

Isocitrate Dehydrogenase (IDH) Mutations in Gliomas:
Effect on Tumor Progression, Metabolism, Treatments, and Patient Outcomes

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Abstract

Gliomas are a type of brain tumor that forms from glial or progenitor cells in the brain or spinal cord, and their classification and prognosis depends on genetic mutations, especially in isocitrate dehydrogenase 1 and 2 (IDH1/2). These modifications are most common in low grade gliomas and secondary glioblastomas, where they produce the oncometabolite D-2-hydroxyglutarate (D-2HG), disrupting cell metabolism and epigenetic regulation. This review analyzes how IDH1/2 mutations affect tumor metabolism, patient prognosis, and treatment response by surveying existing research in the field. Findings show that IDH-mutant gliomas have altered metabolic activity, significantly better survival than wild-type tumors, greater sensitivity to surgery, radiation, chemotherapy, and newer targeted therapies such as IDH inhibitors and immunotherapy. Overall, IDH mutations act as key drivers linking tumor metabolism, prognosis, and treatment response, although more research connecting molecular and clinical findings is still needed to improve treatments and therapies.

Introduction

Despite their relatively rare occurrence (20,000 people in the United States diagnosed every year), gliomas carry a disproportionately high fatality rate [1, 2]. One of the biggest challenges in treating gliomas is the Blood Brain Barrier, which prevents drugs from reaching the brain easily, requiring different, more creative ways of administering treatment to the brain in an efficient way [1,4]. The significant variety of these tumor also complicates treatment development [1, 3]. Gliomas are central nervous system tumors that arise from glial or progenitor cells in the brain [4, 5]. The WHO categorizes tumors into different grades, lower grades indicates a slower growing tumor, whereas high grade tumor are more aggressive and malignant [3, 6, 20]. The sources analyzed showed IDH mutations were linked to slower growth of the tumors and less likely showed aggressive mutations (like Phosphatase and Tensin homolog (PTEN) loss and Epidermal Growth Factor Receptor (EGFR) amplification) that are commonly seen in wild type form. IDH mutations also alter the metabolism of the tumor and mutant variants tend to be more sensitive to treatment [2, 6, 21].

Methods

This literature review examined 42 sources published between 2009 and 2025 that included peer-reviewed journal articles and an academic textbook chapter on glioblastoma and IDH mutations. Sources were identified using PubMed and Google Scholar using the keywords such as “glioblastoma”, “IDH mutation”, “glioma metabolism”, “gliomas” and “glioma prognosis.” The review examined tumor behavior, diagnosis, prognosis, and treatment outcomes in diffuse gliomas across the sources. It also compared survival and prognostic outcomes between IDH-mutant and IDH-wild-type tumors across studies to identify consistent patterns, differences, and gaps in the existing literature. No primary data collection was performed as part of this review.

Results

IDH mutations profoundly affect gliomas in these key areas:

Tumor Progression

- IDH mutations occur early in tumor formation, altering gene regulation and trapping cells in an immature state [3, 7, 8, 10, 14].
- IDH mutant gliomas begin as low-grade lesions unlike wildtype glioblastomas, which start out as aggressive tumors [2, 4, 6, 8, 16, 17, 18].

Metabolism

- Mutant IDH1/2 enzymes produce D-2HG, an oncometabolite, that disrupts many normal cell processes [6, 7, 8, 11, 12, 13].
- Cells, therefore, rely on mitochondrial energy, drain their antioxidant defenses, and lower their NAD+ levels. These can be exploited for therapies [3, 8, 11, 15, 16].

Treatments

- IDH mutant gliomas respond better to treatments like chemotherapy, radiation, and surgical resection [2, 3, 16, 18, 29, 30, 31].
- New treatments includes drugs like vorasidenib and ivosidenib, which can reduce growth in lower grade tumors, but have more limited efficacy against grade 4 tumors [10, 16, 32, 33, 34, 35, 36].
- Immunotherapies, including vaccines that target specific mutations, elicit an immune response and increase long-term survival in IDH mutant gliomas [11, 16, 18, 37, 38, 39, 40].

Patient Outcomes

- Gliomas with IDH mutations predict a prognosis with a much longer lifespan compared to wild-type gliomas [2, 3, 6, 9, 11, 18, 22, 25, 42].

Discussion

The following known limitations exist despite the favorable prognosis associated with IDH mutations:

- The prognostic benefit that IDH mutations have is unique to gliomas and does not apply to other cancers like AML [8, 11, 27, 28].
- If a tumor acquires a specific aggressive mutations (like CDKN2A/B) the survival advantage is lost and prognosis matches wild-type glioblastomas [18, 19, 26].

While the initial biochemical processes that trigger the glioma are well understood, the exact mechanisms by which the mutations impede cancer progression need further research. In addition, research and trials can be expanded to include pediatric populations. [8, 10, 16, 18, 32]

Conclusion

IDH mutation status is a stronger indicator of prognosis and survival than the tumor grade alone. It is now a key factor in WHO’s classification and dictates treatment plans, including drug selection and chemoradiation timings [3, 10, 16, 18, 23, 24, 32, 33].

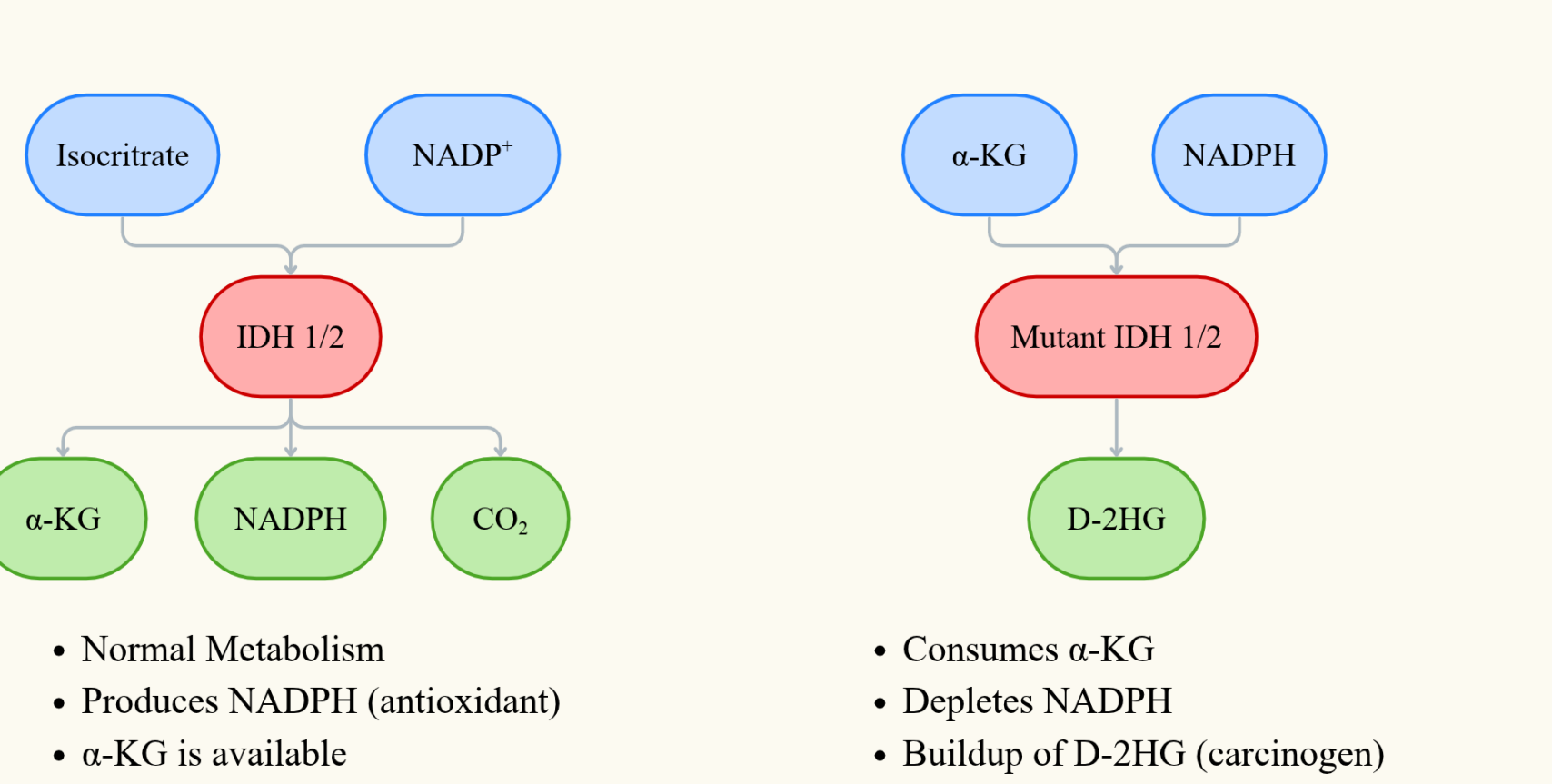
References

Complete list of references provided in the next slide and can also be accessed using the link or QR code below.

<https://tinyurl.com/dpadhu>



Figure 1. Normal vs. Mutant IDH1/2 Pathways in Diffuse Glioma



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