Curr Opin Neurol. 2025 Sep 4. doi: 10.1097/WCO.0000000000001426. Online ahead of print.

# Isocitrate dehydrogenase mutation and microenvironment in gliomas: do immunotherapy approaches matter?

Michael Platten [1 2 3 4 5]

Affiliations

PMID: 40916936 DOI: 10.1097/WCO.0000000000001426

## Abstract

**Purpose of review:** Gliomas with mutations in the gene for isocitrate dehydrogenase (IDH) display a unique immune microenvironment that is distinct from IDH-wildtype gliomas. This unique immune microenvironment is shaped by 2-hydroxyglutarate (2-HG), an oncometabolite produced by mutant IDH. These features provide an opportunity to develop and test targeted immunotherapies for IDH-mutant gliomas.

**Recent findings:** IDH-mutant gliomas are characterized by an immunosuppressive tumor immune microenvironment (TIME) that suppresses the infiltration and activation of tumor-specific T cells. This is owed both to direct effects of the oncometabolite 2-hydroxyglutarate on glioma-infiltrating T cells and myeloid cells and indirect effects on the chemotactic profile of tumor cells. These immunosuppressive effects are reversed by IDH inhibitors recently approved for the treatments of IDH-mutant gliomas. At the same time, clinical trials have demonstrated encouraging results for targeted immunotherapies using vaccines targeting the most frequent mutation IDH1R132H.

**Summary:** The reversal of the immunosuppressive effects by IDH inhibitors has opened exciting avenues for combinatorial immunotherapies such as vaccines and immune checkpoint inhibitors.

**Keywords:** glioma; immune checkpoint inhibitor; immunotherapy; isocitrate dehydrogenase; microenvironment; vaccine.