^+$ and on Mg^{2+}.

The enzymatic reaction catalyzed by IDHs is a two-step process, in which the first step involves oxidation of isocitrate to oxalosuccinate, with the second step involving decarboxylation of the carboxyl group beta to the ketone, ultimately forming α-KG (Fig. 1). The Mg^{2+} cofactor is required for the stabilization of the transitional states during the two-step reaction. The IDH1 and IDH2 enzymes are structurally organized as homodimers, while the IDH3 enzyme is organized as a heterodimer, composed by two alpha subunits, one beta subunit and one gamma subunit. The structure of IDH is composed of 14 alpha helices and 18 beta sheets. The alpha helices are located all over the structure, whereas the beta sheets (parallel and anti-parallel) are found mainly through the center of the molecule.

The crystal structure of mammalian IDH1 and IDH2 was determined and showed that each enzyme is composed of a homodimer.[1,2] Each homodimer is, in turn, composed by a large domain, a clasp domain and a small domain, and contains two asymmetric and identical active sites (composed by a cleft formed by the large domain of a subunit and the small domain of the other IDH homolog). The active sites of the enzyme are accessible to substrate and cofactors; the function of the clasp is to maintain the two subunits together to form the active enzymatic site. Each IDH enzyme possesses: (a) an inactive open conformation, which is maintained through intramolecular interactions between Ser95 and Asp279 residues that serve to block access to the active site; and (b) a catalytically active closed conformation, where the Mg^{2+}-isocitrate complex is able to bind between the large and small domains of the enzyme, consequent to relief of the steric impediment by Asp279 to the Mg^{2+}-isocitrate complex binding.[1,2]

In its active conformation, the enzyme catalyzes α-KG and NADPH production and then either remains in its active conformation
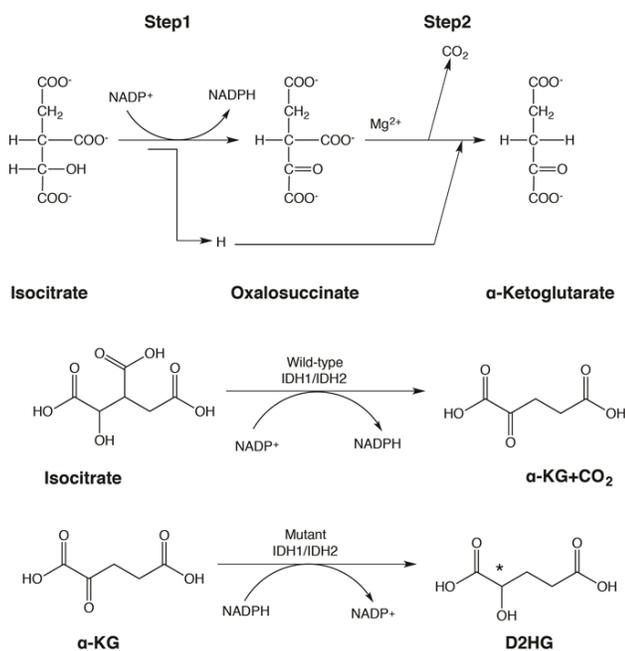
Fig. 1. Enzymatic reactions catalyzed by wild-type and mutant IDH1 and IDH2. (A) Normal IDH1 and IDH2 enzymes catalyze a two-step reaction. In the first step, isocitrate is oxidized to an unstable intermediate (oxalosuccinate), with concomitant reduction of $NADP^+$ to NADPH. In the second step, the oxalosuccinate losses its beta-carbonyl group, which is released as CO_2, giving rise to the formation of α-KG. The two H^+ atoms produced during conversion of isocitrate to oxalosuccinate are used for $NADP^+$ reduction to NADPH and for conversion of oxalosuccinate to α-KG. (B) Mutant IDH1 and IDH2 enzymes catalyze a reaction wherein α-KG is reduced to (R)-2-hydroxyglutarate (D-2-HG) with concomitant oxidation of NADPH to $NADP^+$. From a structural point of view, α-KG and D-2-HG are very similar and differ only in replacement of the ketone group that is present in α-KG, with the hydroxyl group present in D2HG.

(continuing to catalyze the isocitrate decarboxylation) or returns to its inactive conformation (restoring the Ser94-Asp279 interaction). The main biologic/physiologic function of IDH1/2 is related both to the biosynthesis of essential metabolites in the context of the tricarboxylic acid (TCA) cycle and in providing, together with the pentose phosphate pathway, one of the two essential cellular systems for the generation of NADPH (Fig. 2).

NADPH is required to maintain reduced glutathione pools and to support reductive biosynthesis. Cytosolic NADPH is mainly regenerated via the oxidative pentose phosphate pathway and in the reactions catalyzed by IDH, malate enzyme and aldehyde dehydrogenase and methylene tetrahydrofolate dehydrogenase. Particularly, for that which concerns IDHs, the reductive carboxylation of α-KG to isocitrate by IDH2 consumes mitochondrial NADPH, with citrate/isocitrate transported to the cytoplasm where these metabolites can be oxidized by IDH1 to produce cytosolic NADPH (Fig. 2).[3] The reverse cycle produces mitochondrial NADPH.[3]

In line with these observations, it is not surprising that lower NADPH levels have been reported in IDH1-mutant glioblastoma cells.[4] The reaction catalyzed by IDH is one of the irreversible reactions in the TCA cycle and, therefore, needs to be carefully regulated. Thus, IDH is allosterically regulated in a positive way by adenosine diphosphate (ADP) and inhibited by adenosine triphosphate (ATP), NADPH or NADH. As such, IDH catalyzes its reaction only when ADP levels are low, while in the presence of high ATP, NADPH or NADH levels, the enzyme is inhibited, because there are existing sufficient amounts of these TCA cycle products

that are available for other metabolic cycles.

In addition to TCA, glutamine-glutamate-α-KG metabolism represents an important step in the physiologic effects of IDH and is a critical pathway in IDH-mutant tumors. In this metabolic pathway, glutamine is first lysed to glutamate by the enzyme glutaminase, after which the glutamate is converted to α-KG by three different enzymes: glutamate dehydrogenase, alanine transaminase or aspartate transaminase (Fig. 2). Glutaminolysis is active in proliferating and, particularly, in tumor cells, where it represents the crucial source of nitrogen for amino acid synthesis via glutamate production and transamination. Importantly, the hypoxic microenvironment present in tumors stimulates glutamine flux into citrate for production of NADPH by IDH and for lipid production (reviewed in 5).[5]

IDH genes encode the metabolic enzymes $NADP^+$-dependent isocitrate dehydrogenase, involved in the catalyzation of the oxidative decarboxylation of isocitrate to synthesize an α-KG. The two distinct IDH1 and IDH2 enzymes show a high degree of sequence similarity (about 70%) and are encoded by two distinct genes: *IDH1* located on 2q33, and *IDH2* located on 15q26. These genes are frequently mutated in some tumor types and represent the metabolic genes most frequently mutated in human cancers. It is reported that *IDH1/2* genes are mutated in 50–80% of low-grade gliomas and secondary glioblastomas, about 20% of acute myeloid leukemia (AML), 50–60% of chondrosarcomas, about 10% of intra-hepatic cholangiocarcinoma (CCA) and 10% of melanomas.

The IDH1 and IDH2 enzymes catalyze identical enzymatic reactions, but are localized to different cellular compartments, with the IDH1 enzyme localized in the cytosol and the IDH2 enzyme localized in the mitochondria. The frequency of IDH1 and IDH2 mutations are different in various tumor types; *IDH1* and *IDH2* mutations are almost equally frequent in AML, while *IDH1* mutations are predominant in gliomas, chondrosarcomas and CCAs. The mutant IDH enzymes have lost the capacity to efficiently carry out the normal oxidative reaction (*i.e.* conversion of isocitrate and $NADP^+$ to α-KG, CO_2 and NADPH), but they have acquired a novel enzymatic function (*i.e.* conversion of α-KG to D-2-hydroxyglutarate (2-HG)).

In normal tissues, 2-HG is present only at very low levels. In IDH1/2-mutant tumor cells, however, it is markedly accumulated and has been shown to act as a potent oncometabolite, responsible for the induction of many of the epigenetic alterations observed in these tumor cells.[6,7] The oncogenic effects induced by 2-HG are mainly related to the inhibition of α-KG-dependent dioxygenases activity. The metabolic consequences of IDH1/2 mutations are not completely understood. However, some studies have indicated that overexpression of mutant IDH1 or IDH2 alters the levels of several metabolites, including some amino acids, glutathione metabolites and TCA cycle intermediates.[8] Other studies have shown an increased sensitivity to glutaminase inhibitors and an inactivation of NADPH-dependent reactive carboxylation due to reduced glutaminase activity.[9,10]

Studies of metabolic flux have shown that IDH1 mutations can induce an increase in cellular metabolic flux along the TCA cycle, as well as in respiration, and can compromise the conversion of glutamine to citrate, AcCoA and fatty acids under hypoxic conditions.[11] Importantly, cells expressing mutant IDH1 are sensitive to pharmacologic inhibition of mitochondrial oxidative metabolism.[11] Yet, small molecules inhibiting IDH1 enzymatic activity and preventing D-2-HG accumulation fail to rescue abnormal metabolism under hypoxia.[11] This observation suggests that a double-targeting strategy may represent an important therapeutic option, based on inhibition of both mutant enzymatic activities by using IDH inhibitors and targeting mutant IDH1-induced metabolic li-
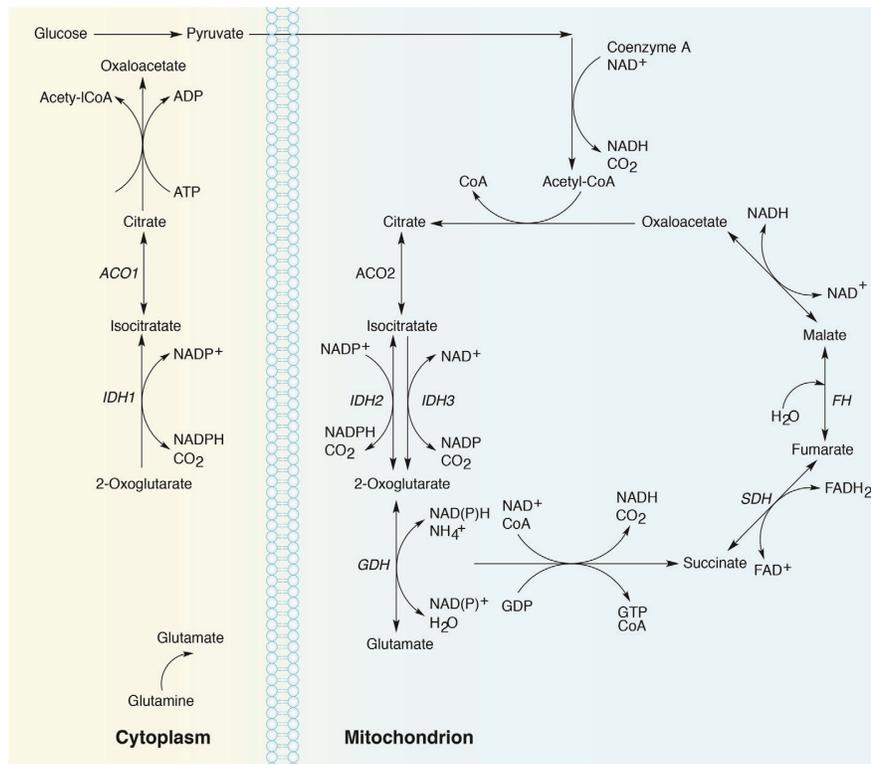
Fig. 2. Function of IDH1/2 and IDH3 enzymes in the context of the tricarboxylic acid (TCA) cycle. In this schematic representation, the mitochondrial reactions involving IDH2 and IDH3 and the cytoplasmic reactions involving IDH1 are shown. IDH1 is located in the cytoplasm and catalyzes the $NADP^+$-dependent conversion of isocitrate to α-KG (also known as 2-oxoglutarate). IDH2 is located in the mitochondria and catalyzes the same reaction. IDH3 is located in the mitochondria and catalyzes the NAD^+-dependent irreversible transformation of isocitrate to α-KG. The two aconitases (ACO1 and ACO2), glutamate dehydrogenase (GDH), succinate dehydrogenase (SDH) and fumarate hydratase (FH) are also shown.

abilities by drugs such as metformin or phenformin.[11]

In the first section of this review, the main biologic and molecular features of the different types of IDH-mutated tumors are analyzed. In the second section, the development of anticancer therapies targeting mutant IDH enzymes is analyzed, including details of each therapy's actual development and its future perspectives.

Main features of IDH-mutant tumors

IDH mutations in chondrosarcomas

IDH1/2 (predominantly *IDH1*) mutations have been reported in 50–70% of central chondrosarcomas (Table 1), in about 70% of conventional chondrosarcomas and 54% of dedifferentiated chondrosarcomas. These mutations have been found in all tumor grades of the chondrosarcomas, but have not been observed in peripheral chondrosarcomas or in soft tissue tumors.[12,13] Interestingly, these mutations have also been found in enchondromas, common benign tumors of bone that can be precursors of chondrosarcomas, and very frequently also in enchondromatosis syndromes such as Ollier disease (81% of *IDH1/2* mutations) and Maffucci syndrome (77% of *IDH1/2* mutations), associated with DNA hypermethylation.[14] These patients are at increased risk of developing highly-malignant chondrosarcomas, as well as gliomas and AMLs. These observations have suggested that the acquisition of *IDH1/2* mutations is an early event of chondrosarcoma development and may

represent a driver event for tumor development. Such a theory is supported by the following two observations: (a) expression of mutant IDH is sufficient to induce benign enchondromas in mouse models, and (b) additional mutations accumulate in chondrosarcomas (such as p16/CDKN2A loss), compared to enchondromas, and, in cooperation with *IDH1/2* mutations are required for malignant tumor development.[15,16]

In enchondromatosis syndromes, enchondromas progress to chondrosarcomas in up to 30% of cases. Furthermore, in these syndromes, there is a tendency to develop various types of tumors, including gliomas. Comparison of gliomas developed in enchondromatosis syndromes to those of sporadic IDH-mutated gliomas showed that the former were diagnosed at an earlier age, were more frequently multicentric and were more frequently located within the brainstem than sporadic IDH-mutated gliomas.[17] At the molecular level, enchondromatosis gliomas were characterized by *IDH* mutations, but, in contrast to the sporadic IDH-mutated gliomas, do not harbor the 19/19q co-deletion.[17] *IDH1/2* genes were mutated in about 7% of Ewing sarcoma family tumors.[18]

A recent study provided evidence that mutant IDH1-R132C was able to promote chondrogenic differentiation and to inhibit osteogenic differentiation of normal mesenchymal stem cells.[19] The frequent presence of mutant IDH in chondrocytic tumors offers a potential therapeutic target, by which enzymatic function can be inhibited with specific small molecule inhibitors. The effect of these inhibitors was tested on chondrosarcoma cell lines and showed an inhibitory effect on cell proliferation, cell survival and cell migration.[20]

Table 1. Most frequent IDH1 and IDH2 mutations observed in human cancers

Tumor	IDH1 Mutation (%)	IDH2 Mutation (%)	Reference
Acute myeloid leukemia	7–9 (R132H 50%) (R132C 40%) (R132S 10%)	14–18 (R140Q 60%) (R172Q 40%)	Mardis *et al*, 2009 [46]; Marcucci *et al*, 2010 [49]; Paschka *et al*, 2010 [48]
Astrocytomas diffuse and anaplastic (grade II/III)	64–72 (R132H 90%) (R132C 5%) (R132S 3%) (R132G 1%)	1–5 (R172K) (R172M)	Wang *et al*, 1999 [23]; Hartmann *et al*, 1999 [25]
Oligodendroglioma (grade II/III)	70–82	5–6	
Oligoastrocytoma (grade II/III)	66–81	1–6	
Secondary glioblastoma (grade IV)	85	0	
Primary glioblastoma (grade IV)	5–8	1	
Chondrosarcoma	46–52 (R132)	4–12 (R172)	Amary *et al*, 2011 [12]; Damato *et al*, 2012 [13]
Myelodysplastic syndromes	1–2 (R132)	8–10 (R140)	Patnaik *et al*, 2012 [78]; DiNardo *et al*, 2016 [80]
Angioimmunoblastic T lymphomas	0	20 (R172)	Cairns *et al*, 2012 [87]; Odejide *et al*, 2014 [88]; Wang *et al*, 2015 [89]
Cholangiocarcinoma	15–25 (R132)	1–7 (R172)	Borger *et al*, 2012 [90]; Kipp *et al*, 2012 [91]; Wang *et al*, 2013 [92]; Goyal *et al*, 2015 [93]

The most frequent amino acid substitutions are indicated and their frequencies at the level of IDH1- or IDH2-mutated patients are reported for acute myeloid leukemias and gliomas.

IDH mutations in bone tumors

Giant cell tumors (GCTB) are benign but locally-destructive tumors, and include the osteoclast-type multinuclear giant cells. A recent study reported a very high frequency (80%) of IDH2-R172S mutations in GCTB.[21] Furthermore, the IDH2-R172S mutation was reportedly observed in 25% of osteosarcoma patients.[22]

IDH mutations in gliomas

Studies carried out over the last 10 years have shown the frequent occurrence of *IDH* mutations in gliomas. *IDH* mutations are very frequently (>80%) observed in low-grade and secondary glioblastomas, but in <10% of primary glioblastomas (Table 1).[23,24] Particularly, *IDH1* mutations were reported to occur in 70–80% of grade II-III astrocytomas, oligodendrogliomas and oligoastrocytomas, while only a small group (3–5%) of these tumors were found to display *IDH2* mutations, with the *IDH1/2* mutations being mutually exclusive.[23] It is, therefore, evident that according to the *IDH* mutation status, *IDH1* mutations have been detected exclusively in low-grade and secondary glioblastomas. In contrast, primary glioblastomas have very low mutation rates for *IDH1* or *IDH2*. Finally, a small percentage of grade II gliomas do not have genetic alterations in *IDH* or functional mutation in TP53.

Evidence has been provided to support the notion that secondary glioblastomas lacking *IDH1* mutations develop (through a tumor progression process) from an anaplastic glioma (grade III); whereas, the majority of secondary glioblastomas displaying *IDH1* mutations appear to develop (through progression) from a World Health Organization (WHO) grade II glioma.[25] Given this peculiar stratification between primary and secondary glioblastomas, the presence of *IDH* mutations represent a valuable tool for distinguishing these two conditions. Furthermore, this conclusion is also supported by findings from molecular analyses, showing that primary glioblastomas exhibiting *IDH* mutations have a mutational profile similar to that typically displayed by secondary glioblas-

tomas, thus supporting the hypothesis that primary glioblastomas with *IDH* mutations originate from pre-existing precursor lesions that were not diagnosed at the time of their occurrence and were therefore misclassified as primary.[26]

Various other studies have shown that *IDH* mutations are an early event in gliomagenesis, occurring before other genetic abnormalities such as TP53 mutations, loss of 1p/19q, and copy number changes in *EGFR* and *PTEN* genes.[27,28] Mouse model studies using IDH1 mutant xenografts have provided evidence to support that expression of the mutant IDH1 protein is required to sustain glioma cell growth and that pharmacological inhibition of mutant IDH1 with the IDH1-R132H inhibitor results in xenograft growth inhibition.[29]

Importantly, mutations in *IDH1/2* genes define a subset of human gliomas with a hypermethylation phenotype (G-CIMP), that provide a favorable outcome; in contrast, the absence of *IDH1/2* mutations identifies a subgroup of low-grade gliomas characterized by poor prognosis.[30] Although IDH mutant status is associated with better survival, all IDH mutant/O^6-methylguanine-methyltransferase (MGMT) methylation subsets have consistently displayed higher risk of malignant transformation than of death, compared to IDH-wild type (WT) low-grade gliomas.[31] Recent studies have suggested the classification of gliomas into IDH-WT cases, IDH-mutant group with co-deletion of chromosome arms 1p and 19q (IDH mutant-codel) and IDH-mutant group without co-deletion (IDH mutant-non-codel).[30,32] A very recent study based on a very large set of gliomas indicated the existence of three types of IDH-mutated gliomas: (a) the Codel group, consisting of IDH-mutant-codel low-grade gliomas; (b) the G-CIMP-low group, including IDH-mutant-non-codel gliomas (both LGGs and glioblastomas) and manifesting a lower degree of DNA methylation; (c) the c-CIMP-high group, including IDH mutant-non-codel gliomas (both LGGs and glioblastomas) and with higher levels of DNA methylation.[31] The G-CIMP-low group reportedly has a worse survival than the c-CIMP-high and codel groups.[33]

Paired analysis of tumor samples from a large number of glioma patients—comparing higher-grade, progressed samples to their

lower-grade counterparts—allowed for an integrated genomic characterization of IDH1-mutant glioma malignant progression.[34] Various oncogenic pathways were shown to drive progression; these included, activation of the MYC and RTK-RAS-PI3K pathways and up-regulation of FOXM1 and E2F2, as well as epigenetic silencing of developmental transcription factors bound by PRC2.[34] These findings suggest that IDH mutations are early events in gliomagenesis and cooperate with other more tardive genetic alterations to promote glioma progression.[34]

As stated above, *IDH1* mutations have been observed in <10% of glioblastomas. Glioblastoma patients with *IDH1* mutations are younger and associated with a longer survival than those without *IDH1* mutations.[19] However, in patients with recurrent glioblastomas, the presence of *IDH1* mutations is not predictive of progression-free survival (PFS) or radiological response.[35]

In contrast to the IDH-mutant LGGs, the IDH-WT LGGs represent a very heterogeneous group of gliomas, with various imaging and molecular characteristics at the level of genetic abnormalities and expression profiles.[36] Although these tumors have better PFS and overall survival rates than glioblastomas, their outcomes and clinical presentations are highly variable.[36] These observations are in line with previous studies showing that some patients with low-grade gliomas display molecular features of primary glioblastomas, such as *EGFR* alterations and loss of the *CDKN2A* locus, both of which are mutually exclusive of *IDH* mutations.[37]

The oncogenic mechanism of mutant IDH in glioma cells involves production of the onco-metabolite 2-HG, which interferes with iron-dependent hydroxylases pertaining to the TET family. Given the function of TET enzymes, it is not surprising that IDH-mutant gliomas manifest a CpG island methylator phenotype.[38] Particularly, IDH-mutant gliomas exhibit hypermethylation at cohesion and binding sites of the CTCF; the reduced CTCF binding, in turn, causes deregulated gene expression and, particularly, enhanced PDGFRA expression.[26] Importantly, treatment of IDH-mutant gliomaspheres with demethylating agents, in part, restores CTCF function and reduces PDGFRA expression.[38] These observations suggest that mutant IDH promotes gliomagenesis allowing aberrant oncogene expression.[38] When 2-HG levels were elevated in the urine of patients with IDH-mutant and compared with that in patients with IDH-WT glioma, the levels were found to not be affected by the histopathologic grade nor genetic subtype presence of a canonical or noncanonical *IDH* mutation.[39] Furthermore, *in vitro* and *in vivo* studies have shown that, in human gliomas, the *IDH2* mutation leads to greater production of 2-HG than does the *IDH1* mutation.[40]

The presence of *IDH1/2* mutations in gliomas has a prognostic impact: particularly, glioma patients with IDH-mutant tumors and low/normal Ki67 values have a significantly better prognosis than patients with IDH-WT gliomas showing high Ki67 labeling.[41] A large portion of IDH-mutant gliomas display ATRX nuclear loss (about 90% of astrocytomas with ATRX nuclear loss display *IDH1/2* mutations and have an astrocytic morphology and a younger age of onset); in contrast, IDH-mutant gliomas with ATRX retention are strongly associated with loss of heterozygosity at 1p/19q and oligodendroglioma cell morphology.[42] According to *IDH* mutation status, 1p19q codeletion and ATRX-loss grade II gliomas can be subdivided into the following four groups: *IDH*mut-codel (43%), *IDH*mut-codel-*ATRX* loss (39%), *IDH*mut-noncodel-ATRXwt (6%), and *IDH*wt.[43] The median survival was much better for the *IDH*mut-codel than for the other three groups.[43] Moreover, IDH-mutant gliomas are more likely to recur locally and within the radiation field than are IDH-WT tumors, which have a greater tendency toward recurrence distant from the original site of tumor development. Finally, studies carried out in

the last few years have shown that grade II and III astrocytomas with *IDH* mutation have an improved survival, with maximal success rates for surgical resection, and are able to predict response to temozolomide; furthermore, the *IDH*-mutant glioblastomas were shown to display an increased response to concurrent radiotherapy and temozolomide treatment.

The oncogenic mechanism of 2-HG in glioma cells is related not only to DNA hypermethylation but also to additional biochemical mechanisms. Li and colleagues recently showed that R-2-HG induces hypersuccinylation in glioma cells; in fact, this onco-metabolite, through competitive inhibition of the enzyme succinate dehydrogenase, was shown to cause accumulation of the succinyl-CoA metabolite and hypersuccinylation at the level of mitochondria.[44] In turn, the hypersuccinylation was responsible for respiration inhibition, mitochondrial depolarization and development of a cancer metabolic phenotype.[44] The development of mitochondrial dysfunction induced accumulation of BCL-2 anti-apoptotic protein, with consequent resistance of tumor cells to apoptotic stimuli.[44] The hypersuccinylation contributes to IDH-mediated gliomagenesis, as supported by the experimental evidence showing that relief of the hypersuccinylation condition (either by overexpressing a desuccinylase or by glycine supplementation) reversed BCL-2 accumulation and exerted an inhibitory effect on tumor growth.[44]

The possibility of a link between succinylation and IDH2 was also supported by a recent study showing that when the deacetylase Sirtuin 5 (an NAD$^+$-dependent mitochondrial deacetylase) was induced by oxidative stress the desuccinylation of IDH2 was promoted, and, through this mechanism, activated the enzyme, as well as G6PD by deacetylation, thereby maintaining NADPH levels and redox balance to protect the cells against oxidative damage.[45]

IDH mutations in myeloid neoplasia

IDH mutations in AML

AML is a heterogeneous hematologic malignancy, characterized by the accumulation of various somatic genetic abnormalities and of immature myeloid cells arrested at various stages of maturation. Studies carried out in the last 2 decades have led to the identification of two broad types of genetic mutations, which cooperate to support development of the leukemic process. The class I mutations confer a survival/growth advantage to hematopoietic stem cells (HSCs) and progenitor cells (HPCs), such as the mutations in *NRAS* or *KRAS*, the loss of *NF1* or the mutations in *FLT3* receptor tyrosine kinase. The class II mutations promote self-renewal and block the differentiation of HPCs, such as the t(8:21) fusion involving *AML1-ETO* or the t(15;17) fusion involving *PML-RARα*.

In 2009, Mardis and colleagues reported frequent occurrence of *IDH1/2* gene mutations occurring in AMLs, a finding that was later confirmed by the Genome Atlas Research Network.[46,47] These studies and others have provided evidence that *IDH1/2* mutations occur in about 20% of AML patients, including 6–16% *IDH1* mutations and 8–19% *IDH2* mutations (Table 1). Many studies have reported the main features of IDH-mutated AMLs, providing evidence that these AMLs are characterized by a preferential occurrence in older patients, a preferential normal cytogenetic profile or other intermediate-risk cytogenetics, an increased percentage of leukemic blasts in the bone marrow and peripheral blood at diagnosis, a more frequent association with *NPM1* and *FLT3* mutations, a frequent association with *DNMT3A* mutation, and mutual exclusivity with *TET2* and *WT1* mutations.[48–51]

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.