Alpha-Hydroxyglutaric acid

- R-2-hydroxyglutarate-mediated inhibition of KDM4A compromises telomere integrity
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- Reviewing the IDH1 Mutation-Mediated Mechanism of Drug Resistance and Revisiting Its Overcoming Strategies
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- 2-Hydroxyglutarate magnetic resonance spectroscopy for preoperative IDH molecular profiling - A review of the literature and real-world clinical translation in a busy neurosurgical neuro-oncology unit
- Metabolism and therapeutic response in acute myeloid leukemia with IDH1/2 mutations

Alpha-hydroxyglutaric acid (α-hydroxyglutaric acid or α-HGA) is an organic acid that is involved in cellular metabolism. It exists in two forms: D-alpha-hydroxyglutaric acid (D-α-HGA) and L-alpha-hydroxyglutaric acid (L-α-HGA), which are mirror images of each other and have different biological activities.

D-α-Hydroxyglutaric aciduria (D-α-HGA) is a rare metabolic disorder characterized by elevated levels of D-α-HGA in the body. It is caused by a deficiency of the enzyme D-2-hydroxyglutarate dehydrogenase (D2HGDH), which is responsible for metabolizing D-α-HGA into alpha-ketoglutarate (α-KG) in the mitochondria. The accumulation of D-α-HGA disrupts normal cellular processes and can lead to neurological symptoms and developmental delays.

L-α-Hydroxyglutaric aciduria (L-α-HGA) is another rare metabolic disorder characterized by elevated levels of L-α-HGA. It is caused by a deficiency of the enzyme L-2-hydroxyglutarate dehydrogenase (L2HGDH), which converts L-α-HGA into α-KG. L-α-HGA accumulation can also result in neurological symptoms and developmental delays, similar to D-α-HGA.

Both D-α-HGA and L-α-HGA are inherited in an autosomal recessive manner, meaning an affected individual must inherit two copies of the mutated gene (one from each parent) to develop the disorder.

The diagnosis of D-α-HGA or L-α-HGA is typically confirmed by measuring the levels of the respective hydroxyglutaric acid in urine, blood, or cerebrospinal fluid. Treatment for these disorders involves managing symptoms and may include dietary modifications and supportive therapies.

Research is ongoing to better understand the underlying mechanisms and develop potential treatments for alpha-hydroxyglutaric acidurias.

α-Hydroxyglutaric acid (2-hydroxyglutaric acid) is an alpha hydroxy acid form of glutaric acid.

Mutations in the genes encoding the metabolic enzymes isocitrate dehydrogenase 1 (IDH1) or 2 (IDH2) are present in nearly all grade 2 diffuse gliomas in adults.

The mutant enzyme produces the metabolite 2-hydroxyglutarate, which accumulates in glioma tissue and competitively inhibits various α-ketoglutarate–dependent enzymes, resulting in a broad range of changes in DNA hydroxymethylation, gene expression, cellular differentiation, and the tumor microenvironment.

Isocitrate dehydrogenase (IDH) mutations are highly frequent in glioma, producing high levels of the oncometabolite D-2-hydroxyglutarate (D-2HG). Hence, D-2HG represents a valuable imaging marker for IDH-mutant glioma.

As patients with IDH-mutant glioma enter early-phase vaccine and immune checkpoint inhibitor clinical trials, there is emerging evidence that implicates the oncometabolite, 2-hydroxyglutarate (2HG), generated by the neomorphic activity of mutant IDH, as a potential barrier to current immunotherapeutic approaches. Richardson et al. reviewed the immunomodulatory and immunosuppressive roles of 2HG within the unique IDH-mutant glioma tumor immune microenvironment and discuss promising immunotherapeutic approaches currently being investigated in preclinical models [1)].

Li et al. developed and evaluated a super-resolution 3D MR spectroscopy strategy to map D-2HG and tumor metabolism in IDH-mutated human glioma.

Between March and September 2018, participants with IDH1-mutated gliomas and healthy participants were prospectively scanned with a 3-T whole-brain 3D MR spectroscopic imaging protocol optimized for D-2HG. The acquired D-2HG maps with a voxel size of 5.2 × 5.2 × 12 mm were upsampled to a voxel size of 1.7 × 1.7 × 3 mm using a super-resolution method that combined weighted total variation, feature-based nonlocal means, and high-spatial-resolution anatomic imaging priors. Validation with simulated healthy and patient data and phantom measurements was also performed. The Mann-Whitney U test was used to check that the proposed super-resolution technique yields the highest peak signal-to-noise ratio and structural similarity index. Three participants with IDH1-mutated gliomas (mean age, 50 years ± 21 [standard deviation]; two men) and three healthy participants (mean age, 32 years ± 3; two men) were scanned. Twenty healthy participants (mean age, 33 years ± 5; 16 men) underwent a simulation of upsampled MR spectroscopic imaging. Super-resolution upsampling improved peak signal-to-noise ratio and structural similarity index by 62% ($P < .05$) and 7.3% ($P < .05$), respectively, for simulated data when compared with spline interpolation. Correspondingly, the proposed method significantly improved tissue contrast and structural information for the acquired 3D MR spectroscopic imaging data.

High-spatial-resolution whole-brain D-2-hydroxyglutarate imaging is possible in isocitrate dehydrogenase 1-mutated human glioma by using a super-resolution framework to upsample three-dimensional MR spectroscopic images acquired at lower resolution [2)].

A study showed some evidence that both IDH1 mutation and 2-HG can lead to EMT-like phenotype and proliferation and migration in glioma cells. EMT-like biomarkers changed in IDH1 mutation cells generated via lentiviral transduction technology or treated in 2-HG [3].

Gas chromatography time-of-flight mass spectrometry was applied to CSF samples collected from 15 consecutive high-grade aSAH patients (modified Fisher grade 3 or 4). Collected CSF samples were analyzed at two time points (admission and the anticipated vasospasm timeframe). Metabolite levels at both time points were compared and correlated with vasospasm status and Glasgow Outcome Scale (GOS) of patients at 1 year post-aSAH. Significance level was defined as $p < 0.05$ with false discovery rate correction for multiple comparisons.

Of 97 metabolites identified, 16 metabolites, primarily free amino acids, significantly changed between the two time points. These changes were magnified in modified Fisher grade 4 compared with grade 3. Six metabolites (2-hydroxyglutarate, tryptophan, glycine, proline, isoleucine, and alanine) correlated with GOS at 1 year post-aSAH independent of vasospasm status. When predicting patients who had low disability (GOS 5 vs. GOS ≤4), 2-hydroxyglutarate had a sensitivity and specificity of 0.89 and 0.83 respectively.

This preliminary study suggests that specific metabolite changes occur in the brain during the course of aSAH and that quantification of specific CSF metabolites may be used to predict long-term outcome in patients with aSAH. This is the first study to implicate 2-hydroxyglutarate, a known marker of tissue hypoxia, in aSAH pathogenesis [4].

1)
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