Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

An epigenetic insight into the gliomas

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ARTICLE INFO

Keywords:
Glioma
Epigenetics
Acetylation
Methylation
Histone modifications

Received: Jul 11, 2023
Accepted: Jul 19, 2023
Available Online: 25.07.2023

DOI:
10.5455/annalsmedres.2023.07.154

Abstract

Glioma is one of the most aggressive tumors that develop in the glial cells of the brain. It has subtypes such as astrocytomas, oligodendrogliomas and ependymomas. Gliomas comprise about 30% of all brain tumors and are mostly malignant. Gliomas are classified into four grades and the severity of the disease increases with the grade. Like many cancer types, development of gliomas is under the control of genetic, epigenetic and environmental factors. Epigenetics is the area that examines the expression changes in genes that do not change the structure of DNA, but cause behavioral changes in uncontrolled proliferation, growth, migration, death and many other processes in the cell by affecting the gene. Methylation, acetylation, micro RNAs (miRNAs), histone modifications are among the well-known epigenetic factors. This review aims to describe the most common and well-identified epigenetic changes that can result in glioma formation.

Introduction

Glioma is the most frequent and one of the deadliest types of malignant primary brain tumors, accounting for roughly 30% of all brain tumors [1]. Some glioma symptoms may progress gradually, while others may appear suddenly. The precise mechanism of glioma genesis is yet unknown.

The World Health Organization (WHO) classified gliomas, glioneuronal and neuronal tumors into four grades and six families in the Classification of Central Nervous System Tumors [2]. Low-grade gliomas are grades I and II, while high-grades are III and IV, and the malignancy rate increases as the grade increases. Glioma types are classified as low-grade glioma (WHO II: oligodendroglioma, oligodendrocyte astrocytoma and diffuse astrocytoma), anaplastic glioma (WHO III), glioblastoma multiforme (GBM, WHO IV), brain gliomatosis (astrocytoma-based, WHO II-IV), and ependymomas (WHO II, III). However, new classification system also includes many subtypes in a more detailed fashion. These six families now include pediatric low grade gliomas and glioneuronal tumors, astrocytoma, *MYB or MYBL1*-altered, polymorphous low grade neuroepithelial tumor of the young (PLNTY), diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC), diffuse low-grade glioma-MAPK altered, multinodular and vacuolating neuronal tumor (MVNT) and myxoid glioneuronal tumor (MGT) [2].

Unfortunately, there is no cure for the majority of high-grade gliomas. In tumors with high-grade, surgery, chemo and radiotherapuetic treatment options are always on the table, either alone or in combination. These tumors are frequently treated with temozolomide (TMZ), a drug that can easily pass the blood-brain barrier (BBB). Having said that, treatment of glioma can result in a variety of side-effects, including hematological toxicity, and that glioblastoma is highly resistant to radiotherapy (RT) and chemotherapy (CT) [3]. The drug resistance is mainly associated with O6-methylguanine-DNA methyltransferase (MGMT) [4]. In preclinical and clinical trials, targeted therapies include immuno-, molecular, gene, and stem cell therapies. In some cases, such as non-small cell lung cancer [5], malignant melanoma [6], and chronic myeloid leukemia [7], targeted molecular therapy has obtained great success, which has been esteemed critical for glioma therapy.

With developments in molecular diagnostic pathology of malignant glioma, epigenetic abnormalities/changes such as microRNA (miRNA) expression, DNA methylation,

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chromatin remodeling, and histone alterations have been linked to glioma formation [8]. Recent literature has shown that a variety of genes and enzymes responsible for regulating the epigenetic alterations have emerged as new targets for many malignanicies, including glioma.

Abnormal DNA methylation profile of glioma

In glioblastoma, abnormally methylated DNA can be employed as a predictive and diagnostic biomarker. Numerous investigations have revealed that the glioma cells exhibit different DNA methylation patterns than normal cells. One of the most prominent features of glial tumor cells is the co-existence of hypermethylation in CpG island and hypomethylation. As a result, the methylation profile of selected genes in glioma can be used as an excellent indicator for clinical diagnosis [9].

The most well-known epigenetic alteration in tumor tissue is hypermethylated promoter of the gene. Normally, the promoter's methylation status controls how genes are expressed. While DNA repair and tumor suppressor genes (TSGs) are usually hypermethylated in tumor tissues, the majority of CpG islands are typically hypomethylated. [10].

This aberrant methylation can cause gene transcription to be suppressed and biological functions to be lost. DNA-5-hydroxymethylcytosine (5hmC), an epigenetic marker produced by 5mC oxidation, has been linked to the development of glioma. According to recent research, tumor grade and DNA 5hmC are inversely associated [11]. The CpG island methylator phenotype (G-CIMP) is also utilized to predict the prognosis of juvenile and adult gliomas [12]. Many glioma genes have been found to be abnormally methylated. Among these genes are *MGMT*, *PTEN*, *CDKN2A*, and *EGFR* [13].

Abnormal DNA methylation is a key determinant of inactivated TSGs. Several TSGs, including *p16INK4a*, *p14ARF*, *MLH1*, and *NDRG2*, have also been discovered in glioma. To govern cell cycle progression, the retinoblastoma tumor suppressor protein (pRb) is maintained in its dephosphorylated activation state by the *p16INK4a* protein. In more than 50% of the patients with glioblastoma multiforme (GBM), *p16INK4a* gene was deleted, and expression of *p16INK4a* has changed in 80% of glioma cell lines. As a result, restoring *p16INK4a* will reduce proliferation of the cells and arrest cell growth [14]. *PTEN* is a frequently methylated tumor suppressor gene in glioma, which results in PI3K/Akt signaling pathway activation and enhanced cell proliferation [15]. *CDKN2A* is another TSG that is commonly methylated in gliomas, resulting in dysregulated cell cycle [16]. In glioma, *EGFR* is a frequently overexpressed oncogene that can be triggered by DNA methylation and result in enhanced cell proliferation and survival [17].

MGMT is an essential DNA repair gene that may repair alkyl damage induced by 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU-carmustine) and is commonly methylated in glioma, leading in decreased expression and treatment resistance [18]. Esteller et al.have discovered that *MGMT* promoter was hypermethylated in more than 40% of the patients [19]. Methylation levels are linked to tumor development and prognosis. The transcriptional start site of *MGMT* bind to four fully inserted nucleosome-like structures that govern gene transcription when unmethylated. Methylation of CpG islands causes heterochromatinization, which goes along with nucleosome rearrangement and random localization, masking transcription start sites and blocking transcription factor binding [20]. Additionally, the foremost determinant of TMZ sensitivity in the treatment of gliomas is the degree of *MGMT* promoter (MGMTp) methylation [21], which improves the prognosis of both anaplastic astrocytomas and glioblastomas. While MGMTp methylation is more pronounced in primary, IDH-wild type glioblastomas (30-50% of glioblastomas) and oligodendrogliomas (>90%), it is less frequent in diffuse-grade astrocytomas [22]. CpG methylation of the promoters of *p73* [23], *LATS1* and *LATS2* genes [24] was also linked to glioma formation and development, in addition to the genes described above.

Isocitrate dehydrogenase 1 (IDH1) is a key source of NADPH in a variety of tissues in the body, including the brain. *IDH1/2* mutations, which are glioma biomarkers, exhibit a distinct DNA hypermethylation structure known as Glioma CpG Island methylator Phenotype/G-CIMP, which differs significantly from IDH wild type (IDHwt) [25]. Epigenetic modifiers are α-ketoglutarate-dependent enzymes such as TET2, an enzyme used in DNA demethylation or KDM2A, the lysine-specific histone demethylase. However, these enzymes are also engaged in other physiological functions blocked by 2-hydroxyglutarate (2HG), such as ALKBH family DNA repair enzymes, chemotherapeutic response, or hypoxia sensing/signaling by influencing HIF1 regulatory proteins [25].

Low-grade diffuse astrocytomas and anaplastic astrocytomas, which have mutation rates of 75% and 66%, respectively, as well as mixed promyelocytomas, oligodendrogliomas, and secondary sex polymorphism neuroblastomas, are the cancers most likely to harbor *IDH1/2* methylation regulating protein mutations. The *IDH1* mutation has been linked to the prognosis of G-CIMP and GBM, and it has been found to be favorably correlated with patient survival rates.

In conclusion, aberrant DNA methylation is a common epigenetic alteration in glioma that can leads to dysregulated gene expression and promotion of tumor growth. A comprehensive examination of the molecular mechanism of abnormal DNA methylation is important to develop targeted therapies for this devastating disease. Understanding these molecular mechanisms may help identify new targets in the treatment of abnormal DNA methylation and treat glioma patients with a better prognosis.

MicroRNAs and glioma

miRNAs are crucial in the transcriptional regulation of various tumor genes, in addition to growth and proliferation of cells. Individual miRNA applications and gene editing approaches may facilitate the diagnostic procedures and treatment of glioblastoma. It has been predicted that around 50% of all miRNAs target glioma cancer genes or their functional regions. miRNAs have the ability to influence 3% of all genes related to glioma and 1/3rd of all coding genes. Furthermore, a single miRNA can affect hundreds of GBM mRNAs at the same time, whereas an

mRNA of a gene related to glioma can be controlled by one or more miRNAs.

miRNAs have a variety of crucial functions in glioma progression. They affect carcinogenesis, regulatory pathway control, glioma stem cell formation, and the expression of genes linked to cancer. While knocking off miR-221/222 can control TIMP3 levels and lessen cell invasion, miR-221/222 is positively associated with glioma infiltration and cell invasion. Knocking down miR-221/222 triggered TIMP3 expression and significantly slowed tumor growth in the xenograft model. [26]. Another study found that miR221/222 overexpression lowered p27kipl levels [27]. p27kipl suppresses the G1-S phase cell cycle by interacting to CDK2 and cyclin E complex. Downregulated miR-221/222 can thus upregulate p27kip1 to inhibit tumor development.

miR-21, one of the most commonly found microRNAs in glioma, has become a promising target for targeted therapy as it increases proliferation and invasion of tumor cells [28]. On the flipside, miR-124 is present at a reduced level in glioma cells and can inhibit tumor growth and spread. miR-7 has been shown to inhibit proliferation and invasion of glioma cells, and recovering the expression of miR-7 has inhibited tumor growth. miR-34a is another microRNA with low expression in gliomas. It can inhibit tumor growth and increase sensitivity to chemotherapy [29, 30]. On the other hand, miR-145 can suppress the growth and invasion of glioma cells, and overexpression of miR-145 can trigger cell death [31].

The potential of microRNAs in the treatment of glioma is still under investigation, but there are some serious challenges. For example, delivery of microRNAs to the brain can be difficult due to the BBB, which limits access to many drugs to the brain. In addition, the specificity and off-target effects of microRNA treatments should be carefully evaluated to minimize potential side effects.

Despite these challenges, the potential for microRNAs to regulate gene expression and influence tumor growth is good news for glioma patients.

Chromatin remodeling and glioma

Mutations occurring in remodeling complex often cause chromatin remodeling abnormalities. This causes chromatin remodeling to fail, preventing DNA damage from accessing the DNA and leading to abnormal gene expression. If TSGs or proteins that direct the cell cycle are affected by mutations, cancer may eventually develop [32].

According to Liau et al., chromatin remodeling creates drug resistance in GBM. When kinase inhibitors are used, GBM stem cells (GSC) can be returned to an extended, slow cycling condition [33]. The Notch signaling pathway is involved, and the level of KDM6A/B, a histone demethylase, increases significantly, which increases H3K27Ac levels and removes trimethylation in the cis regulatory region of H3K27. In this cellular transformation, chromatin remodeling is the key, which can be used to provide a new target for successful therapeutics development.

The tumor cells that are resistant to drugs can be eliminated and disease recurrence can be prevented by focusing on epigenetic and developmental pathways. A recent study found evidence that lymphoid-specific helicase (LSH), an overexpressed chromatin remodeling protein, promotes development of glioma. The increased regulation of E2F1 and glycogen synthase kinase-3 (GSK-3), the transcription factors in astrocytomas and GBM, has been linked to glioma progression and correlated with LSH. *LSH* expression and cell proliferation were reduced when E2F1 expression was reduced, whereas *LSH* expression was raised when GSK3 expression was suppressed [34]. In glioma tissue, lipoprotein receptor-associated protein 6 (LRP6), an upstream regulator of the GSK3 signaling cascade, has also been found to be overexpressed. LRP6 knockdown inhibited E2F1 binding to the *LSH* promoter, reducing *LSH* expression and finally leading to cell growth inhibition. Taken together, the molecular relationship between expression of LSH in glioblastoma and activation of the LPR6/GSK3/E2F1 axis shows that LSH may play a novel function in malignant astrocytomas and GBM. We will learn more about the problem and establish LSH as a possible therapeutic target for treating these lethal brain tumors if we can determine the involvement of LSH in the formation of gliomas.

Histone modification irregularities in glioma

Changes in histone modifications can result in transcriptional irregularities in gene expression, resulting in glioma formation and progression. Histone deacetylases (HDACs), key enzymes that trigger deacetylation of histones, and histone methyltransferases (HMTs), other important enzymes that methylates different regions of the histones, are two histone modification proteins that are garnering interest. HDAC1 [35], HDAC2, HDAC3 [36], HDAC5 and HDAC9 [37] were among the HDAC enzymes that revealed significant changes in glioma cells. GBM has been demonstrated to have lower mRNA levels of class II and IV HDACs than low-grade astrocytomas and normal brain tissues [38]. GBM has been demonstrated to have lower mRNA levels of class II and IV HDACs than low-grade astrocytomas and normal brain tissues. HDAC inhibitors (HDACIs) are being studied for their potential utility in cancer treatment. HDACIs are widely used in the treatment of glioma together with RT and CT. HDACIs' anti-tumor mechanism involves stopping the cell cycle, encouraging cell differentiation, activating apoptosis, reducing tumor cell proliferation, and angiogenesis [39].

G9a, EZH2, MLL1 and MLL2, which are histone methyltransferases in glioma cells [40-43], can alter histone lysine methylation levels. These changes are linked to genomic integration and transcriptional regulation [44]. Another prospective gene that gained attention for the diagnosis and therapy of glioma is protein arginine methyltransferase 5 (*PRMT5*), whose expression is related with a bad prognosis in patients with glioma [45].

Limiting the growth of glioma cells and inducing apoptosis can be accomplished by inhibiting the activity of histone methyltransferases, or HDACs. This shows that protein inhibitors could be potential treatments for glioma. Histone methyltransferase G9a, which is responsible for demethylation of H3K9, has been associated with glioma development and progression, and inhibiting it may be useful in the treatment of glioma [46].

The Polycomb group (PcG) protein family is a collection of gene regulatory factors involved in embryonic development [47]. They are classified as PRC1 and PRC2 protein complexes based on their function [48]. PRC2 is a multiprotein complex that is in charge of methylating H3 at lysine 27 (H3K27Me). The PRC2 protein complex is formed by the catalytic component Zeste Gene Enhancer Homolog 2 (EZH2) [48]. Existing research indicates that *EZH2* is overexpressed in a number of tumor tissues, including glioma, and is related with tumor metastasis [49]. Cellular research has shown that suppressing the *EZH2* gene or using *EZH2* inhibitors can reduce proliferation of glioma cells [50]. Therefore, focusing on *EZH2* for glioma treatment may open a new avenue for the clinic.

Conclusion

Glioma is a very complicated type of tumor with many subtypes. Many genetic and epigeetic factors play roles in development of these tumors. Understanding the underlying mechanisms is critical for developing novel therapeutic approaches. The discovery of these molecular markers can be used to establish a glioma diagnosis and pave the path for upcoming investigations into both therapeutics and diagnostics.

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