

The importance of epigenetic factors in glioma oncogenesis

A importância dos fatores epigenéticos na oncogênese dos gliomas

Giovanna Gonçalves Moreira¹ , Alan Francisco Pereira Araújo¹ , Lara Couto Duarte¹ , Rodrigo Soares de Andrade, PhD² 

¹University Center of Patos de Minas (UNIPAM), Patos de Minas, MG, Brazil, Undergraduate in Medicine;

²University Center of Patos de Minas (UNIPAM), Patos de Minas, MG, Brazil, Professor of the Medicine Course.

ABSTRACT

Introduction: Gliomas are tumors originating in the central nervous system that represent a large proportion of all neoplasms and have a significant mortality rate. Given this, the study of neurogenetic biomarkers is highly relevant as it allows for new approaches, detection methods, and treatments. Not only genetic alterations, but also epigenetics have a significant influence on tumor mechanisms through reactions that alter DNA expression, thus possessing great clinical relevance.

Objective: The objective of this study was to identify the importance of the aforementioned mechanisms in oncogenesis and tumor progression.

Methodology: Thus, the search for studies to compose this work was carried out in the following databases: Google Scholar, BVS, SciELO, Latindex, and PubMed, during the period from april to august 2025.

Discussion: In light of this, it is possible to verify that mutations in the IDH1 and IDH2 genes can lead to the silencing of tumor suppressor genes; furthermore, epigenetic events can lead to the expression of genes that contribute to oncogenesis. Recent studies show that alterations in DNA and RNA methylation, involving EGFR/mTORC2/EZH2 and NSUN5, favor tumor plasticity and immune evasion in gliomas. In addition, non-coding RNAs, such as lncRNAs and snoRNAs, influence the epigenetics of gliomas, influencing chemoresistance, tumor cell maintenance, and adaptation.

Conclusion: In conclusion, epigenetics, along with neurogenetic biomarkers, shows promise as a target for diagnostic and therapeutic innovations, so that more effective and precise approaches can be formulated for the management of this pathology.

Keywords: gliomas, biomarkers, epigenetics, oncogenesis.

RESUMO

Introdução: Gliomas são tumores com origem no sistema nervoso central que representa uma grande proporção de todas as neoplasias e que possuem uma taxa de mortalidade importante. Visto isso, o estudo de biomarcadores neurogenéticos possui grande relevância ao permitir novas abordagens, formas de detecção e tratamentos. Não só as alterações genéticas, como também a epigenética possui grande influência nos mecanismos tumorais por meio de reações que alteram a expressão do DNA, assim possuindo grande relevância clínica.

Objetivo: O objetivo deste estudo foi identificar a importância dos mecanismos supracitados na oncogênese e progressão tumoral.

Metodologia: Dessa maneira, a busca por estudos para compor este trabalho foi realizada nas bases: Google Scholar, BVS, SciELO, Latindex e PubMed, durante o período de abril a agosto de 2025.

Discussão: Diante disto, é possível verificar que mutações nos genes IDH1 e IDH2 podem levar ao silenciamento de genes supressores tumorais, além disto, eventos epigenéticos podem levar a expressão de genes que contribuem para a oncogênese. Estudos recentes mostram que alterações na metilação de DNA e RNA, envolvendo EGFR/mTORC2/EZH2 e NSUN5, favorecendo a plasticidade tumoral e a evasão imune em gliomas. Ademais, RNAs não codificantes, como lncRNAs e snoRNAs, influem sobre a epigenética dos gliomas, influenciando a quimiorresistência, a manutenção de células tumorais e a adaptação destas.

Conclusão: Conclui-se assim, que a epigenética juntamente com os biomarcadores neurogenéticos se mostram como alvo de inovações diagnósticas e terapêuticas promissoras, para que abordagens mais eficazes e precisas possam ser formuladas para o manejo de tal patologia.

Palavras-chave: gliomas, biomarcadores, epigenética, oncogênese.

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Corresponding author:

Giovanna Gonçalves Moreira;

E-mail: giovannagmcp5@gmail.com

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INTRODUCTION

Gliomas are primary tumors of the central nervous system (CNS) originating from glial cells, such as astrocytes and oligodendrocytes. These tumors account for approximately 80% of malignant cases¹. Accordingly, in Brazil, it is estimated that there are approximately eleven thousand cases of primary CNS tumors annually, resulting in more than nine thousand deaths².

The identification of neurogenetic biomarkers has emerged as a promising tool to transform the clinical approach to gliomas, enabling early detection, precise stratification of risk factors, and the development of personalized therapies¹. In 2016, the World Health Organization (WHO) updated its guidelines for the classification of CNS tumors, incorporating molecular markers, an approach that was expanded in the 2021 edition with the inclusion of new biomarkers².

Among the main targets of study are mutations in the isocitrate dehydrogenase 1 and 2 genes (IDH1 and IDH2). These genes play crucial roles in cellular metabolism, catalyzing the conversion of isocitrate to α -ketoglutarate, a process that is significantly altered in tumor cells due to mutations³.

In addition to genetic alterations, epigenetic mechanisms play a fundamental role in the oncogenesis of gliomas. Epigenetics can be understood as the study of modifications in gene expression without alterations in the DNA sequence, which involves three main levels of regulation: DNA methylation, histone modifications, and regulation by non-coding RNAs (ncRNAs)⁴.

The integrated analysis of genetic and epigenetic alterations offers a comprehensive understanding of the biology of gliomas, constituting an essential basis for the identification of innovative therapeutic targets and for the personalization of therapeutic strategies, especially in the face of the high lethality of these neoplasms.

OBJECTIVES

General Objective

To identify the relevance of epigenetic mechanisms in the oncogenesis of gliomas, with emphasis on DNA methylation, histone modifications, and regulation by non-coding RNAs (ncRNAs), exploring their implications in tumor progression and the development of new therapeutic strategies.

Specific Objectives

- To evaluate the potential of epigenetic mechanisms as prognostic biomarkers and therapeutic targets in the context of gliomas;

- To understand the role of mutations in the IDH1 and IDH2 genes in the genesis and progression of gliomas, considering their epigenetic and metabolic impacts;
- To analyze how epigenetic alterations contribute to pro-tumor transcriptional reprogramming in gliomas when associated with mutation in the EGFR gene;
- To characterize the mechanisms by which non-coding RNAs (ncRNAs), including lncRNAs, circRNAs, and snoRNAs, influence gene regulation and tumor cell metabolism, favoring the maintenance and progression of gliomas.

METHODOLOGY

This study consisted of an integrative literature review conducted in six stages: 1) identification of the topic; 2) establishment of criteria for inclusion and exclusion of studies and literature search; 3) definition of the information to be extracted from the selected studies; 4) categorization of studies; 5) evaluation of the studies included in the integrative review and interpretation; and 6) presentation of the review.

The search for articles involving the intended outcome was carried out using the terminologies registered in the Health Sciences Descriptors (DeCs). The descriptors used were: "glioma", "epigenetics", "oncogenesis", "nervous system", "neoplasia". The Boolean operators "AND" and "OR" were used to cross-reference all the aforementioned descriptors.

Subsequently, a bibliographic survey was conducted through electronic searches in the following databases: Google Scholar, BVS, SciELO, Latindex, and PubMed. The search was carried out between April 2025 and August 2025.

As inclusion criteria, it was limited to articles written in any language, published between 2020 and 2025, that addressed the research topic and that were available electronically in their full format. Articles whose title and abstract were not related to the research topic were excluded.

Because this is an integrative literature review, based exclusively on secondary data already published and publicly available, without direct involvement of human beings or collection of individual information, this study is exempt from review by a Research Ethics Committee, according to Resolution No. 510/2016 of the National Health Council.

RESULTS AND DISCUSSION

After the publication review phase, 21 articles were found, which were selected based on the title and abstract of the publications, considering the defined inclusion and exclusion criteria. Subsequently, the publications were read in full, again paying attention to the

inclusion and exclusion criteria, and 9 articles were not used due to the exclusion criteria. Twelve articles were selected for final analysis and construction of the review.

Seeking the best way to present the data, these were entered into a table (Table 1) containing relevant information from all the works used in the production of this study, such as author(s), year of publication, country of origin, type of study, objective and main findings, for later discussion.

Table 1 – Works selected from 2020 to 2025 on the importance of epigenetic factors in the oncogenesis of gliomas.

Author/Year	Country	Type of study	Objective	Main results
Latowska et al., 2020	Poland	Integrative Literature Review	Intensify the search for potential new molecular markers in order to develop new effective treatments for patients.	The expression of certain <i>lncRNAs</i> is associated with chemoresistance and glioma progression.
Sledzinska et al., 2021	Poland	Integrative Literature Review	To analyze and synthesize the most recent research on prognostic and predictive biomarkers in gliomas.	Addition of molecular markers in the classification of gliomas.
Valadares et al., 2021	Brazil	Cross-sectional, retrospective, and descriptive study.	To perform a retrospective analysis of the anatomopathological and immunohistochemical reports of gliomas.	<i>GFAP</i> is an intermediate filament used as a marker in diagnostic neuropathology.
Huang et al., 2023	China	Exploratory Literature Review	To identify <i>lncRNA</i> risk stratification systems related to RNA methylation for glioma.	<i>snoRNAs</i> are involved in regulating <i>rRNA</i> maturation and maintaining tumor stem cells.
Long et al., 2023	China	Integrative Literature Review	To discuss possible research directions for the study of RNA modification and its potential role in the origin, diagnosis, and treatment of gliomas.	Epitranscriptomic modifications, which regulate RNA transcription and translation, are associated with the development of several types of cancer.
Maeda, 2023	Brazil	Integrative Literature Review	To describe representative examples of <i>lncRNAs</i> associated with cancer.	<i>CpG</i> regions susceptible to methylation, leading to silencing;
Wang et al., 2023	China	Exploratory Literature Review	To identify altered methylation states of <i>UMRs</i> in single-base resolution.	Mutations at critical points in <i>IDH1/2</i> are well known to trigger oncogenic mutations in gliomas.
Baroni et al., 2024	Brazil	Integrative Literature Review	Integrating biomarkers with epidemiological risk factors will support the personalization of therapeutic strategies.	Mutations in the <i>IDH1</i> gene and <i>MGMT</i> promoter methylation were key determinants for the prognosis and treatment of glioma.
Chen et al., 2024	China	Integrative Literature Review	To analyze how the integration of epigenetic clock data is promising in the treatment of glioma.	Epigenetic clocks are relevant to aging and tumor development.
Harachi et al., 2024	Japan	Exploratory Literature Review	To determine whether <i>mTORC2</i> plays a role in regulating the DNA hypomethylation phenotype.	<i>mTORC2</i> is a novel regulator of DNA hypomethylation in cancer.
Wu et al., 2024	China	Exploratory Literature Review	To analyze how the modification of 5-methylcytosine RNA acts in tumor pathogenesis.	The enzyme <i>NSUN5</i> has been associated with modulating stress responses and immune system evasion in gliomas.
Zhang et al., 2025	China	Exploratory Literature Review	To understand the mechanisms involved in RNA methylation in gliomas and highlight their translational implications.	Long non-coding RNAs have been identified as molecular guides for epigenetic complexes such as <i>PRC2</i> , promoting <i>H3K27</i> methylation at specific locations and silencing tumor suppressor genes.

Source: Author's own work, 2025

The central nervous system (CNS) plays a fundamental role in coordinating bodily functions, and tumors affecting this region, defined as gliomas because they originate in glial cells, encompass as a variety of intracranial and spinal cord neoplasms³. Understanding the elements that contribute to the development of these pathologies is essential not only for early identification and appropriate management, but also for the development of effective preventive strategies.

Table 1 presents the characteristics of the four studies included in this review, totaling 202 children with cerebral palsy of different types (bilateral spastic, spastic, ataxic, and mixed forms), aged 4 to 14 years. The mean or range of participants' ages is presented in Table 1, according to each study. The interventions investigated VR training using platforms such as Nintendo Wii or Xbox Kinect, with sessions of 30 to 60 minutes, delivered two to five times per week, and a total duration ranging from two weeks to three months. Comparator groups included conventional physiotherapy, transcranial direct current stimulation, and specific balance training. Outcomes assessed covered domains such as balance, gross motor function, gait parameters, center-of-mass displacement, and upper limb skills. The studies are organized chronologically from oldest to most recent.

Mutations in the *IDH1* and *IDH2* genes, common in low-grade gliomas, lead to the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG). This metabolite inhibits α -KG-dependent enzymes such as TET and JHDMs, promoting hypermethylation in CpG islands, characteristic of the glioma CpG island methylator phenotype (G-CIMP)⁵. This alteration silences tumor suppressor genes and repair mechanisms, such as *MGMT* and *ERCC1*, contributing to tumor proliferation⁵. Consistently studies have observed, it was observed that in gliomas with mutated *IDH* there is "partial erosion in poorly methylated regions and chromatin reprogramming that activates oncogenes", indicating that methylation alterations in regulatory regions promote the expression of genes that favor oncogenesis⁶.

Epigenetics, understood as the set of modifications that regulate gene expression without altering the DNA sequence, has proven to be one of the main axes of cellular transformation in the context of glioma oncogenesis⁶. This field encompasses three central mechanisms: DNA methylation, histone modifications, and regulation by non-coding RNAs (ncRNAs)^{4,6}. The author further emphasizes that DNA methylation, for example, has been extensively studied in gliomas, especially through the action of DNA methyltransferases (DNMTs) and TET dioxygenases. Recent studies have shown that mutations in *IDH* lead to the production of 2-HG, which inhibits TETs and induces a pattern of gene hypermethylation known as G-CIMP. This phenomenon alters the expression of genes involved in cell differentiation, DNA repair, and immune response, directly contributing to tumor progression⁶.

Complementing these findings, a study demonstrated that in glioblastomas with a mutation in the *EGFR* gene, there is a reduction in *DNMT3A* expression mediated by *mTORC2*, with the participation of the *EZH2* enzyme. This epigenetic interference generates global genomic hypomethylation and pro-tumor transcriptional reprogramming⁷. Complementarily, researchers have been exploring post-transcriptional RNA methylation, such as that catalyzed by *NSUN5*. This enzyme has been associated with the modulation of stress responses and immune system

evasion in gliomas, revealing the importance of the interface between RNA methylation and tumor cell plasticity⁸.

In addition to DNA methylation, another central component of epigenetics in glioma tumorigenesis is histone modification. These modifications occur through acetylation, methylation, phosphorylation, and ubiquitination of specific histone residues, altering chromatin compaction and, consequently, access to genes that regulate the cell cycle and apoptosis. In gliomas, enzymes such as histone deacetylase 6 (HDAC6) have proven crucial^{4,6,8}. One study identified that HDAC6 overexpression modulates lncRNA-miRNA-mRNA interaction networks that favor cell proliferation, reinforcing the functional relevance of these modifications⁹. Furthermore, long non-coding RNAs (lncRNAs), such as SNHG6, have been identified as molecular guides of epigenetic complexes such as PRC2, promoting H3K27 methylation at specific loci and silencing tumor suppressor genes¹⁰.

Epigenetic regulation is also strongly influenced by non-coding RNAs. These RNAs, such as miRNAs, lncRNAs, snoRNAs, and circRNAs, not only regulate mRNA translation but also directly modulate the epigenetic machinery¹⁰.

Recent studies highlight, for example, the construction of prognostic signatures based on lncRNAs associated with epitranscriptional marks, such as m6A, m5C, and m1A methylation. One study showed that the expression of certain lncRNAs, such as RP11-9819.4 and RP11-752G15.8, is associated with chemoresistance and glioma progression, making them potential targets for combination therapies with temozolomide¹¹. In turn, snoRNAs, such as SNORD47, have also been implicated in the regulation of rRNA maturation and the maintenance of tumor stem cells, acting as mediators of metabolic and translational adaptation under tumor stress conditions¹².

Thus, when considering the complex network of epigenetic interactions that includes DNA methylation, histone alterations, and the regulatory activity of ncRNAs, it becomes evident that glioma oncogenesis depends not only on classic genomic mutations but also on heritable and reversible mechanisms that shape the functional profile of tumor cells. A deeper understanding of these pathways has direct implications for prognosis and, above all, for the identification of more precise therapeutic targets, which reinforces the need for greater investment in epigenetic research applied to gliomas.

CONCLUSION

Mutations in the IDH1 and IDH2 genes play a central role in tumor genesis by compromising DNA repair, inducing promoter hypermethylation, and silencing tumor suppressor genes, in addition to affecting cell differentiation processes. Simultaneously, epigenetic methylation intensifies tumor potential by favoring immune system

evasion, while non-coding RNAs, specifically lncRNAs and miRNAs, collaborate with these mutations by silencing suppressors, promoting chemotherapy resistance, and stimulating tumor progression. This confluence of molecular mechanisms highlights not only the complexity of oncogenesis associated with IDH genes but also reveals new potential targets for diagnosis and therapy.

A deeper understanding of these processes at the molecular level is therefore fundamental to scientific advancement in this area. The use of biomarkers and molecular markers, based on the identified mechanisms, promises to improve detection, prognosis, and clinical intervention strategies, paving the way for more precise and effective approaches in the management of this highly prevalent pathology.

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