Mini Review

Glioma-derived mutations in IDH: From mechanism to potential therapy

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Heterozygous mutations in either the R132 residue of isocitrate dehydrogenase I (IDH1) or the R172 residue of IDH2 in human gliomas were recently highlighted. Heterozygous mutations in the IDH1 occur in the majority of grade II and grade III gliomas and secondary glioblastomas and change the structure of the enzyme, which diminishes its ability to convert isocitrate (ICT) to α-ketoglutarate (α-KG) and provides it with a newly acquired ability to convert α-KG to R(-)-2-hydroxyglutarate [R(-)-2HG]. The IDH1 and IDH2 mutations are relevant to the progression of gliomas, the prognosis and treatment of the patients with gliomas harboring the mutation. In this paper, we reviewed these recent findings which were essential for the further exploration of human glioma cancer and might be responsible for developing a newer and more effective therapeutic approach in clinical treatment of this cancer.

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1. Introduction

Infiltration of the central nervous system by neoplastic cells in patients with glioblastoma multiforme (GBM) leads to neurological dysfunction and eventually to death. Gliomas contain specific histological subtypes, the most common of which are astrocytomas, oligodendrogliomas, and ependymomas. They are highly invasive, rapidly spreading form of brain cancer that is resistant to surgical and medical treatment. These tumors have been classified as grade I to grade IV on the basis of histopathological and clinical criteria established by the World Health Organization (WHO) [1]. Generally, WHO grade I gliomas, considered to be benign, are often curable with complete surgical resection and rarely, if ever, evolve into higher-grade lesions [2]. In contrast, gliomas of WHO grade II or III are invasive, progress to higher-grade lesions, and have a poor outcome. Despite advances in surgical techniques, radiation therapy and adjuvant chemotherapy, WHO grade IV tumors (glioblastomas), which are the most invasive form, have a dismal prognosis [3,4]. The elucidation of the mechanisms underlying the aggressive nature of GBM aims at improving radio-, chemo- and gene therapy [5,6].

Isocitrate dehydrogenase (IDH) whose activities are dependent on either nicotinamide adenine dinucleotide phosphate (NADP+-dependent IDH1 and IDH2) or nicotinamide adenine dinucleotide (NAD+-dependent IDH3) catalyzes the oxidative decarboxylation of isocitrate (ICT) to produce α-ketoglutarate (α-KG). A recent cancer genome sequencing project revealed that the gene encoding IDH1 was somatically mutated predominantly in secondary GBM [7]. Three subsequent studies of targeted IDH1 gene sequencing confirmed this finding, together identifying IDH1 mutations in about 5% of primary GBM but frequently in more than 70% of secondary GBM or low-grade gliomas [8,9]. The studies of mechanistic role of the somatic mutation in tumor demonstrated that the mutation inhibited IDH1 catalytic activity converting ICT to α-KG and induced hypoxia-inducible factor 1α (HIF-1α) [10], which made IDH1 acquiring the ability to catalyze α-KG to R(-)-2-hydroxyglutarate [R(-)-2HG] [11]. Mutated IDH1 consumed rather than produced NADPH, thus likely lowering NADPH levels even further. The low NADPH levels could sensitize glioblastoma to irradiation and chemotherapy, thus explaining the prolonged survival of patients with mutated glioblastoma [12]. Moreover, two mouse monoclonal antibodies targeting the IDH1 R132H mutation IMab-1 [13] and mIDH1R132H [14], both of which should be significantly useful for diagnosis and biological evaluation of mutation-bearing gliomas, have been established. Here, we review these new findings which may represent future directions for brain tumor studies and treatment.

2. Occurrence and characteristic of IDH mutations

Extraordinary high rates of spontaneous mutations in the gene encoding cytosolic NADP+-dependent IDH1 have been reported in diffuse gliomas of World Health Organization (WHO) grades II and III of astrocytic and oligodendroglial lineages and predominantly in secondary GBM [8,9,15,16] and in lower frequency mutations in the gene encoding mitochondrial NADP+-dependent IDH2 [9]. Of the five IDH gene in the human genome, IDH1 encodes for NADP+-dependent IDH1, which can be found in cytoplasm, peroxisomes [17] and endoplasmic reticulum [18]. The IDH1 protein
forms a homodimer [19] and plays a significant role in cellular control of oxidative damage through production of NADPH [20,21]. IDH2, another NADP+-dependent IDH localized in mitochondria, has a similar function with IDH1 [22]. The other three members of the IDH family are exclusively localized in mitochondria, depend on NAD⁺ for their enzymatic activity and play a relevant role in the Krebs cycle [23]. However, these NAD⁺-dependent IDHs are not known to be mutated in relation to gliomagenesis up to now.

After assessing IDH1 mutations in 321 gliomas of various histological types and biological behaviors, the fact that IDH1 mutations were frequent in low-grade diffuse astrocytomas (88%) and in secondary glioblastomas that developed through progression from low-grade diffuse or anaplastic astrocytoma (82%), high frequencies of IDH1 mutations were found in oligodendrogliomas (79%) and oligoastrocytomas (94%), and there were no cases in which an IDH1 mutation occurred after the acquisition of either a TP53 mutation or loss of 1p/19q suggested IDH1 mutations were very early events in gliomagenesis and might affect a common glial precursor cell population [15]. The data from screening exon 4 of the gene IDH1 for mutations in 596 primary intracranial tumors of all major types indicated that IDH1 mutation combined with either TP53 mutation or total 1p/19q loss was a frequent and early change in the majority of oligodendrogliomas, diffuse astrocytomas, anaplastic astrocytomas, and secondary glioblastomas but not in primary glioblastomas [16]. These studies concluded that IDH1 mutations were early and frequent genetic alterations in the evolution of gliomas. By contrast, primary glioblastomas very rarely contained IDH1 mutations, suggesting that primary and secondary glioblastomas might originate from different progenitor cells, in despite of the fact that they were histologically largely indistinguishable.

Interestingly, all of the IDH1 mutations identified to date produce a single amino acid substitution at R132 and all of the IDH2 mutations are at R172 which are analogous to R132 in IDH1. Sequence analysis of IDH1 and IDH2 in 939 tumor samples revealed somatic mutations at residue R132 of IDH1, including R132H (142 tumors), R132C (7 tumors), R132S (4 tumors), R132L (7 tumors), R132G (1 tumor), and at residue R172 of IDH2, including R172G (2 tumors), R172M (3 tumors), and R172K (4 tumors) [9]. The somatic mutations (R132C, R132G and R132L) affecting residue IDH1 (R132) in GBM were also confirmed in a panel of 672 tumor samples included high-grade glioma, gastrointestinal stromal tumors (GIST), melanoma, bladder, breast, colorectal, lung, ovarian, pancreas, prostate, and thyroid carcinoma specimens [24]. Notably, R132H is the most common IDH1 mutation by analyzing all of the dates. Dramatically, the IDH2 mutations were detected only in glial tumors without the IDH1 mutations [9]. IDH1 mutation of the R132C type was strongly associated with astrocytoma, while IDH2 mutations predominantly occurred in oligodendrogliomas [25].

The IDH1 mutations not only in GBM (16.0%) but also in prostate (2.7%) and β-acute lymphoblastic leukemia (1.7%) have been found after analyzing IDH1 codon 132 mutations in GBM and other common cancers [26]. Recently R132 IDH1 mutations have also been described in a subset of acute myelogenous leukemia (AML) [27]. However, IDH2 codon 172 mutations in human cancers besides glial tumors were absent [28]. In the current study, by direct genomic DNA sequencing, scientists identified a novel homozygous G367A IDH1 mutation, resulting in a G123R amino acid change, in a case of anaplastic thyroid cancer and V71 IDH1 mutation in follicular thyroid cancer [29]. All of these characteristics of IDH1 and IDH2 mutations might raise the possibility of a serious functional consequence as could be predicted by the occurrence of a positively charged amino acid and were responsible for their potential role as new diagnostic and prognostic markers in patients with these tumors.

3. Gain and loss of mutant IDH1 function (Fig. 1)

R132 in IDH1 and R172 in IDH2, evolutionarily conserved residues, participate in forming the activity site of the enzymes, respectively. Structural modeling, which is on the basis of the previously reported human cytosolic IDH1 crystal structure [19], predicts that the side chain of R132 uniquely forms three hydrogen bonds with both the α- and β-carboxyl groups of the substrate ICT but other residues involved in ICT binding form no more than two hydrogen bonds [10]. The fact that IDH1 and IDH2 mutations producing a single amino acid substitution and no obvious frameshift or protein-truncation reduced the enzymatic activity (NADP⁺-dependent) of the encoded protein has been confirmed through investigating the reduction of NADP⁺ to NADPH [9] and increasing km of mutant IDH1 for ICT [10]. The IDH1 protein forms an asymmetric homodimer [19] which catalyzes the oxidative decarboxylation of ICT to produce α-KG. The mutation affects the formation of the WT:WT homodimer. The hypothesis that the formation of the WT:R132H heterodimer impaired the enzyme active was demonstrated. And, as a consequence, α-KG levels were reduced [10].

Moreover, α-KG in the cytoplasm initiates oxygen dependent degradation of hypoxia-inducible factor subunit (HIF-1α) [30,31] which is the master switch of cellular adaptation to low oxygen tension and induces expression of genes implicated in glucose metabolism, angiogenesis, cell motility and invasion, and other signaling pathways that are critical to tumor growth [32]. Thus, decreased cytoplasmic level of α-KG increases levels of HIF-1α and the heterodimer HIF-1 consisting of HIF-1α and HIF-1β is transported into the nucleus for transcriptional activity [30–32]. Expression of the R132H IDH1 mutant, rather than wild-type IDH1, strongly induced the expression of HIF-1α target genes, such as glucose transporter 1 (Glut1), vascular endothelial growth factor (VEGF), and phosphoglycerate kinase (PGK1). Oxalolamata, a competitive inhibitor of IDH1 [33], also induced expression of these HIF-1α target genes [10]. All of these experiments demonstrated that the mutation changed the structure of the enzyme, and then diminished its ability to convert ICT to α-KG.

Dramatically, when losing a native function, the mutant IDH1 has a gain of function. A recent report showed that (i) mutated IDH1 had imperfect capacity to catalyze the oxidative decarboxylation of ICT to α-KG, generating NADPH from NADP⁺, but rather had a gain of function enabling IDH1 to convert α-KG and NADPH into R(−)-2HG and NADP⁺ by investigating isocitrate-dependent NADPH production and α-KG-dependent NADPH consumption in cell lysates, (ii) the crystal structure of the mutant IDH1 enzyme revealed a distinct and novel active site so that it obtained the acquired function converting α-KG, and NADPH into R(−)-2HG and NADP⁺. R(−)-2HG often accumulates in the inborn errors of metabolism that occur in the disorder 2-hydroxyglutaric aciduria [34,35], which is caused by deficiency in the enzyme R(−)-2HG dehydrogenase [36]. Patients with R(−)-2HG dehydrogenase deficiencies accumulate R(−)-2HG in the brain as assessed by MRI and CSF analysis, develop leukoencephalopathy, and have an increased risk of developing brain tumours [37–39], and result in increased reactive oxygen species (ROS) levels [40,41]. Recently, a study found that R(−)-2HG accumulated in acute myelogenous leukemia (AML) with IDH1 and IDH2 mutations. IDH1/2 mutations conferred an...
enzymatic gain of function that dramatically increased R(-)-2HG in AML [42]. Therefore, determining the level of R(-)-2HG could be used to measure mutant IDH1/2 enzyme activity, which provide some prognosis informations of the patients harboring the mutations.

4. Utility of IDH mutations in cancer treatment

IDH1 and IDH2 mutations may have significant utility for the diagnosis, prognosis, and treatment of patients with these tumors. It is well known that primary and secondary glioblastomas are histologically largely indistinguishable. IDH1 mutation is a strong predictor of a more favorable prognosis and a highly selective molecular marker of secondary glioblastomas that complements clinical criteria for distinguishing them from primary glioblastomas [43]. Therefore, the detection of IDH1 mutations is of major diagnostic and prognostic importance for glial patients.

IDH1 mutations were predominantly found in secondary glioblastoma and in younger patients but rarely existed in primary glioblastomas [15,24,25,43–45]. IDH1 appears to have a native function as a tumor suppressor that, when mutationally inactivated, contributes to tumorigenesis in part through induction of the HIF-1 pathway [10]. However, tumors with IDH1 or IDH2 mutations had distinctive genetic and clinical characteristics, and patients with such tumors had a better outcome than those with wild-type IDH genes [9]. Presence of IDH1 mutations in anaplastic astrocytomas and oligodendrogial tumors was shown to be associated with a significantly better outcome [45]. Interestingly, those few primary glioblastomas with IDH1 mutations also have a significantly better prognosis [46]. Mutated IDH1 consumes rather than produces NADPH [11]. Low levels of cytoplasmic NADPH, which result in impaired reduction of glutathione (GSH) and affect the thioredoxin system [34], may sensitize glioblastoma to irradiation and chemotherapy.

On the one hand, IDH1 regulates HIF-1α levels by controlling the level of α-KG. A cell-permeable derivative of α-KG (octyl-α-KG) were confirmed to have the ability of suppressing the HIF-1α induction caused by either IDH1 knockdown in HeLa cells, which suggested that drugs mimicking α-KG might merit exploration as a therapy for gliomas harboring an IDH1 mutation according to this mechanism [5].

On the other hand, clinical relevance make it a very attractive target to develop a mutation-specific antibody. Two mouse monoclonal antibodies targeting the IDH1 R132H mutation IMab-1 [13] and mIDH1R132H [14], both of which should be significantly useful for diagnosis and biological evaluation of mutation-bearing gliomas, have been established. IMab-1 displays specific cytosolic staining pattern in the tumor cells, whereas shows no staining in normal cells such as endothelial cells or blood cells [13]. The feature of antibody binding of mIDH1R132H to tumor cells is of major diagnostic interest for surgical specimens from small low-grade astrocytomas or oligodendrogliomas frequently not containing solid tumor but rather tumor infiltrated brain tissue [14]. Utility of immunohistochemistry with an antibody specific for the IDH1 mutations is a powerful and easy adjunct to practical neuropathological diagnosis.

5. Conclusion

These recent studies have shown the relations of HIF-1α, R(-)-2HG, NADPH and mutated IDH1 in gliomas, and provided some effective strategies for the diagnosis, prognosis, and treatment of patients with these tumors. However, whether IDH1 mutation is helpful for patients or not, considering that mutated IDH1-dependent HIF-1α production improves tumorigenesis but mutated IDH1-dependent NADPH consumption sensitizes glioblastoma to irradiation and chemotherapy. It should be determined in the future.

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References


