D J Med Sci 2024;10(1):34-41
doi: 10.5606/fng.btd.2024.144

Review

Glioblastoma multiforme: Subtypes based on IDH, ATRX, H3F3A, MGMT and p53 mutations

Fatime Akgeyik, Alper Demirezen, Oytun Erbaş

Institute of Experimental Medicine, Kocaeli, Türkiye

ABSTRACT

Glioblastoma multiforme (GBM) is the most aggressive form of primary brain cancer, characterized by rapid progression and poor prognosis. Recent advancements in molecular profiling have revealed significant heterogeneity within GBM, prompting the classification of distinct subtypes based on key genetic mutations. A fundamental aspect of GBM categorization that affects prognosis and treatment response is the identification of isocitrate dehydrogenase (IDH)-mutant and IDH-wildtype subgroups. While changes in MGMT and p53 emphasize the significance of deoxyribonucleic acid repair mechanisms and tumor suppressor pathways, mutations in ATRX and H3F3A highlight the relevance of chromatin remodeling and histone modifications in gliomagenesis. This review provides an overview of the molecular landscape of GBM subtypes defined by mutations in IDH, ATRX, H3F3A, MGMT, and p53.

Keywords: Glioblastoma multiforme, modifications, mutations, pathways.

Abnormal division and proliferation of cells in the brain organ, which is located in the skull and has very important functions in the functioning and organization of the body, cause brain tumors. These tumors are classified as primary tumors and secondary tumors.[1] The tumors in this classification can be benign or malignant tumors. However, these tumors can also be fatal.[2,3] Brain tumors have no age discrimination on people. They occur in children, adults, and elderly people. However, it is necessary to open a separate parenthesis for children, since brain tumor developing in children are detected later than in children who develop other types of cancer. This situation causes other neurological disorders in children.[4,5]

Glioblastoma is a type of brain tumor. Blood-brain tumor poses a challenge for the treatment of brain tumors, for glioblastoma. Various brain tumor and neurological studies have encouraged research into the use of advanced technologies such as deep learning, convolutional neural networks, and extreme learning machines for brain tumor classification, segmentation, and diagnosis. These technologies have shown promising results in accurately classifying and detecting different types of brain tumors such as meningiomas, gliomas, and pituitary tumors.[6-8]

Glioblastoma multiforme (GBM) is a primary brain tumor composed of aggressive malignant cells that is associated with a poor prognosis.[9] World Health Organization has a classification for central nervous system tumors, and GBM is divided into two subtypes. These are classified as isocitrate dehydrogenase (IDH)-wild type and IDH-mutant type. Glioblastoma multiforme has molecular and cellular heterogeneity rather than histological features.[10] It is also known for its inter-patient and intra-tumor variability, which contributes to the complexity of its management and treatment. The delineation of GBM is critical in clinical treatments, in the context of therapeutic strategy and prognostic stratification. However, the optimal target volume in radiation therapeutic strategy for GBM remains a matter of debate in the medical community.[11]

Received: March 08, 2024
Accepted: March 09, 2024
Published online: May 10, 2024

Correspondence: Fatime Akgeyik.
E-mail: akgeyikfatime25@gmail.com

Cite this article as:
Akgeyik F, Demirezen A, Erbaş O. Glioblastoma multiforme: Subtypes based on IDH, ATRX, H3F3A, MGMT and p53 mutations. D J Med Sci 2024;10(1):34-41. doi: 10.5606/fng.btd.2024.144.

Prevalence of glioblastoma multiforme

The incidence of GBM ranges from 0.59 to 5 per 100,000 people and has been associated with poor survival and prognosis.[12] It is characterized by its highly malignant nature and poor overall survival, making it an important public health problem.[13] The rapid progression and poor prognosis of the tumor underscore the need for effective treatment strategies. Glioblastoma multiforme prevalence is a critical factor in understanding the burden of this disease and guiding public health policies and research efforts aimed at improving patient outcomes.[14]

Clinical significance of glioblastoma multiforme

The aggressive nature of GBM combined with its poor prognosis is of great interest for clinical practice. It is the most common and lethal type of primary malignant brain tumor and the median survival rate varies between 15 and 17 months.[15] Despite extensive research and clinical efforts, the median survival rate at one year is only 35.7% and the median overall survival is 14.6 months, highlighting the challenges in managing this disease.[16] The clinical efficacy of programmed cell death protein 1/programmed cell death ligand 1 checkpoint blockades in GBM has not been found to be significant, underlining the difficulty in finding effective treatment strategies. Furthermore, GBM is associated with short survival and high recurrence rates, posing a significant clinical challenge.[17] Heterogeneities in prognosis, clinicopathological features and immunotherapeutic responses further complicate the clinical management of GBM.[18] Additionally, dysregulation of various molecular factors, such as microRNAs and metabolism-related genes, has been associated with the clinical progression and prognosis of GBM, highlighting the multifaceted nature of this disease. Overall, the clinical relevance of GBM lies in its formidable challenges such as poor prognosis, treatment resistance, and molecular heterogeneity, which continue to increase the urgent need for effective therapeutic interventions and personalized management strategies.[19]

GLIOBLASTOMA MULTIFORME SUBTYPES

IDH mutation and effects

Mutations in IDH are known to be an important factor in cancers such as acute myelogenous leukemia), and gliomas. These mutations result in the production of 2-hydroxyglutarate, which is linked to altered cellular metabolism, epigenetic modifications, and disruption of normal cellular differentiation processes. Furthermore, IDH mutations have been reported to affect the tumor microenvironment, leading to increased sensitivity of tumor cells to chemotherapy and alterations in the immune response.[20]

It has been shown that mutations occurring as a result of genetic alterations of the IDH gene trigger hypoxia-inducible factor 1 alpha signaling by hypoxia, an important oncogenic pathway in malignant gliomas. Isocitrate dehydrogenase gene defects or mutations reduce glutathione levels and have been associated with increased levels of reactive oxygen species and sensitivity to chemotherapy. The cellular metabolism, epigenetic and other biochemical functional effects of IDH defects have been the subject of extensive research, particularly in the context of therapeutic targeting of cancers carrying these defects.[21-23]

ATRX gene and role

The ATRX gene belongs to the SWI/SNF family and has been associated with various biological processes and diseases, including mental retardation, alpha-thalassemia, and cancer.[24] Defects or mutations resulting from inherited changes in the ATRX gene have been associated with syndromal mental retardation and down-regulation of alpha-globin expression. ATRX is required for the development of senescence in response to cytostatic chemotherapy.[25] Gliomas have been found to be strongly associated with IDH1/2 and H3F3A mutation as a result of ATRX mutation. In addition, ATRX mutations result in a truncated protein and reduced protein expression, further elucidating its role in disease pathogenesis.[26]

p53 mutation and cellular functions

The p53 gene, a tumor suppressor gene, is a gene with serious functions in the protection

of cellular homeostasis and tumorigenesis. Some sources also refer to it as the "guardian of the genome". Defects or mutations occurring in the p53 gene have been associated with various cellular diseases and cancer types. p53 gene contains the necessary codes for the synthesis of p53 protein. This protein ensures cell cycle arrest and blockage, deoxyribonucleic acid (DNA) replication errors and repair, apoptosis, and aging of the cell.[27] As a result of the defect in the p53 gene, these tasks cannot be fulfilled or are poorly fulfilled, leading to meaningless proliferation in the cell and contributing to tumor formation.[28]

In line with the scientific studies conducted by research scientists, they found that p53 mutations block cellular apoptosis and promote and accelerate the tumorigenesis reaction.[29] In addition, p53 mutations have been associated with genetic instability.[30]

The effect of p53 mutations on cancer development has been found in various cancer subtypes such as skin cancer, colorectal cancer, lung cancer, liver cancer, esophageal cancer, and oral squamous cell carcinoma.[31-33] Scientific studies on p53 gene mutations have been found to be severely associated with cancer and subtypes of cancer, and have been found to be associated with poor prognosis and cancer survival.[34]

Since positive staining of the p53 protein often indicates the presence of p53 gene mutations, immunohistochemical analysis has been proposed as a technique to detect p53 mutations.[35] It is crucial to remember that not all p53 mutations cause abnormal accumulation of detectable p53 protein, emphasizing the complex nature of p53-related pathways in cancer formation.[36]

H3F3A gene and histone modifications

H3.3 histone variation encoded by the H3F3A gene is required for chromatin dynamics and histone modifications. The control of chromatin structure and gene expression is largely dependent on histone modifications including acetylation, methylation, phosphorylation, and ubiquitination.[37] These changes have the ability to directly affect the structure and function of chromatin and attract effector proteins to chromatin, which can alter patterns of gene expression.[38] Additionally, it has been proposed that different histone modifications with similar functions may interact and enhance the stability of a chromatin state.[39]

The H3F3A gene encodes the H3.3 variation, which is involved in spermatogenesis and chromatin maturation, among other biological activities.[40] Moreover, high-grade juvenile gliomas have been found to harbour mutations in the H3F3A gene, underlining the clinical importance of the gene in malignancy.[41] Polyadenylated mRNAs and introns in the H3F3A and paralogue H3F3B genes distinguish them from the standard H3.1 and H3.2 histone proteins.[42]

Several studies have also been conducted on the landscape of histone modifications and various histone modifications such as histone code, charge neutralization pattern and signaling network have been shown to play unique roles in the expression of genes. Histone proteins play a crucial role in biological activities due to their post-translational modifications that affect chromatin structure, gene transcription, and epigenetic information.[43]

MGMT gene and its effects on DNA repair

The MGMT gene synthesizes O^6-methylguanine-DNA methyltransferase, which is responsible for the removal of alkyl groups at the O^6 position of guanine and functions as an important DNA repair protein.[44] This repair mechanism is extremely important because the function of MGMT is to neutralize the cellular cytotoxicity of alkylating agents, which may lead to resistance to chemotherapy.[45] Findings from scientific studies have shown that MGMT promoter methylation status is associated with clinical outcomes in GBM patients and affects responses to treatments such as temozolomide.[46] Tumor cells with methylated MGMT promoters are more sensitive to the cytotoxic effects of radiation and alkylating agents due to their impaired DNA repair ability.[47]

Regulation of MGMT expression has a critical function in cancer therapy. For example, down-regulation of MGMT expression increases the efficacy of chemotherapy by sensitizing cancer cells to alkylating agents such as temozolomide.[48] The interaction between MGMT and other cellular pathways such as autophagy affects DNA damage

repair processes and chemosensitivity in cancer cells.[49]

Association of ATRX gene with GBM

The highly aggressive form of brain tumor known as GBM has been found to be significantly affected by the ATRX gene. Research has shown a link between many aspects of GBM biology and patient outcomes and ATRX mutations. Studies show that some genetic features typical of proneural GBMs, including PDGFRA amplification, TP53 mutation, and IDH-1 mutation, are linked to reduced ATRX expression.[50]

In line with the findings obtained from scientific studies, it has been shown that there is a strong correlation between ATRX deletion and IDH1-R132H mutation and underlined the importance of ATRX in the molecular categorization of astrocytic malignancies.[51] Increased sensitivity to PDGFR and receptor tyrosine kinase inhibitors in GBM cells has been associated with ATRX deficiency, suggesting possible therapeutic implications for targeting ATRX-deficient GBMs.[52]

Both adult and pediatric GBMs have been found to have ATRX mutations, although different genetic signatures are seen in the former compared to the latter. The importance of ATRX alterations on tumor progression and genomic stability has been highlighted by the demonstration that loss of ATRX increases tumor growth and inhibits DNA repair processes in gliomas.[53]

The effect of p53 mutations on GBM

In the GBM setting, p53 mutations have been extensively investigated and have been associated with important consequences for tumor behavior and patient outcomes. Research has repeatedly shown that individuals with GBM who have p53 mutations have a worse clinical prognosis and higher radioresistance. Research on the therapeutic implications of p53 mutations in GBM is still ongoing, as these mutations may influence how well patients respond to treatment and how quickly the disease progresses.[54]

Studies have shown how controversial the role of p53 mutations is in the biology of astrocytic tumors such as GBM. It has been found that p53 gene mutations are required for the development of GBM and it has been emphasized that the molecular processes linked to p53 alterations in this aggressive brain tumor need to be understood. Rare p53 mutations were found in brain tumors in children, underlining the wide range of p53 modifications in various patient populations.[55]

According to findings from scientific studies, the relationship between changes in p53 gene mutations and changes in p53 protein expression has been examined, which has helped to clarify the complex relationship between p53 modifications in GBM at both the genetic and protein levels. The correlation between p53 mutations and unique molecular patterns in recurrent GBM subtypes underlines the dynamic character of p53 modifications in tumor growth.[56]

Inherited variations in the H3F3A gene and GBM

Somatic mutations in the H3F3A gene have been found to be an important factor in the development of GBM, in pediatric cases. Studies have shown that differences in the H3F3A gene affect the behavior of tumors and the prognosis of patients, as it is associated with multiple genetic and biological subtypes of GBM. Since specific epigenetic modifications and gene expression profiles in pediatric high-grade gliomas have been linked to H3F3A mutations, the K27M mutation, the molecular features of H3F3A mutant cases are unique.[57]

A correlation between H3F3A mutations and other genetic abnormalities such as TP53 mutations has been noted in juvenile GBM, indicating possible interaction between various molecular pathways in tumorigenesis. The discovery of H3F3A mutations in juvenile high-grade gliomas has implications for prognostic and diagnostic indicators in clinical practice, as well as insights into the genetic landscape of these malignancies.[58]

The importance of understanding the effects of H3F3A mutations on tumor biology and treatment responses is highlighted by the unique clinical features and molecular profiles of H3F3A mutant GBMs, which involve differential control of transcription factors and epigenetic

alterations. The fact that both adult and pediatric GBMs have H3F3A mutations highlights the role these mutations play in gliomagenesis and tumor heterogeneity.[59]

MGMT gene and GBM

In GBM, the MGMT gene is essential because it affects tumor behavior, how well treatment works, and how patients fare. Methylation of the MGMT promoter has been found to be a positive prognostic factor and a predictive biomarker for response to radiation therapy, in the absence of adjuvant chemotherapy. When GBM patients get alkylating medications like temozolomide, there is a correlation between this epigenetic modification and a prolonged lifetime.[60]

It has been demonstrated that MGMT downregulation by promoter methylation increases the chemosensitivity of malignant gliomas to temozolomide, a common chemotherapy drug for GBM. The importance of this epigenetic alteration in treatment response is shown by the finding that adult GBM patients treated with temozolomide had a better prognosis when the MGMT promoter was methylated.[61]

Research has also demonstrated that MGMT expression levels have a significant role in predicting the prognosis of GBM patients, with a poor response to alkylating drugs being associated with an unmethylated MGMT promoter status. MGMT has been found to be a negative effector of GBM invasion, indicating that it plays a role in the tumors' aggressive nature. In conclusion, the pathophysiology and response to treatment of GBM are greatly influenced by the MGMT gene and its epigenetic control through promoter methylation. It is essential to comprehend how MGMT changes affect DNA repair activity and chemosensitivity in order to create prognostic markers and individualized treatment plans for individuals suffering from this difficult brain tumor.[62-65]

In conclusion, the division of GBM into subtypes according to genetic alterations has fundamentally changed our knowledge of this aggressive form of brain cancer. By examining important genetic markers like p53, ATRX, H3F3A, MGMT, and IDH, scientists have discovered unique molecular profiles that have important ramifications for prognosis and therapeutic approaches, as well as providing insight into the heterogeneity of GBM. Fundamental biological distinctions have been brought to light by the identification of GBM subtypes that are IDH-mutant and IDH-wildtype. Isocitrate dehydrogenase mutations have been linked to a better prognosis and possible sensitivity to specific therapy. Changes in MGMT and p53 have emphasized the significance of DNA repair mechanisms and tumor suppressor pathways, while mutations in ATRX and H3F3A have shed light on the role of chromatin remodeling and histone modifications in gliomagenesis. The identification of GBM subtypes according to mutations in IDH, ATRX, H3F3A, MGMT, and p53 signifies noteworthy progress in our comprehension of this lethal malignancy. By elucidating the molecular complexities of GBM etiology, these discoveries provide promise for more accurate diagnosis, prognosis, and treatment, advancing the development of individualized therapeutic approaches for individuals facing this tough adversary.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, literature review, writing the article, references and fundings: F.A., A.D.; Design, data collection and/or processing, analysis and/or interpretation: A.D.; Control/supervision, critical review: O.E.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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