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WHAT IS THE MOLECULAR BASIS OF GLIOMA? INSIGHTS INTO BIOMARKERS, METABOLIC REPROGRAMMING, AND EMERGING TREATMENT STRATEGIES

Relevance: The new classification of central nervous system (CNS) tumors by the World Health Organization (WHO) based on the histological and molecular features allowed a new area for research. Molecular classification of brain cancer is based on the isocitrate dehydrogenase (IDH) enzyme, which is crucial in converting isocitrate into alpha-ketoglutarate during the citric acid cycle.

The study aimed to provide an overview of the classification of CNS by WHO and diagnostic methods of brain tumors.

Results: The article describes brain tumor diagnostic methods, including tissue biopsy, magnetic resonance imaging (MRI), and liquid biopsy, and reviews molecular biomarkers comprising alterations of genes associated with gliomas and epigenetic changes that reduce the expression of particular genes. The authors consider how these findings can be used in treatment.

Conclusion: Molecular reprogramming in cells with mutated IDH causes neomorphic mutations, which leads to changes abundance of alpha-ketoglutarate (αKG) and D-2-hydroxyglutarate (D-2-HG), an increase which stimulates the formation of tumors. Targeted therapies can reduce the concentration of this oncometabolite in cells.

Keywords: glioma, glioblastoma, isocitrate dehydrogenase (IDH), D-2-hydroxyglutarate (D-2-HG).

Introduction

Glioma is a type of brain cancer that arises from the glial cells that support the neurons in the brain. It is a devastating disease that is difficult to treat, and the prognosis for patients with glioma is often poor. They are the most common primary brain tumors, accounting for approximately 80% of all malignant brain tumors [1]. Until 2016 subtypes of glial cells, in which neoplasms grow, classified gliomas into astrocytoma, glioblastoma, oligodendroglioma, and ependymoma. There are four grades of glioma and glioblastoma (GBM) is an IV-class glioma with the lowest survival rate of 5% after 5 years after diagnosis [2].

Aim: In the following review, we aimed to provide an overview of molecular classification of brain tumors and propose treatment strategies depending on the mutation type.

Materials and methods: A comprehensive literature search was performed to identify relevant articles on the classification of CNS tumors, biomarkers, changes in metabolic pathways, and possible treatment strategies. The search was carried out in various electronic databases, including PubMed, Scopus and Web of Science. The search was limited to articles published between 2007 and 2023 to ensure that the most recent and relevant research in this area is included. The initial search yielded a total of 75 articles. The received papers were checked based on their titles and abstracts to assess their relevance to the topic of interest. As a result, research papers focusing on the molecular aspects of glioma, biomarkers, metabolic reprogramming, and potential treatment strategies were included. Articles were excluded, if they were not in English, or were not directly related to the specific objectives of this review article. After review, 37 articles were selected, con-

taining various study designs, including in vitro and in vivo experiments, and clinical studies.

Results and discussion:

CNS tumor classification.

CNS tumor classification suggested by WHO in 2007 was based on histological features of tumour cells[3] Rapidly developing molecular techniques demanded new classification, and as a result in 2016, when along with histogenesis, molecular features were taken into account by WHO. For example, while in 2007 classification of diffuse gliomas placed astrocytoma, oligodendroglioma, and oligoastrocytoma into separate groups based on their histology, in 2016 astrocytoma, oligodendroglioma, and oligoastrocytoma with mutant and wild-type IDH gene, p/19q codeletion and not otherwise specified designation (not enough molecular data) was in the same group [3].

In 2021 [4] classification added even more details on its molecular aspects, including changes in DNA sequences like IDH1 and IDH2, TP53 and H3 histone mutations, TERT promotor mutation [5], and EGFR gene amplification. Also, the importance of distinguishing adult and children gliomas led to the formation of the following groups in the last classification: 1) adult-type diffuse gliomas, 2) pediatric-type diffuse low-grade gliomas, 3) pediatric-type diffuse high-grade gliomas, and 4) circumscribed astrocytic gliomas. Apart from changes in the sequence of DNA, epigenetic changes also were taken into account, and methylation tests are suggested to be utilised as a part of a diagnostics procedure along with sequencing, FISH, and assays to assess molecular changes [5].

Appropriate classification and observation of clinical characteristics are required to study any pattern and suggest treatment strategies depending on the brain tumor type. Changes in classification of CNS tumour show that genetic mutations in tumors are becoming key factors in diagnosis, prognosis, and treatment planning.

Diagnostics.

Advances in genetic testing have led to the identification of specific DNA mutations that are associated with glioma, and these mutations can be used for personalized treatments.

Traditionally, the detection of glioma mutations has been based on tissue biopsy samples to observe its histology and DNA mutations. However, it is known as an invasive and sometimes impossible method due to the difficulty to access of deeper layers of the brain. Moreover, repeated biopsies are required to make a reliable diagnosis, and suggest treatment strategies.

As an alternative less invasive strategy imaging techniques such as MRI can be used. Imaging can be used to track responses to therapies reflecting the changes in size [6]. However, it is not specific and can be used only as part of diagnostics to provide information about the presence, size, and histological type of brain tumor [7], for further identification of nature and improved diagnosis, molecular analysis is necessary [8]

Molecular diagnostics.

Liquid biopsies, which involve analyzing DNA in bodily fluids, are emerging as a promising tool for diagnosing and monitoring glioma. Some studies compared strategies of identification mutations in DNA and confirmed a high concordance of results between DNA isolation from circulating tumour DNA in body fluids and standard tissue biopsies [9]. *They could accurately detect glioma-specific mutations* in blood plasma [10], serum [11], cerebrospinal fluid [12–22], and saliva [23] to identify mutations in a patient's DNA at earlier stages than some imaging techniques [24]. Body fluids are directly exposed to tumor tissue in the brain and contain DNA fragments that are shed from the tumor cells in the brain. Extracellular DNA may appear in body liquids as a result of direct splitting off from tumour cells, phagocytic activity, necrosis, and apoptosis. As tumour cells are not stable, they release more circulating DNA compared to healthy patients, which can be a primary indicator of tumour. [25] Sources of nucleic acid in body liquids are cell-free DNA, cell-free RNA, and circulating tumor cell DNA [24], the length of which is shorter than the genome and usually varies between 140 [23] and 21000 base pairs [25]. As the aforementioned diagnostic method, liquid biopsies also have a number of limitations as low concentration of circulating tumour DNA and this method is applicable only for specific types of tumour depending on their location and properties of affected tissues [23].

Identifying biomarkers that can predict the prognosis of patients with glioma is an important area of research. Gene malfunction can be caused by either mutation or gene expression alterations. All grade III and grade IV tumours are treated by surgery and the following chemotherapy, mostly alkylating chemotherapy, which prevents protein synthesis and cell division [26]. Depending on the mutated gene, the response to chemotherapy may vary, this led to molecular classification of tumours. However, it is

important to keep in mind that multiple biomarkers should be used for better management.

Gene alterations

Based on the major genetic alterations including IDH mutation and 1p/19q co-deletion, gliomas can be classified into three subtypes [27]: IDH mutation; mutant IDH, and 1p/19q codeletion; wild-type IDH. IDH gene is important in diagnostics and management strategies because according to WHO IDH is mutated in >80% of clinical cases with grade IV secondary glioblastomas and <10% of primary glioblastomas [28]. Also, mutations in many other genes, associated with gliomas, correlate with IDH mutation. Thus, mutations in ATRX, TP53 gene, and 1p/19q co-deletion are rare in wild-type IDH [27], while mutations in TERT promoter, EGFR, and H3-3A gene are more common in wild-type IDH [2]. However, TERT and EGFR mutations cannot be a biomarker for glioma [29]. Moreover, patients with mutated IDH have less severe symptoms, a better prognosis than wild-type, and a better response to temozolomide. Thus, the overall survival period of glioblastoma patients with IDH1 mutations with a median survival of 3.8 years compared to 1.1 years of patients with wild-type IDH1 [30]. However, these patients often struggle with epilepsy [31]. Patients with both IDH mutation and 1p/19q co-deletion have the best prognosis. 1p/19q co-deletion is rarely found with wild-type IDH and is crucial in the diagnosis of oligodendroglioma [27]. So, this classification helps to predict survival and propose treatment strategies.

The function of telomerase reverse transcriptase (TERT) is telomere lengthening. Normally, telomeres shorten after each DNA replication causing cellular aging. However, mutations in codons C228T and C250T enhance the expression of transcription factors by creating a novel binding site for transcriptional enhancers, causing the length of telomeres to increase and making the cell immortal, which is considered a hallmark of oncogenesis. There is no observed association between TERT promoter mutations and other mutations such as IDH and TP53 [32].

The epidermal growth factor receptor (EGFR) was amplified or mutated in up to 60% of cases in glioblastoma patients. EGFR interacts with transcription factors causing a cascade of reactions that promotes growth [33].

Epigenetics

MGMT (enzyme O6-methylguanine-DNA methyltransferase) promoter methylation is also common in glioblastoma patients and has a low survival rate [2]. The methylation status of the MGMT promoter has gained significant importance as a key factor in determining prognosis and predicting the response to Temozolomide (TMZ). TMZ is an alkylating agent that induces DNA damage by introducing methyl groups to specific positions on guanine and adenine. Individuals with MGMT expression resulting from an unmethylated promoter or other mechanisms are likely to exhibit a limited response to conventional alkylating therapy. [27,34]

Overexpression of another gene, which is called SOX (sex-determining part of Y chromosome) could be used as a biomarker to identify GBM. Additionally, SOX2 may enhance the ability of glioma cells to migrate and invade surrounding tissues. Consequently, SOX2 shows promise as a potential target for therapeutic interventions in GBM patients, but further experiments are required to clearly understand the specific mechanism by which SOX contributes to the development of GBM [35]

Metabolic reprogramming.

Metabolic reprogramming of cells is the main characteristic of tumour. There are three IDH isoforms: IDH1, IDH2, and IDH3 with the same functions. The former is in a cellular cytoplasm while, the two others are inside mitochondria, where the Citric acid cycle takes place. Wild-type isocitrate dehydrogenase 1 is an enzyme that catalyzes the reaction of decarboxylation of isocitrate forming alpha-ketoglutarate (αKG) in the Citric acid cycle during cellular respiration.

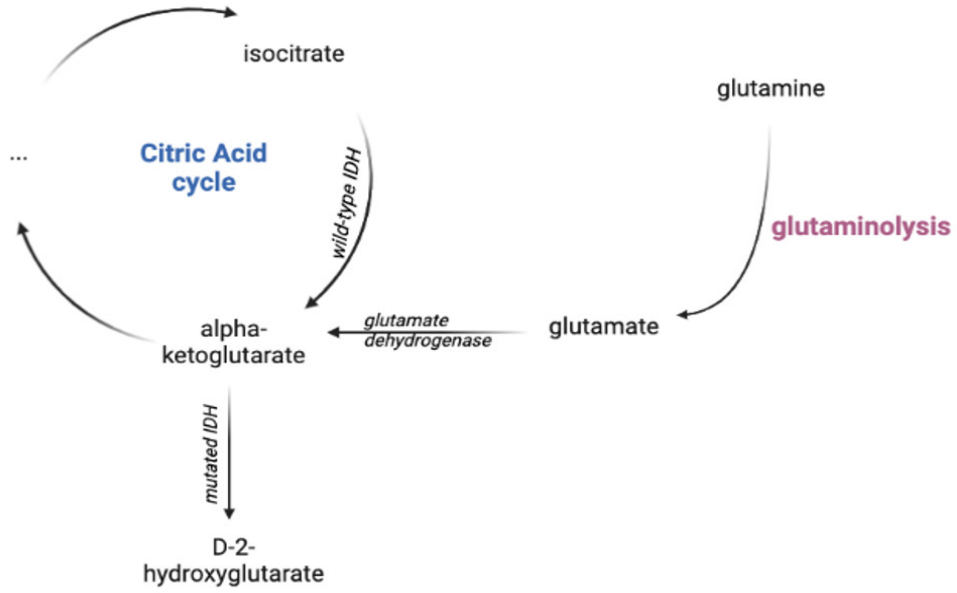
In most glioma cases because of point mutation arginine is substituted with other amino acids, which leads to the decreased affinity of IDH to isocitrate as a result of conformational changes in a structure of a protein. Instead, in individuals with both mutated alleles, the enzyme is inactive. The function of heterozygotes alters, and IDH with one mutated allele converts αKG to D-2-hydroxyglutarate (D-2-HG) using reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a co-factor. It leads to the lack of the αKG and the accumulation of D-2-HG oncometabolite. Accumulation of 2-HG disrupts cellular processes, contributes to DNA hypermethylation, and promotes tumorigenesis. Interestingly, D-2-HG has no known function in mammals during homeostasis, and its concentration normally is low <300 μM, and produced as a result of mistakes in metabolism, hence can be used as a pharmacodynamic marker [28].

These changes cause metabolic reprogramming and alter the source of αKG to the glutamine pathway by glutamate dehydrogenase [36]. That is the reason why mutated IDH has a better response to the inhibition of the glutaminolysis pathway, as a

result inhibiting the conversion of glutamine to glutamate and hence, glutamate into αKG [37] (figure 1). Another reason for slow-growing IDH mutant glioma is an accumulation of D-2-HG that causes hypermethylation of genes that regulate enzymes that participate in glycolysis, the first step of cellular respiration [36].

Thus, as the Citric acid cycle is altered, and glutaminolysis and glycolysis pathways are inhibited, lower energy is produced for cellular functions such as cell division and growth, which is unfavorable for the spread of tumour cells. Understanding the biochemical changes happening in mutated cells helps to implement targeted therapies for tumor treatment.

Figure 1
Simplified reprogrammed pathway with mutated IDH allele (created with Biorender, an online tool for biological figures by authors)



The current treatment options for brain cancers, regardless of their molecular characteristics, remain limited. The standard approach involves surgical removal, when feasible, followed by postoperative radiation and chemotherapy with adjuvant temozolomide. Despite advances in understanding the genetics of brain cancer, still, the median survival of patients with glioblastoma is still low. That is why an appropriate and efficient treatment strategy should be found.

Targeted Therapies

Targeted therapies, which are drugs that specifically target certain molecules or genetic mutations in cancer cells, are also being studied for the treatment of glioma. As IDH mutations cause the accumulation of D-2-HG, therapeutic strategies are targeted to reduce the amount of oncometabolite. IDH inhibitors have emerged as a promising therapeutic approach in the treatment of glioblastoma (GBM). These small molecule inhibitors specifically target the abnormal activity of mutant IDH enzymes, aiming to restore their normal function and reduce the levels of 2-hydroxyglutarate (2-HG). By doing so, they aim to inhibit aberrant cell growth and induce cellular differentiation in GBM cells harboring IDH mutations. Clinical trials investigating IDH inhibitors, including ivosidenib and vorasidenib, have shown encouraging outcomes, including improved overall survival and manageable side effects. Combination Therapies: IDH inhibitors can also be combined with other treatment modalities to enhance their efficacy. Preclinical studies have shown that combining IDH inhibitors with radiation therapy or chemotherapy agents, such as temozolomide, can produce synergistic effects. These combination approaches target multiple pathways simultaneously, potentially overcoming

resistance mechanisms and improving treatment outcomes. [36].

Challenges and Future Directions.

While IDH-targeted therapies hold great promise, several challenges need to be addressed for their successful implementation in GBM treatment:

- Patient Selection: Proper patient selection is crucial, as IDH mutations are not present in all GBM cases. Accurate identification of IDH-mutant GBM through molecular profiling is essential to ensure that patients who can benefit from IDH-targeted therapies receive appropriate treatment.

- Resistance Mechanisms: Resistance to IDH inhibitors can develop over time, limiting their long-term effectiveness. Further research is needed to elucidate the underlying resistance mechanisms and develop strategies to overcome or prevent resistance.

- Combination Strategies: Identifying the optimal combination partners for IDH inhibitors and determining the most effective treatment regimens require extensive preclinical and clinical investigation.

Conclusion

In conclusion, the new classification of CNS tumors based on histological and molecular features has provided a valuable framework for research in the field. The molecular classification, particularly involving the IDH enzyme, has emerged as a crucial factor in understanding brain cancer. Notably, the neomorphic mutations occurring in cells with mutated IDH have been identified as key contributors to tumor formation, leading to alterations in the abundance of alpha-ketoglutarate and D-2-HG. Elevated levels of D-2-HG have been implicated in promoting tumorigenesis. Thus, targeted therapies aimed at reducing the concentration of this oncometabolite in cells hold promise as a potential treatment approach. The integration of molecular insights into the classification and management of CNS tumors has opened up new possibilities for personalized and targeted therapies. Further research and clinical studies are warranted to explore the full potential of these targeted treatments and to develop effective strategies for reducing the impact of IDH mutations in brain cancer patients.

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