IDH1 gene mutation

IDH1 gene mutations refer to genetic alterations that occur in the isocitrate dehydrogenase 1 (IDH1) gene. The IDH1 gene encodes the enzyme isocitrate dehydrogenase 1, which is involved in cellular metabolism and the citric acid cycle.

Mutations in the IDH1 gene are most commonly observed in certain types of cancer, particularly gliomas (brain tumors) and acute myeloid leukemia (AML). The most prevalent mutation in the IDH1 gene is a substitution of arginine (R) with histidine (H) at position 132 (IDH1-R132H). This mutation leads to a change in the structure and function of the IDH1 enzyme.

The IDH1-R132H mutation confers a gain-of-function property to the mutated IDH1 enzyme. Instead of catalyzing the normal conversion of isocitrate to alpha-ketoglutarate (a key intermediate in cellular metabolism), the mutant IDH1 enzyme catalyzes a different reaction. It converts alpha-ketoglutarate into an abnormal metabolite called D-2-hydroxyglutarate (D-2-HG). This results in the accumulation of D-2-HG in cells, which disrupts normal cellular processes and contributes to tumorigenesis.

The presence of IDH1 mutations, particularly the IDH1-R132H mutation, has diagnostic and prognostic implications in certain cancers. It can be detected through genetic testing or molecular diagnostics, and its presence in tumor cells can help in the classification and management of specific cancers. Additionally, targeted therapies are being developed to specifically inhibit the mutant IDH1 enzyme and reduce the levels of D-2-HG as a potential treatment strategy for IDH1-mutant cancers.

It's important to note that IDH1 mutations are specific to the IDH1 gene and should not be confused with mutations in the IDH2 gene, which is a closely related gene that also encodes an isocitrate dehydrogenase enzyme (IDH2).

● IDH-wildtype is a normal enzyme in the Krebs cycle, catalyzing isocitrate → α-ketoglutarate

● mutant IDH occurs in many tumors, but not in normal cells. IDH1 is the most common mutation.

One metabolite is alpha-Hydroxyglutaric acid which may participate in tumorigenesis

● IDH mutations are found in 70–80% of secondary GBMs and their precursors (grade II & grade III gliomas), but in only 5% of primary GBMs

● prognosis in tumors with mutated IDH is better than those with IDH-wildtype

● WHO recommends testing for IDH mutations in all astrocytic tumors.

see IDH-mutant glioma.

Isocitrate dehydrogenase (IDH1) gene is the most prominent molecular marker of glioma prognosis, response to therapy, and patient survival. There are conflicting data about the effect of IDH1 mutation on glial cell proliferation, invasion, and migration characteristics. results highlighted that IDH1 mutation upregulates the mTOR signaling pathway and promote cell proliferation, invasion, and migration. [1)]

The combination of P53 and IDH1 as an immunohistochemical panel showed a specificity of 96% and sensitivity of 91% for differential diagnosis of reactive gliosis and low-grade astrocytoma. These 2 markers can be extremely helpful for this differential diagnosis [2].

IDH1 Arg132 mutations and IDH2 Arg140 and Arg172 mutations accounting for >90% of aberrations [3] [4]. IDH1 and IDH2 mutations reduce the enzymatic capacity of these proteins to bind isocitrate, their substrate, and convert it into alpha-ketoglutaric acid (α-KG), generating carbon dioxide and replenishing NADH and NADPH as side products [5]. This is one of the irreversible steps in the tricarboxylic acid cycle important for cellular respiration. Mutant IDH1 (cytoplasmic) and IDH2 (mitochondrial) enzymes also show a modified enzymatic capacity to convert α-KG into 2-hydroxyglutarate (2-HG), a small oncometabolite. Equally important, IDH1 and IDH2 mutations stratify individuals into molecular subtypes with distinct clinical outcomes – the mutations are associated with lower-grade astrocytomas, oligodendrogliomas (grade II/III) and secondary gliomas with better overall survival, progression-free survival and chemosensitivity than glioblastomas that are wild type for both genes [6] [7] [8].

Data support an evolutionary model in which IDH mutation glioma cells exist in symbiosis with supportive neuronal cells and astrocytes as suppliers of glutamate and lactate, possibly explaining the diffuse nature of these cancers. The dependency on glutamate and lactate opens the way for novel approaches in the treatment of IDHmut gliomas [9].

IDH1 mutation is important for prognosis of gliomas and represents a distinctive category of glioma.

Increased overall survival for patients with glioma is associated with mutations in the metabolic regulator isocitrate dehydrogenase 1 (IDH1).

Acquisition of IDH1 or IDH2 mutation (IDHmut) is among the earliest genetic events that take place in the development of most Low-grade glioma (LGG). IDHmut has been associated with longer overall patient survival. However, its impact on malignant transformation (MT) remains to be defined.

Studies demonstrate the value of unbiased genomic analyses in the characterization of human brain cancer and identify a potentially useful genetic alteration for the classification and targeted therapy of Glioblastomas [10].

Mutations in the IDH1 and IDH2 genes encoding isocitrate dehydrogenases suggest a role for this abnormal metabolic pathway in the pathogenesis and progression of primary brain tumors. Use of magnetic resonance spectroscopy can provide preoperative detection of IDH-mutated gliomas and affect surgical planning. In addition, IDH1 and IDH2 mutation status may have an effect on surgical resectability of gliomas. The IDH-mutated tumors exhibit better prognosis throughout every grade of glioma, and mutation may be an early genetic event, preceding lineage-specific secondary and tertiary alterations that transform LGGs into secondary glioblastomas [11].

A study confirms that long-term survival in Glioblastoma patients is if at all only weakly correlated to

IDH-mutation [12].

Miroshnikova et al., found that glioma aggression and patient prognosis correlate with HIF1A levels and the stiffness of a tenascin C (TNC)-enriched ECM. Gain- and loss-of-function xenograft manipulations demonstrated that a mutant IDH1 restricts glioma aggression by reducing HIF1α-dependent TNC expression to decrease ECM stiffness and mechanosignalling. Recurrent IDH1-mutant patient gliomas had a stiffer TNC-enriched ECM that the studies attributed to reduced miR-203 suppression of HIF1α and TNC mediated via a tension-dependent positive feedback loop. The work suggests that elevated ECM stiffness can independently foster glioblastoma aggression and contribute to glioblastoma recurrence via bypassing the protective activity of IDH1 mutational status [13].

Analysis

Conventional methods for isocitrate dehydrogenase 1 (IDH1) detection, such as DNA sequencing and immunohistochemistry, are time- and labor-consuming and cannot be applied for intraoperative analysis. To develop a new approach for rapid analysis of IDH1 mutation from tiny tumor samples, a study used microfluidics as a method for IDH1 mutation detection.

Forty-seven glioma tumor samples were used; IDH1 mutation status was investigated by immunohistochemistry and DNA sequencing. The microfluidic device was fabricated from polydimethylsiloxane following standard soft lithography. The immunoanalysis was conducted in the microfluidic chip. Fluorescence images of the on-chip microcolumn taken by the charge-coupled device camera were collected as the analytical results readout. Fluorescence signals were analyzed by NIS-Elements software to gather detailed information about the IDH1 concentration in the tissue samples.

DNA sequencing identified IDH1 R132H mutation in 33 of 47 tumor samples. The fluorescence signal for IDH1-mutant samples was 5.49 ± 1.87 compared with 3.90 ± 1.33 for wild type ($p = 0.005$). Thus, microfluidics was capable of distinguishing IDH1-mutant tumor samples from wild-type samples. When the cutoff value was 4.11, the sensitivity of microfluidics was 87.9% and the specificity was 64.3%.

This new approach was capable of analyzing IDH1 mutation status of tiny tissue samples within 30 minutes using intraoperative microsampling. This approach might also be applied for rapid pathological diagnosis of diffuse gliomas, thus guiding personalized resection [14].

1)
Avsar T, Kose TB, Oksal MD, Turan G, Kilic T. IDH1 mutation activates mTOR signaling pathway, promotes cell proliferation and invasion in glioma cells. Mol Biol Rep. 2022 Aug 7. doi: 10.1007/s11033-022-07750-1. Epub ahead of print. PMID: 35934766.
2)
Geramizadeh B, Kohandel-Shirazi M, Soltani A. A Simple Panel of IDH1 and P53 in Differential Diagnosis Between Low-Grade Astrocytoma and Reactive Gliosis. Clin Pathol. 2021 Feb 11;14:2632010×20986168. doi: 10.1177/2632010×20986168. PMID: 33634261; PMCID: PMC7887675.
3) 6)
Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, Kos I, Batinic-Haberle I, Jones S, Riggins GJ, Friedman H, Friedman A, Reardon D, Herndon J, Kinzler KW, Velculescu VE, Vogelstein B, Bigner

DD. IDH1 and IDH2 mutations in gliomas. N Engl JMed. 2009; 360:765–773
4) , 7)

Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, Olivi A, McLendon R, Rasheed BA, Keir S, Nikolskaya T, Nikolsky Y, Busam DA, Tekleab H, Diaz LA, Jr, Hartigan J, Smith DR, Strausberg RL, Marie SK, Shinjo SM, Yan H, Riggins GJ, Bigner DD, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008; 321:1807–1812
5) , 8)

Yen KE, Bittinger MA, Su SM, Fantin VR. Cancer-associated IDH mutations: biomarker and therapeutic opportunities. Oncogene. 2010; 29:6409– 6417
9)

Lenting K, Khurshed M, Peeters TH, van den Heuvel CNAM, van Lith SAM, de Bitter T, Hendriks W, Span PN, Molenaar RJ, Botman D, Verrijp K, Heerschap A, Ter Laan M, Kusters B, van Ewijk A, Huynen MA, van Noorden CJF, Leenders WPJ. Isocitrate dehydrogenase 1-mutated human gliomas depend on lactate and glutamate to alleviate metabolic stress. FASEB J. 2018 Jul 12:fj201800907RR. doi: 10.1096/fj.201800907RR. [Epub ahead of print] PubMed PMID: 30001166.
10)

Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, Olivi A, McLendon R, Rasheed BA, Keir S, Nikolskaya T, Nikolsky Y, Busam DA, Tekleab H, Diaz LA Jr, Hartigan J, Smith DR, Strausberg RL, Marie SK, Shinjo SM, Yan H, Riggins GJ, Bigner DD, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008 Sep 26;321(5897):1807-12. doi: 10.1126/science.1164382. Epub 2008 Sep 4. PubMed PMID: 18772396; PubMed Central PMCID: PMC2820389.
11)

Chen R, Ravindra VM, Cohen AL, Jensen RL, Salzman KL, Prescot AP, Colman H. Molecular features assisting in diagnosis, surgery, and treatment decision making in low-grade gliomas. Neurosurg Focus. 2015 Mar;38(3):E2. doi: 10.3171/2015.1.FOCUS14745. PubMed PMID: 25727224.
12)

Amelot A, De Cremoux P, Quillien V, Polivka M, Adle-Biassette H, Lehmann-Che J, Françoise L, Carpentier AF, George B, Mandonnet E, Froelich S. IDH-Mutation Is a Weak Predictor of Long-Term Survival in Glioblastoma Patients. PLoS One. 2015 Jul 9;10(7):e0130596. doi: 10.1371/journal.pone.0130596. eCollection 2015. PubMed PMID: 26158269; PubMed Central PMCID: PMC4497660.
13)

Miroshnikova YA, Mouw JK, Barnes JM, Pickup MW, Lakins JN, Kim Y, Lobo K, Persson AI, Reis GF, McKnight TR, Holland EC, Phillips JJ, Weaver VM. Tissue mechanics promote IDH1-dependent HIF1α-tenascin C feedback to regulate glioblastoma aggression. Nat Cell Biol. 2016 Nov 7. doi: 10.1038/ncb3429. [Epub ahead of print] PubMed PMID: 27820599.
14)

Aibaidula A, Zhao W, Wu JS, Chen H, Shi ZF, Zheng LL, Mao Y, Zhou LF, Sui GD. Microfluidics for rapid detection of isocitrate dehydrogenase 1 mutation for intraoperative application. J Neurosurg. 2016 Jun;124(6):1611-8. doi: 10.3171/2015.4.JNS141833. Epub 2015 Nov 6. PubMed PMID: 26544771.

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