IDH1 Gene Mutations: A New Paradigm in Glioma Prognosis and Therapy?

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Despite intensive therapies, including surgery, radiotherapy, and chemotherapy, the outcome of glioma patients remains dismal, with a median overall survival time for patients with the most aggressive subtype (glioblastoma [GBM]) reaching only 15 months. Current research efforts focused on identifying genetic alterations implicated in GBM might help to define subgroups of patients with different prognoses and different responses to specific treatments. In this context, a recent genomewide mutational analysis conducted on 22 GBM samples identified a recurrent point mutation affecting codon 132 of the isocitrate dehydrogenase 1 gene (*IDH1*), located on chromosome locus 2q33. This mutation was present in 12% of GBMs and resulted in an Arg to His substitution in >90% of the cases [1]. *IDH1* encodes cytosolic isocitrate dehydrogenase 1, which is involved in the control of oxidative cellular damage [1]. Subsequent sequencing studies on larger glioma patient cohorts have been conducted by our lab and others [2–7]. These studies showed that the *IDH1* mutation is inversely associated with grade in diffuse glial tumors, affecting 71% of grade II, 64% of grade III, and 6% of primary glioblastomas (Table 1). It is of interest to note that *IDH1* is

markedly more mutated in secondary glioblastomas (76%), probably because these tumors are derived from lower grade gliomas [8, 9]. Moreover, the *IDH1* mutation was tightly associated with a 1p19q codeleted genotype [5, 8]. To date, five different *IDH1* mutations have been described, with the R132H mutation being the most prominent one (>90%).

Moreover, mutation of *IDH1* appears to be a very strong prognostic factor in diffuse gliomas, whatever the grade. Indeed, patients whose tumor harbored an *IDH1* mutation had a significantly longer survival time than patients with a tumor of the same grade but wild type (wt) for *IDH1*. For example, in grade III tumors, the median survival time of patients with mutated *IDH1* is about fourfold higher than that for patients with wt *IDH1* (81.1 months versus 19.4 months, respectively). Multivariate analysis confirms that mutations in the *IDH1* gene are independent factors of better outcome in patients with gliomas [5]. A few studies have also reported the frequency of *IDH1* mutations in other malignancies: only rare mutations were detected in prostate carcinomas and B-acute lymphoblastic leukemia (<3%) [10]. In acute myeloid leukemia, Mardis et al. [11] reported

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Table 1. Reported rates of *IDH1/IDH2* mutation according to glioma grade

		Tumor grade I	Tumor grade II	Tumor grade III	Primary GBM (IV)	Secondary GBM	All grades
<i>IDH1</i>	<i>n</i> ^a	253	1,034	1,118	1,392	123	3,920
	Mutated (%)	1 (0.4)	738 (71)	719 (64)	80 (6)	94 (76)	1,632 (42)
	(literature range, %)	(0.0–0.7)	(58–86)	(25–79)	(3–16)	(73–88)	(36–71)
<i>IDH2</i>	<i>n</i> ^a	21	542	667	193	13	1,436
	Mutated (%)	0 (0.0)	13 (2.4)	27 (4.0)	0 (0.0)	0 (0.0)	40 (2.8)
	(literature range, %)		(2.1–3.6)	(3.8–5.7)			ND

^aNumber of tumors analyzed in the literature [1–10].

Abbreviations: GBM, glioblastoma; IDH, isocitrate dehydrogenase; ND, not determined.

that *IDH1* mutations were found in 8% of samples and were associated with a normal cytogenetic status. No *IDH1* mutation was reported in a broad range of other tumor types, including gastrointestinal stromal tumors, melanoma, and bladder, breast, colorectal, lung, ovarian, pancreas, and thyroid carcinomas [1, 3], and in brain metastases of colorectal cancers [12]. Taken together, these results suggest that mutations in *IDH1* play a unique role in the pathogenesis of gliomas. Although rare, mutations of the related *IDH2* gene were also detected in astrocytic and oligodendroglial gliomas lacking *IDH1* mutations [7] (Table 1).

Mutations in *IDH1* appear as a new molecular feature in gliomas, encouraging investigations of the role of cellular metabolic pathways in brain tumors. Indeed, very few proteins involved in these pathways have been implicated in the mechanisms of oncogenesis and tumor development. Only mutations in succinate dehydrogenase, fumarate hydratase, and N-acetylgalactosaminyltransferase 12 have been reported to play crucial roles in paraganglioma, leiomyosarcoma, and colon cancer, respectively. These studies underscore the idea that alterations in cellular metabolism could contribute to tumorigenesis [13–15]. These results raise a wealth of questions. What are the cellular and molecular consequences of *IDH1* mutations in the context of brain tumors? What is the link between *IDH1* mutation and better outcome? What role does *IDH1* play in response to chemotherapy and/or radiotherapy? Should *IDH1* status be used as a stratification factor in clinical trials?

Whereas the functions of IDH1 have been extensively studied in yeast [16, 17], very few studies have aimed at characterizing human IDH1. The human genome possess five *IDH* genes, coding for three distinct IDH enzymes whose activities are either nicotinamide adenine dinucleotide phosphate (NADP⁺)-dependent (IDH1 and IDH2) or NAD⁺-dependent (IDH3). Whereas IDH2 and IDH3 are located in the mitochondria, IDH1 is located in the cytoplasm and in peroxisomes. IDH1 catalyzes the oxidative carbox-

ylation of isocitrate to α -ketoglutarate, which allows the reduction of NADPH. The production of NADPH is essential for the regeneration of reduced glutathione, which functions as the main antioxidant in mammalian cells and promotes resistance to apoptosis [15, 18] (Fig. 1). The R132 residue, located in the active site of the enzyme, is conserved in all NADP⁺-dependent IDHs. This residue is involved in substrate binding, forming three hydrogen bonds with isocitrate, whereas other residues involved in isocitrate binding form no more than two hydrogen bonds [19]. Thus, mutation of the R132 residue may impair the interaction of the enzyme with isocitrate. This hypothesis was confirmed by the work of Yan and colleagues. Indeed, those authors demonstrated that *IDH1* mutation results in the inactivation of the enzyme with a dominant negative effect on the IDH1 heterodimer [7, 8, 19]. This translates into a decrease in α -ketoglutarate, with, among other consequences, the inhibition of hypoxia-inducible factor 1 degradation [19]. Even more recently, Dang et al. [20] demonstrated that *IDH1* mutation results not only in a loss of oxidative decarboxylation of isocitrate to α -ketoglutarate but also in a gain of enzyme function for the NADPH-dependent reduction of α -ketoglutarate to 2-hydroxyglutarate, with production of NADP⁺ (Fig. 2). This new enzymatic activity results in an accumulation of 2-hydroxyglutarate, which has been linked to a higher risk for developing brain tumors [21]. The accumulation of this metabolite also induces an increase in oxidative stress in the brain [22]. Under these conditions, both greater reduced glutathione, resulting from the decrease in NADPH, and greater 2-hydroxyglutarate may raise the oxidative stress level in mutant *IDH1* tumor cells.

A robust antioxidant system is particularly critical for tumor cell survival. Tumor cells evolve in an oxidizing microenvironment as a result of reactive oxygen species (ROS) generated by impaired vascularization and the resulting hypoxia [23]. Tumor development also creates local inflammatory conditions that participate in the production

Figure 1. Roles of IDH1/IDH2 in cellular resistance to apoptosis, oxidative stress and anticancer treatments. Abbreviations: IDH, isocitrate dehydrogenase; NADP, nicotinamide adenine dinucleotide phosphate.

Figure 2. *IDH1* mutations result in both loss and gain of enzyme function.

of ROS [24]. IDH1 plays a prominent protective role against oxidative damage induced by ROS via the regeneration of reduced glutathione. In this context, mutation of *IDH1* appears paradoxical: on one hand, mutant *IDH1* cells may be more sensitive to genetic instability caused by an oxidative environment, and thus *IDH1* mutations may contribute to tumor development, and on the other hand, mutant *IDH1* cells are less protected against oxidative cellular damage. Anticancer therapies are also a source of ROS, which contribute to the cytotoxic activities of these treatments. These effects have been extensively demonstrated for ionizing radiation and to a lesser extent for chemother-

apy [25]. This may partly explain the long survival duration observed in patients with mutated *IDH1*. Given the broad range of therapeutic strategies used to treat these patients, *IDH1* mutation may modulate the efficacy of antitumor treatments. To date, the impact of *IDH1* mutations on both radio- and chemotherapy responses has not been reported. Preclinical studies are needed to determine whether *IDH1* status could influence the antitumor activity of drugs and/or radiation. Greater therapeutic sensitivity is expected for *IDH1* mutant cells than for wt *IDH1* tumor cells. If this hypothesis is true, the antitumor efficacy of both conventional and targeted chemotherapy should be considered in regard

to *IDH1* status. For example, a drug evaluated in a nonselected population of patients with high-grade gliomas could be considered globally inefficient because it did not work on wt *IDH1* tumors, but this agent may benefit the mutant *IDH1* subgroup. Currently, the available data suggest that knowledge of the *IDH1* status should be considered in the design of preclinical and clinical studies.

Finally, the close association between mutated *IDH1* and a higher survival rate also suggests that IDH1 could be a relevant target in glioma treatment, especially in primary GBM, a tumor type in which *IDH1* is rarely mutated. The challenge will be to design a therapeutic strategy able to inhibit the activity of IDH1. Such an approach could contribute to sensitize wt *IDH1* tumor cells to the cytotoxic effects of both radio- and chemotherapy and to improve patient outcome.

Though many questions remain unanswered, *IDH1* mutations appear to be very promising factors in both the diagnosis and treatment of glioma patients.

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