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Review Article

Molecular biology and novel therapeutics for IDH mutant gliomas: The new era of IDH inhibitors

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Abstract

Gliomas with Isocitrate dehydrogenase (IDH) mutation represent a discrete category of primary brain tumors with distinct and unique characteristics, behaviors, and clinical disease outcomes. IDH mutations lead to aberrant high-level production of the oncometabolite D-2-hydroxyglutarate (D-2HG), which act as a competitive inhibitor of enzymes regulating epigenetics, signaling pathways, metabolism, and various other processes. This review summarizes the significance of IDH mutations, resulting upregulation of D-2HG and the associated molecular pathways in gliomagenesis. With the recent finding of clinically effective IDH inhibitors in these gliomas, this article offers a comprehensive overview of the new era of innovative therapeutic approaches based on mechanistic rationales, encompassing both completed and ongoing clinical trials targeting gliomas with IDH mutations.

Introduction

Glioma is the most common malignant primary brain tumor among adults that originates from the glial cells. The role of glial cells is to provide support, insulation, and nourishment to the neurons in the brain and spinal cord. Gliomas can occur in any part of the Central Nervous System (CNS), but most commonly develop in the brain. The inclusion of molecular criteria in the conventional WHO Classification of Tumors of the CNS was first introduced in the 2016 revision. It marked a significant shift from relying solely on histopathological features to taking account of molecular biomarkers, especially relevant in isocitrate dehydrogenase (IDH) mutant gliomas [[1], [2], [3]].

The discovery of IDH mutations in gliomas has significantly changed our understanding towards the molecular processes and mechanisms involved in the glioma development and progression. In humans, the IDH gene consists of three different types of isozymes: IDH1, IDH2, and IDH3. The mutations in IDH1 were first discovered by Parsons et al.in 12% of glioblastomas (GBMs), specifically located at 2q.33 [4]. Subsequent extensive studies confirmed that IDH1 and IDH2 mutations were prevalent mostly in secondary GBMs and

lower-grade gliomas (WHO grade II or III), but were rare in adult primary and pediatric GBMs [5,6]. The majority of IDH1 mutations occurred at codon 132, and showed a high frequency (>90%) of c.395G>A (R132H) substitution, with R132C being the next most common mutation [7,8].

The accelerated update in the fifth edition of the WHO Classification of Tumors of the CNS in 2021 was driven by the rapid expansion of our comprehension of the molecular basis of CNS tumors and by the recognition of the significance of molecular modifications in accurate diagnosis, prognosis, and treatment selection [9]. The new classification emphasizes the importance of molecular markers in influencing treatment and prognosis. It introduces three main types of adult-type diffuse gliomas; Astrocytoma (IDH mutant), Oligodendroglioma (IDH mutant and 1p/19q codeleted), and Glioblastoma (IDH wildtype). Previously, glioblastoma included both IDH wildtype and IDH mutant tumors, but currently, it is restricted to IDH wildtype tumors. The updated classification enables a more precise and personalized approach to the diagnosis and management of gliomas with IDH mutations [1,9].

This review summarizes the molecular mechanisms underlying IDH mutant glioma, focusing on the key pathways influenced by IDH mutations (Fig. 1). Notably, IDH mutations lead to the abnormal production of D-2-hydroxyglutarate (D-2HG), an oncometabolite that interferes with crucial cellular processes and contributes to glioma formation [10]. This enzymatic activity has now been successfully targeted for clinical effect in IDH mutant gliomas [[11], [12], [13]]. IDH mutations promote tumorigenesis through the accumulation of D-2HG and its consequential effects on hypermethylation of DNA, RNA, and histone, signaling pathways, mitochondrial dynamics, metabolism, and phenotypic changes in gliomas. Thus, inhibition of 2HG will now lead to a significant change in these tumors, which in anticipated to change future treatment options. By clarifying these molecular pathways, our aim is to provide a comprehensive and deeper understanding of the intricate molecular biology of gliomas with IDH mutations and potential targets for novel therapeutics against them (Fig. 2).

Section snippets

Molecular pathways of D-2HG production driven by IDH mutations in glioma

Understanding the effect of IDH mutations on glioma biology has shed light on the intricate interplay between metabolism, epigenetics, and changes in signaling pathways. IDH1 is found in the cytosol and peroxisome, while both IDH2 and IDH3 are located in the mitochondria matrix and participating in the tricarboxylic acid (TCA) cycle [[14], [15], [16]]. Interferences in the IDH gene result in a disruption in the normal enzymatic activity, causing the inhibition of α-KG production and leading to…

Direct targeting of IDH mutation for the treatment of IDH mutant gliomas

Small chemical compounds designed to inhibit the activity of mutant IDH1 or IDH2 enzymes serve as a direct therapeutic strategy to curtail oncometabolite production and restore normal cellular functions [39]. For IDH mutant gliomas, the rationale behind targeting the mutant enzyme directly is underpinned by several observations. First, specific regions within the enzyme's active site are pinpointed as hotspots in gliomas with IDH [40]. Second, IDH mutations are identified as early oncogenic…

Epigenetic alterations of DNA methylation status

Accumulation of D-2HG in IDH mutant gliomas suppresses the activity of α-KG-dependent dioxygenases (α-KGDD), which are vital for DNA demethylation, a process linked to gene repression. DNA methylation levels

and patterns are controlled by enzymes like DNA methyltransferases (DNMTs) and the Ten-eleven translocation (TET) family, including TET1, TET2, and TET3 [54]. These enzymes primarily catalyze the conversion of 5-methylcytosine (5-mC) into 5-hydroxymethylcytosine (5-hmC), which can further…

Hypoxia-inducible factor (HIF) signaling pathways

Hypoxia-inducible factors (HIFs) are heterodimer transcription factors, consist of oxygen-regulated HIF-1α subunit and HIF-1β subunit which is constitutively expressed [79]. Increased HIF-1α levels have been detected in different cancer types, where it is involved in regulating processes, such as apoptosis, tumor angiogenesis, and cellular proliferation [73] [80]. In glioma patients, the overexpression of HIF-1α has been observed in high-grade glioma tissues and has a strong correlation with…

Mitochondrial respiration and biogenesis

In IDH-mutated tumors, D-2HG has been found to bind to ATP synthase located in the inner mitochondrial membrane which carries out the oxidative phosphorylation (OXPHOS) with electron transport chain (ETC) complexes. ATP synthase produces ATP through phosphorylation of ADP, using energy from the proton gradient across the inner mitochondrial membrane established by ETC complex I, III, and IV. By binding to ATP synthase β subunit (ATP5B), D-2HG inhibits its function and reduces ATP production,…

Standard DNA alkylating agents

The standard approach for treating gliomas usually involves extensive surgical removal, followed by radiotherapy (RT) and chemotherapy with temozolomide (TMZ) or alternatively, the combination of procarbazine, lomustine (CCNU), and vincristine (PCV) [136]. TMZ, taken orally, spontaneously breaks down to produce active metabolites, including 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC) and 4-amino-5-imidazole-carboxamide (AIC), which exert cytotoxicity by methylating DNA…

Immunotherapeutic approaches for the treatment of gliomas with IDH mutations

In tumors with IDH mutations, immunosuppressive effects through several pathways have been observed with the accumulation of D-2HG. In mice that were administered syngeneic mouse glioma that carries the IDH mutation, a decrease in the infiltration of CD8+ T-cell was displayed which was inhibited by D-2HG [157]. A D-2HG inhibitor led to a reversal of immune deficits, resulting in an enhanced recruitment of CD8+ T-cells to the tumor in mice harboring IDH-mutant glioma [157]. In addition, Zhang et …

Conclusion

The identification of IDH mutations marks a significant milestone in the field of neuro- oncology, contributing significantly to advancements in glioma classification and prognosis. We overviewed diverse molecular processes relevant to IDH mutant gliomagenesis and discussed various emerging therapeutic approaches for tumors with this distinctive genetic signature. Enhancing our comprehension and obtaining a more profound insight into the essential molecular mechanisms driven by IDH mutation and …

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Daniel P. Cahill reports a relationship with Massachusetts Institute of Technology, Advise Connect Inspire, German Accelerator, Lilly, GlaxoSmithKline, Iconovir, Incephalo, Boston Pharmaceuticals, Servier, Boston Scientific and Pyramid Biosciences, Merck, US NIH and DoD. that includes: consulting or advisory, equity or stocks, and travel reimbursement. If there...

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