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Isocitrate dehydrogenase mutations in gliomas: mechanisms, biomarkers and therapeutic target

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Abstract

Purpose of the review—Isocitrate dehydrogenases, IDH1 and IDH2, decarboxylate isocitrate to α-ketoglutarate (α-KG), and reduce NADP to NADPH. Point mutations of IDH1 and IDH2 have been discovered in gliomas. IDH mutations cause loss of native enzymatic activities and confer novel activity of converting α-KG to 2-hydroxyglutarate (2-HG). The mechanisms of IDH mutations in gliomagenesis, their value as diagnostic, prognostic marker and therapeutic target have been extensively studied. This review is to summarize the findings of these studies.

Recent findings—Crystal structural studies revealed conformation changes in mutant IDHs, which may explain the gain of function by mutant IDHs. The product of mutant IDHs, 2-HG, is an inhibitor of α-KG-dependent dioxygenases, which may cause genome-wide epigenetic changes in human gliomas. IDH mutations are a favorable prognostic factor for human glioma and can be used as biomarker for differential diagnosis and subclassification rather than predictor of response to treatment. Preliminary data suggested that inhibiting production of the substrate of mutant IDH enzymes caused slow-down of glioma cell growth.

Summary—As valuable diagnostic and prognostic markers of human gliomas, there is still a lack of knowledge on biological functions of mutant IDHs, making targeting IDHs in glioma both difficult and unsecured.

Keywords

Isocitrate dehydrogenase; somatic mutation; glioma

Introduction

IDH1 and *IDH2* are NADP+-dependent isocitrate dehydrogenases, which catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) and reduce NADP to NADPH. *IDH1* and *IDH2* are homodimeric enzymes with different subcellular localizations. *IDH1* localizes in cytoplasm and peroxisome, whereas *IDH2* resides in the mitochondria. *IDH1* mutations were found in the majority of human low grade astrocytoma, oligodendroglioma and secondary glioblastomas. *IDH2* mutations occurred less frequently in gliomas and were mutually exclusive of *IDH1* mutations. Mutations in *IDH1* are proposed as an early event during glioma tumorigenesis, occurring preferentially in younger

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patients and correlating with a favorable outcome [1•-3•]. Following these initial discoveries, somatic mutations in *IDH1* and *IDH2* have been reported in acute myeloid leukemia (AML), though at a lower frequency [4-6]. Other tumor entities in which *IDH*1/2 mutations have been identified include colorectal cancer, prostate cancer, thyroid carcinoma and melanoma [7-11] . Enormous effort has been put forth to elucidate the mechanisms of these mutations in the development of these cancers and to determine their value as a diagnostic or prognostic marker, as well as a therapeutic target.

Oncogenic functions of IDH mutations

The majority of mutations identified were amino acid substitution at R132 of IDH1 and its analog, R172 of IDH2. These residues are highly conserved and involved in forming the active site of the enzymes. The enzymatic activity of mutant IDHs is significantly reduced[3, 12]. Dominant negative effects of the mutant IDHs was observed by Zhao et al [13••]. They found that mutant IDH1 dominantly inhibited wild-type IDH1 activity through the formation of heterodimers and thus inhibited degradation of hypoxia-inducible factor 1α (HIF-1α) by α-KG-dependent prolylhydroxylases. HIF-1α is an important transcription factor involved in crucial aspects of cancer biology, including angiogenesis, cell survival, glucose metabolism and invasion. The induction of the HIF-1α by IDH1 mutations was proposed as one of the mechanisms of the oncogenic effects of IDH mutation[14••]. Nevertheless, inconsistent findings have been reported concerning the dominant negative effect of mutant IDHs as well as the association of IDH mutations with HIF-1α expression in human samples[15•-17•].

The finding that *IDH* mutations are found exclusively in a heterozygous state indicates that these are gain of function mutations. IDH1 R132 and IDH2 R172 mutations confer a neomorphic enzymatic activity by reducing α-KG to 2-hydroxyglutarate (2-HG) while converting NADPH to $NADP^+$[18•, 19]. Both gliomas and AML cells harboring *IDH* mutations show elevated levels of 2-HG. How the IDH1 R132 and IDH2 R172 mutations confer new enzymatic activity was revealed by crystal structure analysis. Dang et al suggested that IDH1 R132H substitution caused change of open conformation to closed conformation, as well as reorganization of the active site of the enzyme[18•]. These changes favor the binding of NADPH as well as NADPH-dependent reduction of α-KG to R(2)-2=HG. Conversely, another structure study suggested closed pre-transition conformation was required for isocitrate binding and that the mutant IDH1 was less capable of forming the closed conformation [20•]. It was recently found that converting α-KG to 2-HG was not actually a novel activity of the mutant IDH1, as wild-type IDH1 also catalyzes this conversion, albeit less efficiently[21]. In wild type IDH1, R132 interacts with C-3 carboxylate of isocitrate, making isocitrate a potent inhibitor of α-KG binding to wild-type IDH1. Mutation of R132 to other amino acids significantly reduces the isocitrate binding while making α-KG binding more favorable. Regardless of the controversy about the mechanism of the neomorphic enzymatic activity, converting α-KG to 2-HG is a shared feature between mutant IDH1 and IDH2. The significant change in the enzymatic profile indicates that gain of function may be more important than loss of function in the oncogenic effects of IDH mutations.

Clues of how this neomorphic enzymatic activity promotes gliomagenesis emerged from several recent studies. A genome-wide DNA methylation profiling of gliomas identified a subgroup of gliomas with high specific DNA methylation status termed glioma-CpG island methylator phenotype (G-CIMP). Interestingly, G-CIMP correlates significantly with *IDH1* and *IDH2* mutations[22•]. The correlation of *IDH1* and *IDH2* mutations with hypermethylation phenotype of gliomas was further confirmed by another 2 studies[23, 24]. The hypermethylation phenotype of gliomas was found to be associated with longer survival and younger age, consistent with the findings of IDH1 and IDH2 mutations. Similarly, in

AML, 2-HG-producing IDH mutants induced global DNA hypermethylation[25]. Study in AML suggested that hypermethylation might be caused by inhibition of tet oncogene family member 2 (TET2), an α-KG-dependent dioxygenase enzyme, which functions to catalyze the formation of 5-hydroxymethylcytosine, likely leading to subsequent demethylation of DNA[26•]. The inhibition of TET2 by mutant IDH may be attributed to decreased α-KG production as well as direct inhibition of TET2 by 2-HG. Direct evidence of 2-HG in inducing epigenetic changes was provided by Xu et al who found that 2-HG is a competitive inhibitor of α-KG-dependent dioxygenases including histone dimethylases and TET 5-methlycytosine (5mC) hydroxylase[14••]. Other investigators also confirmed that 2-HG competitively inhibits α-KG-dependent histone lysine demethylases such as JMJD2A[27•]. Taken together, reduced production of α-KG and increased production of 2-HG by mutant IDHs may coordinate to induce histone and DNA hypermethylation, leading to genome-wide epigenetic changes and predisposing the cells for malignant transformation.

In spite of these tremendous strides in our knowledge regarding mutant IDH1 and mutant IDH2, the effects of IDH mutations in glioma tumorigenesis have yet to be fully revealed. Other mechanisms may include oxidative stress damage[28], aberrant glucose sensing[29] and aberrant apoptosis pathways[30-32]. Moreover, *IDH* mutations were found to be associated with alternative lengthening telomere (ALT) in human glioblastoma[33], and glioma stem cells with ALT were isolated from a human glioblastoma. Given that glioma and AML cells are relatively undifferentiated and that IDH mutations impair the hematopoietic differentiation[25], it will be interesting to investigate whether *IDH* mutations play a role in glioma stem cells.

IDH mutations as biomarkers of glioma

IDH1 and *IDH2* mutations are present in the majority of low-grade diffuse (WHO grade II) and anaplastic (WHO grade III) astrocytic, oligodendroglial, and mixed oligodendroglial neoplasm, as well as secondary glioblastomas. In contrast, IDH mutations are rarely observed in primary glioblastomas and other primary brain tumors. It is speculated that IDH mutations can serve as diagnostic and prognostic markers.

Several studies have investigated the utility of *IDH* mutations as diagnostic marker. Combination of *BRAF* and *IDH1* genetic status can serve as specific marker to differentiate between pilocytic astrocytoma from diffuse astrocytoma, since the majority of pilocytic astrocytomas have *BRAF* fusion but neither *IDH1* nor *IDH2* mutations, while majority of astrocytomas exhibited *IDH1* mutations but not *BRAF* fusions[34]. Another study suggested that examination of chromosome 7 gain, p53-mutant and *IDH1* mutations could distinguish diffuse astrocytoma from reactive astrocytosis[35]. By examining the status of *IDH* mutations in samples originally diagnosed as gangliogliomas, Horbinski et al found that *IDH* mutations in the samples correlated with early recurrence, malignant transformation and death, suggesting these tumors might be infiltrative gliomas that had been misclassified [36]. *IDH* status was also found to be useful for subclassification of gliomatosis cerebri (GC)[37, 38]. *IDH1* mutations were identified in GC in which there was a discernible, solid tumor mass, but not in classical GC without a solid tumor mass. Not surprisingly, *IDH* mutations are only found in adult GC patients and these patients tend to have longer survival.

The pioneering study of *IDH* mutations in glioblastomas identified a significant association between *IDH* mutations and a longer survival and younger age of onset [1]. In adult glioblastoma patients, *IDH* mutations predict prolonged progression-free survival as well as increased overall survival[39, 40]. The prognostic value of *IDH* mutations in predicting clinical outcomes is not limited to glioblastomas, but rather has been confirmed in the whole spectrum of human gliomas [23, 41-43]. However, *IDH* mutations are rare in pediatric gliomas, and occur at primarily older age (>=14 years old); when present, IDH mutations

predict longer survival for these pediatric patients[44, 45]. *IDH* mutations are also associated with longer survival in other, less common gliomas such as gliomatosis cerebri, a rare primary brain tumor[37, 38, 46]. With regard to response to treatment, though some studies suggested a correlation between the presence of *IDH* mutations and response to chemotherapy [47], it is generally believed that *IDH* status is not a marker for response to chemotherapy or radiotherapy [48-50]. It is worthwhile to note that for AML, in which *IDH* mutations are less frequent than glioma, *IDH1* and *IDH2* mutations are associated with significantly worse clinical outcomes. More studies in mechanisms of the oncogenic effects of mutant IDH1 and mutant IDH2 will elucidate how the presence of *IDH* mutations affect outcomes in different tumor types.

Several methods can be used to detect *IDH* mutations in tumor tissues including sequencing, immunohistochemical staining, PCR-restriction fragment length polymorphism (PCR-RFLP) and high resolution melting curve analysis[40, 51-56]. 2-HG, the product of the mutant *IDH1* and *IDH2*, was found to be elevated in the cancer cells, and detection of this oncometabolite correlated with the presence of *IDH* mutations [18, 19]. In AML, elevated 2-HG can be detected in the serum of the patients with *IDH* mutations[57•]. It was recently reported that 2-HG could also be detected by gas-chromatography/mass-spectrometry in formalin-fixed paraffin-embedded glioma specimens [58•]. More recently, a pilot study used proton magnetic resonance spectroscopy (MRS) to examine 2-HG in glioma patients in vivo and found that MRS findings were consistent with the results of detecting 2-HG in resected tumors by liquid chromatography mass spectrometry [59••]. It will be of great interest to investigate if 2-HG can be detected in the cerebrospinal liquid and by non-invasive MRS imaging.

IDH as a therapeutic target

Given that *IDH* mutations are highly prevalent and specific in human malignant gliomas, they may serve as potential therapeutic targets. However, due to the largely unknown mechanisms underlying the oncogenic effects of IDH mutations and association of IDH mutations with better prognosis of gliomas, it currently remains both difficult and controversial to utilize these mutations for therapeutic purposes. One study exploited the gain of function activity of mutant IDH1 enzymes that use α-KG as substrate to produce 2-HG. Using siRNA and small molecule inhibitor bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (BPTES), against glutaminase, an important enzyme in α-KG production, Seltzer et al. was able to inhibit the production of α-KG and observe a slowed growth rate of glioma cells harboring *IDH1* mutations [60••]. Although glutamine has been suggested to be the major source of α-KG in myeloid cells, it may not be the case for glioma in vivo. Additionally, cancer cells with IDH mutations demonstrate decreased α-KG and elevated 2-HG, which may be deleterious for multiple α-KG-dependent enzymes [13, 14, 26]. Moreover, the 2-HG in glioma cells was not changed by inhibition of α-KG production in this study. Both biochemical and biological studies indicate that converting α-KG to 2-HG is an important neomorphic feature of the mutant IDHs. Targeting the production of the 2-HG will be more favorable for inhibiting the oncogenic effects of IDH mutations. To achieve this, more basic functional and biological studies will be warranted.

Conclusions

It is now recognized that *IDH*1/2 mutations cause both loss of function and gain of function of the enzyme. The mutant *IDH1* and *IDH2* share the capability of converting α-KG to 2-HG. Findings from recent studies suggested IDH mutations may exert their effect by affecting α-KG-dependent enzymes, and may be involved in epigenetic events. However, limited data are available on the biological functions of *IDH* mutants. Therefore, the mechanisms of mutant IDH1 and mutant IDH2 in glioma genesis remain largely unknown.

As a prevalent and specific biomarker, IDH mutations correlate with better clinical outcomes in the whole spectrum of gliomas, and can serve as an important diagnostic and prognostic factor. So far, no association of *IDH* mutations with response to treatment of any kind has been validated. Targeting mutant IDH for treatment of gliomas is still in its infancy, and will be hardly practical until more fundamental knowledge is acquired about the biology of mutant IDHs.

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Key Points

- Mutations in IDH1 and IDH2 confer both a loss and gain of function, with a decreased affinity for its substrate, isocitrate, as well as neomorphic enzymatic activity reducing α-KG to 2-HG.
- Reduced production of α-KG and increased production of 2-HG by mutant IDHs may coordinate to induce histone and DNA hypermethylation, leading to genome-wide epigenetic changes and predisposing the cells to malignant transformation.
- IDH mutations hold great diagnostic and prognostic value, however there is little evidence in its predictive factor for response to treatment.
- Despite the prevalence of IDH mutations in WHO Grade II, III, and secondary glioblastomas, the oncogenic mechanisms of the mutations remains unknown, making their utility as therapeutic targets challenging.