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Derleme / Review

DSÖ CNS5 Kriterlerine Göre Tanımlanan IDH-Wild Tip Glioblastomada MikroRNA'ların Biyobelirteç Potansiyeli ve Terapötik Öneminin Tanımlanması

Delineating the Biomarker Potential and Therapeutic Significance of MicroRNAs in IDH-wildtype Glioblastoma as Defined by the WHO CNS5 Criteria

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ÖZ

2021 yılında güncellenen Dünya Sağlık Örgütü (DSÖ) CNS5 sınıflandırması, agresif beyin tümörlerinin bir alt grubu olarak tanımlanan IDH-wild tip glioblastomanın tanı ve tedavi yöntemlerinde önemli bir dönüşüme yol açmıştır. Bu yeni sistem, geleneksel doku analizinin yanı sıra moleküler belirteçleri de içeren daha rafine bir yaklaşım sunarak, benzersiz genetik profillere sahip farklı glioblastoma alt tiplerinin tanımlanmasını kolaylaştırmaktadır. Bu alt tiplere IDH-mutant astrositoma, IDH-mutant ve 1p/19q delesyonu bulunan oligodendroglioma ve IDH-wild tip glioblastoma örnek olarak gösterilebilir. Genetik ve hedefli tedavilerdeki gelişmelere rağmen, bu malign tümörlerin tedavisi için hala arayış devam etmektedir. Bu nedenle daha özellikli tanı ve tedavi yöntemlerine olan ihtiyaç inkâr edilemez. MikroRNA'lar (miRNA'lar) moleküler biyolojinin tıp dünyasına bu bağlamda kazandırdığı moleküller olarak ortaya çıkmaktadır. Bu minik moleküller, gen ekspresyonunun ana düzenleyicileri olarak görev yapmakta ve glioblastoma tanısı, prognoz tahmini ve biyobelirleyici geliştirilmesi için muazzam bir potansiyel barındırmaktadır. Son araştırmalar, miRNA'ların tedavi stratejisi olarak kullanılabileceğini vurgulamakta ve bilimsel ilgiyi bu noktaya çekmektedir. Bu inceleme, DSÖ CNS5 sınıflandırması çerçevesinde IDH-wild tip glioblastoma kapsamında miRNA'ların güncel ilişkilerini incelemektedir. Geniş veri tabanlarından yararlanarak, en son DSÖ sınıflandırmasında tanımlanan genetik anormallikler ile düzensiz miRNA'lar arasındaki karmaşık ilişki bu makale kapsamında araştırılmıştır. Önerilen moleküler biyobelirteçleri ve ilişkili miRNA düzensizliğini analiz ederek, bu agresif kanser tipi için kişiselleştirilmiş, miRNA bazlı tedavilerin geliştirilmesinin önünü açmayı amaçlıyoruz.

Anahtar Kelimeler: Biyobelirteç, Dünya Sağlık Örgütü, Epigenetik, Glioblastoma, MikroRNA

ABSTRACT

The World Health Organization (WHO) CNS5 classification, updated in 2021, has brought about a significant transformation in the diagnosis and treatment of IDH-wildtype glioblastoma, a subgroup of aggressive brain tumors. This new system, which incorporates molecular markers alongside traditional tissue analysis, provides a more refined approach that facilitates the identification of distinct glioblastoma subtypes with unique genetic profiles. Examples of these subtypes include IDH-mutant astrocytoma, IDH-mutant and 1p/19q-deleted oligodendroglioma, and IDH-wildtype glioblastoma. Despite advancements in genetics and targeted therapies, the treatment of these malignant tumors remains an ongoing quest. Therefore, the need for more specific diagnostic and therapeutic approaches is undeniable. MicroRNAs (miRNAs) are emerging as molecules that molecular biology has brought to the medical world in this context. These tiny molecules act as master regulators of gene expression and hold immense potential for glioblastoma diagnosis, prognosis prediction, and biomarker development. Recent research has highlighted the potential of miRNAs as therapeutic strategies, attracting scientific interest to this point. This review examines the current relationships of miRNAs in the context of IDH-wildtype glioblastoma within the framework of the WHO CNS5 classification. Utilizing extensive databases, this article investigates the intricate relationship between genetic abnormalities defined in the latest WHO classification and dysregulated miRNAs. By analyzing proposed molecular biomarkers and associated miRNA dysregulation, we aim to pave the way for the development of personalized miRNA-based therapies for this aggressive cancer type.
Keywords: Biomarker, Epigenetic, Glioblastoma, MicroRNA, World Health Organization

1. Introduction

Glioblastoma, the most aggressive primary brain tumor in adults, remains a formidable challenge despite extensive research efforts (1). The intricate mechanisms underlying this disease contribute to its treatment resistance, highlighting the critical need to define its molecular boundaries and identify disease-specific molecules for accurate diagnosis and effective therapy (1, 2).

Our understanding of glioblastoma has evolved significantly over the past decade. Initially classified based on its aggressive nature ("multiforme" in 2007), the focus shifted to specific molecular markers like isocitrate dehydrogenase (IDH) in 2016. The World Health Organization's (WHO) 2021 classification further refined this definition, classifying glioblastoma as an IDH-wildtype (without the mutation) grade 4 astrocytoma with specific characteristics (2). This ongoing refinement reflects our growing knowledge of the disease and opens avenues for developing targeted approaches.

Despite recent advances, glioblastoma continues to pose a significant challenge (3). The presence of glioblastoma stem cells, which can lie dormant and undetected within the brain, significantly impedes current treatment effectiveness (3). These cells retain the ability to develop into new tumors, posing a major obstacle to eradication. Beyond deciphering the intricate cellular makeup of glioblastoma and the interactions between different cell types, researchers are also pursuing the development of novel blood-based biomarkers (4). These readily accessible molecules, such as autoantibodies (5) or microRNAs (miRNAs/miRs) (6), hold promise for earlier diagnosis, improved prognosis, and potentially a reduction in the need for invasive brain biopsies.

miRNAs, a class of small non-coding RNAs, have emerged as a new frontier in glioblastoma research (7). These molecules act as master regulators, meticulously binding to specific messenger RNA (mRNA) targets. This allows them to fine-tune crucial cellular processes, playing a significant role in how cells function within glioblastoma. Disruptions in miRNA expression are linked to various diseases, including glioblastoma. The discovery that these epigenetic modifications are potentially reversible offers a promising avenue for novel therapies. Researchers are now investigating the potential of miRNA regulators, molecules controlling these modifications, as tools to combat glioblastoma (8).

Researchers are uncovering the potential of miRNAs in understanding glioblastoma. These molecules exhibit altered expression patterns in glioblastoma patients, suggesting their role in disease progression. Scientists are particularly interested in these miRNAs as potential biomarkers. By analyzing miRNA expression patterns, they aim to identify unique "signatures" that can differentiate tumor subtypes, predict treatment response, and even pinpoint potential targets for new therapies (9).

This study takes a unique approach to understanding IDH-wildtype glioblastoma by examining the connection between genetic markers and deregulated miRNA activity. By analyzing this link, we aim to investigate the potential of these deregulated miRNAs as diagnostic tools specific to IDH-wildtype glioblastoma within the framework of the current classification system. This information may be useful for developing effective and targeted clinical approaches.

2. Chronological Overview of Glioblastoma Classification

Diagnosing brain tumors, especially gliomas, has become a much more complex process since the early days in 1926. Back then, clinicians simply looked at the tumor under a microscope, with grade IV being the most aggressive. The first standardized system in 1979 introduced a grading scale, but it wasn't until the 1990s that glioblastomas were classified alongside other astrocytomas. The 2000s witnessed a boom in understanding the role of genes in brain tumors. The WHO incorporated these findings, linking specific gene mutations and chromosome loss to different glioma types (10). The 2007 update refined the grading system, introduced new tumor types, and highlighted the growing importance of analyzing a tumor's genes. A significant shift occurred in 2016 with the "multilayered approach." This emphasized combining traditional microscopic examination with WHO grade and, crucially, the tumor's genetic profile. This approach reshaped glioma classification, making a specific gene mutation (IDH) and chromosome changes (1p/19q) key diagnostic factors (11). However, the rapid pace of scientific discovery necessitated another update. A team of experts formed in 2018 to pave the way for the current system, the 2021 WHO classification system for brain tumors in the fifth edition (WHO CNS5). This latest version reflects the intricate interplay between microscopic examination and genetic analysis, aiming for standardized diagnosis and improved translation of research into patient care (12).

WHO revamped its classification system for brain tumors in the fifth edition (CNS5). This new system goes beyond traditional tissue analysis (histopathology) and incorporates

additional molecular markers. CNS5 divides brain tumors into six distinct families, with adult-type diffuse gliomas being the most common type found in adults. These adult-type gliomas are further categorized using a layered approach to reach a final, integrated diagnosis that includes both the WHO grade and specific tumor type. The 2021 WHO CNS5 classification introduces a key change for glioblastoma diagnosis. IDH-mutant tumors will no longer be classified as glioblastoma within the WHO CNS5 framework (12) (Figure 1).

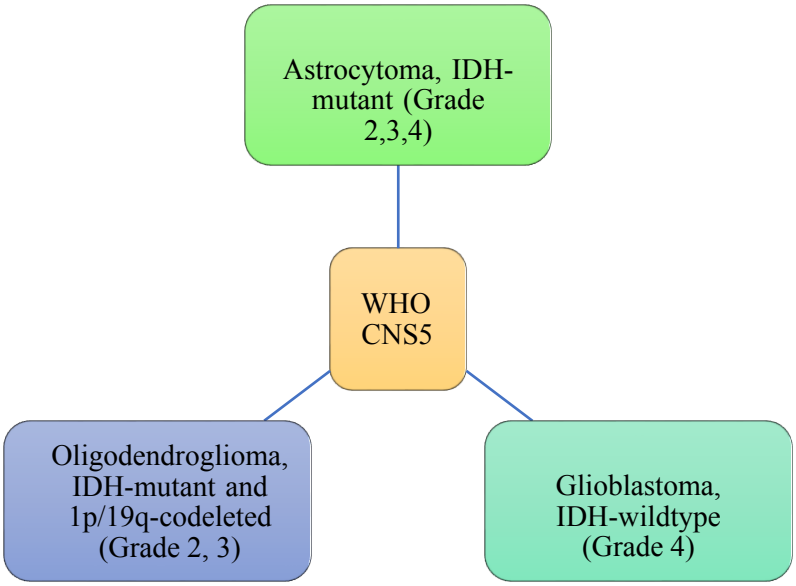


Figure 1. WHO CNS5 simplifies adult glioma grading with molecular markers and Arabic numerals. *CNS: Central nervous system IDH: isocitrate dehydrogenase, WHO: World Health Organization*

3. Current miRNA Candidates and Their Roles in Glioblastoma

The intricate mechanisms governing gene expression are continuously being unraveled, revealing a complexity that extends far beyond the classical DNA-to-mRNA pathway. miRNAs, a class of short, non-coding RNAs, have emerged as powerful regulators that exert their influence following DNA transcription (13, 14). Unlike messenger RNAs (mRNAs) that translate into proteins, miRNAs fine-tune gene expression by silencing or fragmenting specific mRNA molecules, impacting crucial cellular processes such as growth, movement, and death (15).

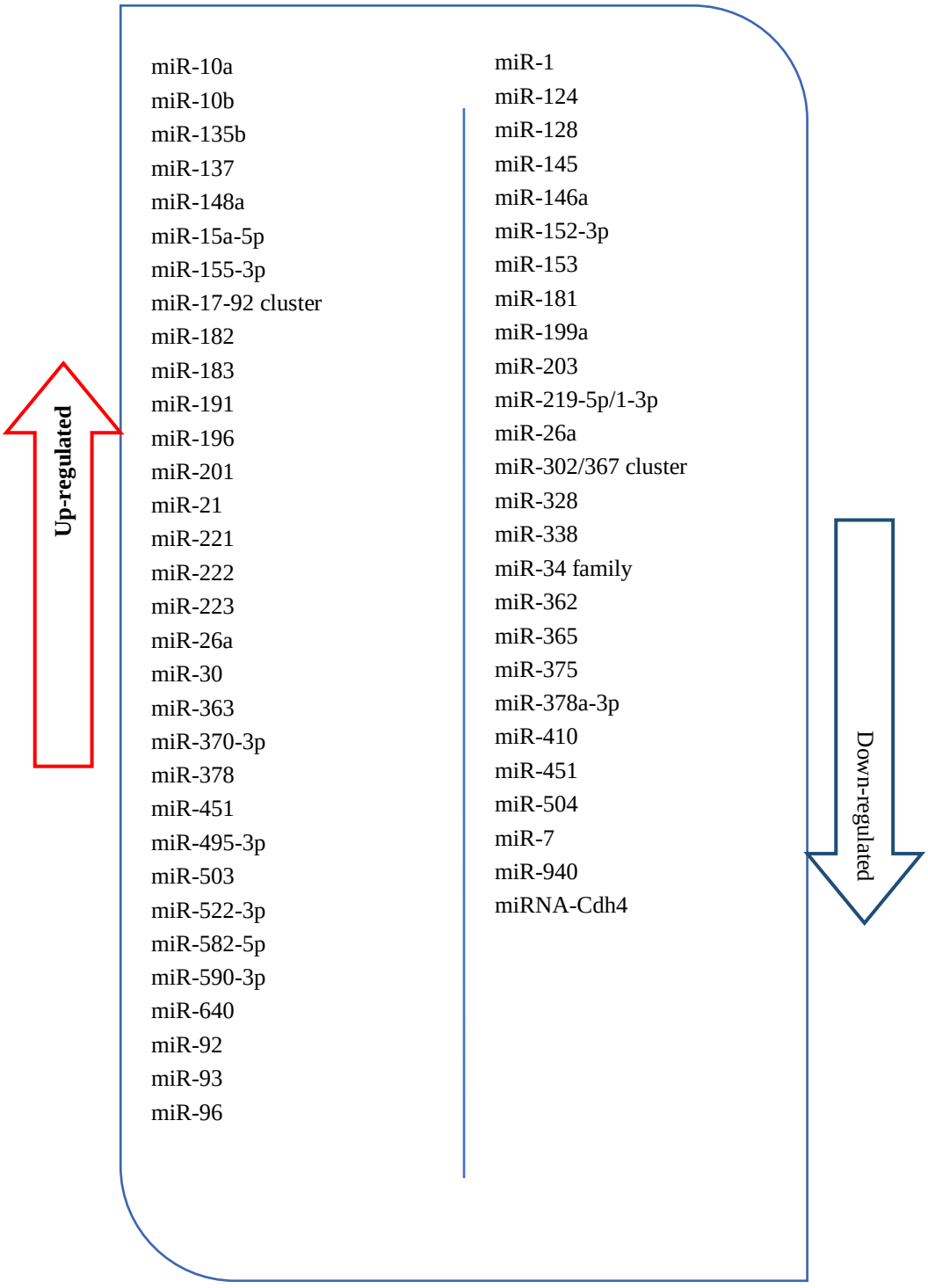
These fascinating molecules undergo a meticulously orchestrated production process. RNA polymerase II initiates the process by transcribing primary miRNA transcripts, which are then subjected to modifications by the microprocessor complex within the nucleus. These pre-miRNAs are subsequently exported from the nucleus by Exportin 5 and further cleaved by the Dicer enzyme in the cytoplasm, giving rise to mature miRNA duplexes (15).

One strand from this duplex is incorporated into the RNA-induced silencing complex, guiding the miRNA to its target mRNA through complementary base pairing (15). This interaction can either halt protein production from the mRNA or lead to its complete degradation, effectively silencing the targeted gene (16). This intricate miRNA network plays a pivotal role in maintaining cellular balance. miRNA dysfunction can significantly impact brain cell processes and contribute to the development of various diseases (17). Notably, these same miRNAs can act as either tumor suppressors or cancer-promoting miRNAs by influencing cell proliferation pathways. Disrupted miRNA expression disrupts cell communication, leading to uncontrolled cell division, a hallmark of cancer (18). Interestingly, cancer cells can utilize tiny packages called extracellular vesicles (EVs) to communicate with each other. These EVs can carry miRNAs that influence the tumor environment and promote cancer growth. Additionally, the stability of miRNAs in bodily fluids, such as blood and urine, makes them promising candidates for non-invasive diagnostics, potentially enabling treatment monitoring and earlier relapse detection (19). Abnormal miRNA expression has emerged as a crucial indicator for glioblastoma progression, development, and survival rates. These miRNAs can either silence tumor suppressor genes, acting like oncogenes, or function as tumor suppressors themselves. This duality makes them attractive targets for potential therapeutic interventions (20). Researchers are actively investigating various miRNAs in glioblastoma (Table 1).

Some miRNAs, such as miR-21, miR-582-5p, miRNA-363 are upregulated and promote cancer growth, while others, like the miR-34 family, are downregulated and act as tumor suppressors (20, 21). This altered miRNA profile disrupts cellular processes and contributes to glioblastoma progression. The therapeutic potential of miRNAs lies in their ability to modulate gene expression with greater flexibility compared to directly targeting DNA. By manipulating miRNA-mRNA interactions, researchers aim to silence specific genes associated with disease progression. This makes miRNAs promising candidates for treatment development in aggressive cancers like glioblastoma (22).

While many studies explore the general role of miRNAs in gliomas, this review takes a different approach. We specifically focus on the new, WHO-recommended genetic markers for glioblastoma and how they relate to miRNA dysregulation. By understanding how these two factors interact, we can potentially use miRNAs for monitoring brain tumors and developing more targeted therapies in the future.

Table 1. Key miRNA candidates known to be oncogenic and tumor suppressors for glioblastoma (6, 21, 23).



4. Glioblastoma, IDH-wildtype Markers and miRNA Relation

A major breakthrough in glioblastoma diagnosis came with the WHO's 2021 CNS5 classification. This update prioritizes advanced molecular analysis over traditional microscopic features like cell death and abnormal blood vessel growth. Specifically, the presence of mutations in the telomerase reverse transcriptase (TERT) promoter gene, amplification of the epidermal growth factor receptor (EGFR) gene, or specific chromosomal abnormalities (+7/-10) can now be used to definitively diagnose glioblastoma (Figure 2). This shift towards molecular markers allows for more accurate tumor grading, even for those appearing less aggressive under a microscope. In essence, these cutting-edge techniques can identify high-grade glioblastomas that might previously have been overlooked (12).

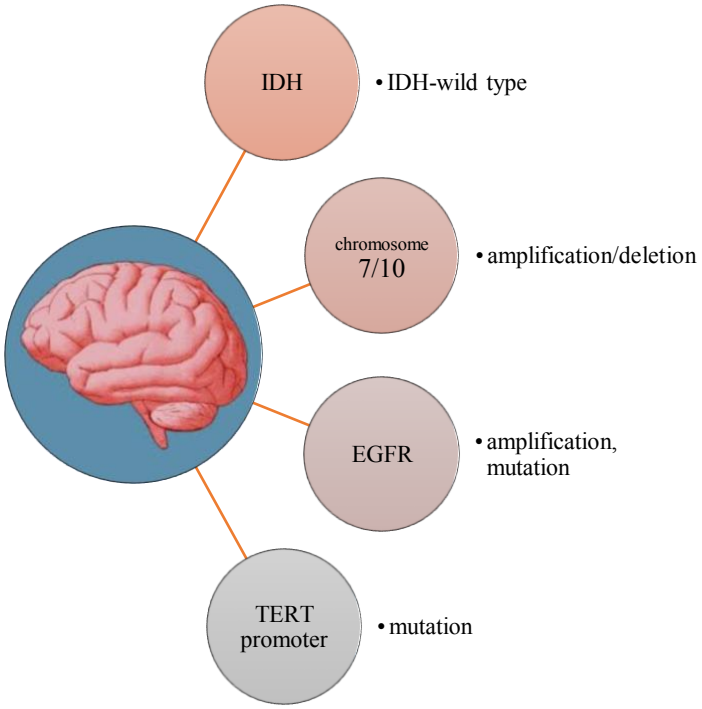


Figure 2. IDH-wildtype glioblastoma and its genetic markers according to the latest classification

TERT promoter mutations are potent drivers of malignant progression in gliomas. These mutations increase the gene expression, enabling uncontrolled cell proliferation and lifespan extension. Their prevalence across various gliomas highlights their significance. Specific mutations are most frequent and predict poor patient outcomes (24-27). In contrast, some miRNAs act as brakes on TERT, the enzyme crucial for cancer cell survival. miR-661 suppresses cell growth, invasion, and telomerase activity. Studies suggest it functions as a tumor suppressor by targeting the gene, a promising therapeutic target. Similarly, miR-21 is a cancer-promoting miRNA that regulates human form of the gene through a member of the STAT protein family.

Targeting this pathway holds promise for future glioblastoma therapies (28, 29). Another study identified six miRNAs, including miR-491-5p, that suppress human TERT activity, suggesting they function as tumor suppressors. miR-491-5p was also downregulated in glioblastoma cells, further supporting this notion (30).

Glioblastoma arises from dysregulation of signaling pathways, particularly those mediated by EGFR. Somatic mutations and amplifications in its genes can constitutively activate these pathways, leading to unchecked cell growth. Specific variants of the gene exacerbate tumor aggressiveness. Deciphering these alterations is crucial for targeted therapies (31, 32). Several miRNAs act as tumor suppressors by targeting EGFR signaling. Studies revealed reduced expression of miR-524 in a specific glioblastoma subtype, linked to both increased its levels and the presence of the gene mutation. This suggests miR-524 acts as a tumor suppressor and a potential therapeutic target (32). miR-7 expression is significantly down-regulated in glioblastoma tissues. It suppresses the receptor and the serine/threonine kinase pathway mediated by Akt, critical for cancer progression. Restoring miR-7 expression in glioblastoma cells reduced their viability and invasiveness, suggesting its potential as a therapeutic approach (33,34). Similarly, miR-200a downregulation contributes to increased signaling protein subunit protein levels, potentially linked to the receptor activity, ultimately enhancing glioma cell proliferation (35). Overall, miRNAs, like those mentioned previously, are potential therapeutic targets because they can disrupt the oncogenic EGFR signaling network in glioblastoma.

The frequent co-occurrence of chromosomal abnormalities suggests a coordinated attack on tumor suppression. These abnormalities disrupt the balance between cell growth and death, promoting uncontrolled proliferation. Because they are associated with poor prognosis, they are potential targets for therapy. Restoring phosphatase and tensin homolog (PTEN) function or inhibiting the PI3K-AKT cascade could be promising avenues for improving patient outcomes (36). Chromosome imbalances in gliomas disrupt miRNA levels. Extra copies of chromosome 7 might increase miRNA levels, while missing parts of chromosome 10 lead to a shortage. This disrupts the regulation of genes involved in cell growth, like the tumor suppressor PTEN. Lower levels of certain miRNAs on chromosome 10 are linked to an overproduction of genes that promote glioma growth. Interestingly, some miRNAs can even suppress the gene.

The loss of it is linked to faster tumor growth and poorer patient outcomes. These findings highlight miRNAs as potential regulators and future therapeutic targets (36, 37). Studies have identified specific miRNAs involved in its regulation. miR-26a is amplified in human glioma samples and suppresses its expression. This suggests a novel mechanism for PTEN regulation in gliomas. Overall, these findings highlight the importance of the PTEN/Akt signaling axis dysregulation in glioma development (38). Another miRNA, miR-182, is located on a chromosome region frequently amplified in glioblastoma cells. Its expression is significantly increased in glioblastoma compared to healthy brain tissue. This suggests a potential role for miR-182 in the disease malignancy (39, 40).

5. miRNAs with Therapeutic Potential Associated with Glioblastoma, IDH-wildtype

Despite limited treatment options, research on glioblastoma is uncovering new avenues. The standard treatment for glioblastoma involves a three-pronged approach: surgery to remove as much of the tumor as possible, followed by radiation therapy and treatment with the drug temozolomide (TMZ) (41). Traditional studies focused on genetic alterations, but recent attention has shifted to the dysregulation of miRNAs. Among these miRNAs, those with therapeutic potential include miRNAs associated with genetic markers indicative of glioblastoma IDH wildtype, classified according to the current system. Ge et al. investigated a potential mechanism for glioblastoma resistance to TMZ therapy linked to low oxygen. They found hypoxia increases miR-26a, regulated by the key regulator of the hypoxic response, which correlates with the drug resistance. miR-26a, with it, protects mitochondria from cell death by interfering with Bax and Bad proteins. This suggests targeting miR-26a might improve the drug therapy by disrupting this protective pathway (42). Wang et al. studied miR-200a, a miRNA, in gliomas. They found lower miR-200a levels in tumors compared to healthy tissue, with even lower levels in higher grade/larger tumors. Notably, patients who responded well to the chemotherapy had higher pre-treatment miR-200a levels. These results suggest miR-200a could be a biomarker for both glioma severity and response to treatment(43). Kouri et al. studied miR-182, a microRNA associated with better patient outcomes, increased effectiveness of the therapy, and less aggressive glioblastoma subtypes. Studies suggest miR-182 has anti-cancer properties, enhancing the drug efficacy, promoting cancer stem cell differentiation, and suppressing tumor growth. To target delivery to brain tumors, they developed ball-shaped genetic material carrying miR-182 sequences (182-SNAs). These 182-SNAs crossed the blood-brain barrier after systemic administration, significantly reducing tumor burden and improving survival in animal models. These findings highlight the potential of miR-182 therapy and this technology for delivering miRNAs to treat malignant brain tumors (44).

In addition to their connections to existing treatment approaches, there are also miRNAs associated with glioblastoma IDH wildtype that hold promise as potential novel therapies. Despite existing gene therapy methods, researchers are exploring alternative approaches for glioblastoma treatment. Bhere et al investigated the use of adeno-associated viral vectors to deliver miR-7. In mice with patient-derived, treatment-resistant glioblastoma stem cells, the vector-miR-7 demonstrated significant tumor reduction. Additionally, it upregulated death receptor involved in apoptosis, a protein crucial for cell death, and triggered a pathway leading to tumor eradication. These findings highlight the potential of the therapy as a unique and advantageous strategy for treating glioblastoma (45). Research on glioblastoma has identified miR-21 as a consistently overexpressed miRNA. This molecule promotes tumor growth and invasion by its activation through various growth factors. Studies suggest a potential mechanism by which miR-21 targets proteins that inhibit a zinc-dependent endopeptidase (MMPs). MMPs degrade the extracellular matrix, facilitating tumor cell movement. Furthermore, miR-21 contributes to resistance to a chemotherapy drug (carmustine) and promotes cell cycle arrest. Conversely, inhibiting miR-21 increases chemosensitivity. These findings, along with the potential synergy of combined miR-21 inhibition and miR-7 induction, highlight the potential of manipulating miRNAs like miR-21 for novel therapeutic approaches in glioblastoma. This approach holds promise for developing more effective treatment strategies (46). Glioma cells exhibit lower levels of miR-346 compared to healthy cells. Our research focused on the impact of increasing miR-346 expression. By artificially boosting miR-346 levels, we observed a halt in glioma cell cycle progression and a suppression of their growth in both lab studies and animal models. These results suggest that miR-346 could be a valuable target for developing novel therapies to combat glioma treatment (47).

6. Conclusion

This research delves into the potential of deregulated miRNAs, linked to the latest 2021 WHO classification of genetic abnormalities in IDH-wildtype glioblastoma. These miRNAs disrupt processes like cell cycle control and cell death, opening doors for their use as biomarkers in monitoring brain tumors. Beyond diagnosis, the study explores the exciting possibility of personalized miRNA therapies. By targeting these specific miRNAs, clinicians might be able to offer more effective treatments with better outcomes for patients. However, further research and clinical trials are essential to translate these promising findings into actual therapies.

Ultimately, this work paves the way for a future of personalized medicine, where glioblastoma treatment can be tailored to each patient's unique genetic makeup.

Conflict of interest

The authors declare that they have no competing interests.

Author Contributions

Idea/Concept: D. Billur, O. Timirci Kahraman **Design and Layout:** D. Billur, O. Timirci Kahraman **Supervision/Consulting:** O. Timirci Kahraman **Resources:** D. Billur, O. Timirci Kahraman **Materials:** D. Billur, O. Timirci Kahraman **Data Collection and/or Processing:** D. Billur, O. Timirci Kahraman **Analysis and/or Interpretation:** D. Billur, O. Timirci Kahraman **Literature Review:** D. Billur, O. Timirci Kahraman **Writing:** D. Billur, O. Timirci Kahraman **Critical Review:** O. Timirci Kahraman

References

1. Yalamarty SSK, Filipczak N, Li X, Subhan MA, Parveen F, AtaideJA, et al. Mechanisms of Resistance and Current Treatment Options for Glioblastoma Multiforme (GBM). Cancers. 2023; 15(7):2116.
2. Torp SH, Solheim O, Skjulsvik AJ. The WHO 2021 Classification of Central Nervous System tumours: a practical update on what neurosurgeons need to know-a minireview. Acta Neurochir (Wien). 2022;164(9):2453-2464.
3. Mattei V, Santilli F, Martellucci S, Delle Monache S, Fabrizi J, Colapietro A, et al. The Importance of Tumor Stem Cells in Glioblastoma Resistance to Therapy. Int J Mol Sci. 2021;22(8):3863.
4. Ali H, Harting R, de Vries R, Ali M, Wurdinger T, Best MG. Blood-Based Biomarkers for Glioma in the Context of Gliomagenesis: A Systematic Review. Front Oncol. 2021;11:665235.
5. Karakaş N, Topcu O, Tüzün E, Kahraman ÖT, Sabancı PA, Aras Y et al. Immunoreactivity against SLC3A2 in high grade gliomas displays positive correlation with glioblastoma patient survival: Potential target for glioma diagnosis and therapy. bioRxiv, 2023-01.
6. Makowska M, Smolarz B, Romanowicz H. microRNAs (miRNAs) in Glioblastoma Multiforme (GBM)-Recent Literature Review. Int J Mol Sci. 2023;24(4):3521.
7. Crespo I, Vital AL, Gonzalez-Tablas M, Patino Mdel C, Otero A, Lopes MC, et al. Molecular and Genomic Alterations in Glioblastoma Multiforme. Am J Pathol. 2015;185(7):1820-33.
8. Hasan H, Afzal M, Castresana JS, Shahi MH. A Comprehensive Review of miRNAs and Their Epigenetic Effects in Glioblastoma. Cells. 2023;12(12):1578.
9. Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, Cretoiu D, et al. miRNAs as Biomarkers in Disease: Latest Findings Regarding Their Role in Diagnosis and Prognosis. Cells. 2020;9(2):276. Published 2020 Jan 23.
10. United States: National Cancer Institute [Internet]. 2024 May 2. Available from: https:// training.seer.cancer.gov/brain/tumors/abstract-code-stage/grading.html
11. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK,, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803-820.
12. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-1251.
13. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75:843–54.
14. Bayraktar E, Bayraktar R, Oztatlici H, Lopez-Berestein G, Amero P, Rodriguez-Aguayo C. Targeting miRNAs and Other Non-Coding RNAs as a Therapeutic Approach: An Update. Non-Coding RNA. 2023; 9(2):27.
15. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front. Endocrinol. 2018;9:402.
16. Wilczynska A, Bushell M. The complexity of miRNA-mediated repression. Cell Death Differ. 2015;22(1):22-33.
17. Petri R, Malmevik J, Fasching L, Åkerblom M, Jakobsson J. miRNAs in brain development. Exp Cell Res. 2014;321(1):84-89.
18. Otmani K, Rouas R, Lewalle P. OncomiRs as noncoding RNAs having functions in cancer: Their role in immune suppression and clinical implications. Front Immunol. 2022;13:913951. 16.
19. Kumar MA, Baba SK, Sadida HQ, Marzooqi SA, Jerobin J, Altemani FH, et al. Extracellular vesicles as tools and targets in therapy for diseases. Signal Transduct Target Ther. 2024;9(1):27.
20. Shea A, Harish V, Afzal Z, Chijioke J, Kedir H, Dusmatova S, et al. MicroRNAs in glioblastoma multiforme pathogenesis and therapeutics. Cancer Med. 2016;5(8):1917-1946.
21. Billur D, Yilmaz SG, Yaltirik CK, Ozdogan S, Ture U, Isbir T. Serum miRNA-582-5p and miRNA-363 as Potential Non-Invasive Biomarkers for Glioblastoma Multiforme. Turk Neurosurg. 2022;32(5):854- 60.

22. Fortunato O, Iorio MV. The Therapeutic Potential of MicroRNAs in Cancer: Illusion or Opportunity?. Pharmaceuticals (Basel). 2020;13(12):438.
23. Ahmed SP, Castresana JS, Shahi MH. Glioblastoma and MiRNAs. Cancers (Basel). 2021;13(7):1581.
24. Yuan X, Dai M, Xu D. TERT promoter mutations and GABP transcription factors in carcinogenesis: More foes than friends. Cancer Lett. 2020;493:1-9.
25. Killela PJ, Pirozzi CJ, Healy P, Reitman ZJ, Lipp E, Rasheed BA, et al. Mutations in IDH1, IDH2, and in the TERT promoter define clinically distinct subgroups of adult malignant gliomas. Oncotarget. 2014;5(6):1515-1525.
26. Arita H, Yamasaki K, Matsushita Y, Nakamura T, Shimokawa A, Takami H, et al. A combination of TERT promoter mutation and MGMT methylation status predicts clinically relevant subgroups of newly diagnosed glioblastomas. Acta Neuropathol Commun. 2016;4(1):79.
27. Gao K, Li G, Qu Y, Wang M, Cui B, Ji M, et al. TERT promoter mutations and long telomere length predict poor survival and radiotherapy resistance in gliomas. Oncotarget. 2016;7(8):8712-8725.
28. Li Z, Liu YH, Diao HY, Ma J, Yao YL. MiR-661 inhibits glioma cell proliferation, migration and invasion by targeting hTERT. Biochem Biophys Res Commun. 2015;468(4):870-876.
29. Wang YY, Sun G, Luo H, Wang XF, Lan FM, Yue X, et al. MiR-21 modulates hTERT through a STAT3-dependent manner on glioblastoma cell growth. CNS Neurosci Ther. 2012;18(9):722-728.
30. Hrdličková R, Nehyba J, Bargmann W, Bose HR Jr. Multiple tumor suppressor microRNAs regulate telomerase and TCF7, an important transcriptional regulator of the Wnt pathway. PLoS One. 2014;9(2):e86990.
31. Hatanpaa KJ, Burma S, Zhao D, Habib AA. Epidermal growth factor receptor in glioma: signal transduction, neuropathology, imaging, and radioresistance. Neoplasia. 2010;12(9):675-684.
32. Zhao K, Wang Q, Wang Y, Huang K, Yang C, Li Y, et al. EGFR/c-myc axis regulates TGFβ/Hippo/Notch pathway via epigenetic silencing miR-524 in gliomas. Cancer Lett. 2017;406:12-21.
33. Kefas B, Godlewski J, Comeau L, Li Y, Abounader R, Hawkinson M, et al. microRNA-7 inhibits the epidermal growth factor receptor and the Akt pathway and is down-regulated in glioblastoma. Cancer Res. 2008;68(10):3566-3572.
34. Liu Z, Jiang Z, Huang J, Huang S, Li Y, Yu S, et al. miR-7 inhibits glioblastoma growth by simultaneously interfering with the PI3K/ATK and Raf/MEK/ERK pathways. Int J Oncol. 2014;44(5):1571-1580.
35. Liu YY, Chen MB, Cheng L, Zhang ZQ, Yu ZQ, Jiang Q, et al. microRNA-200a downregulation in human glioma leads to Gαi1 over-expression, Akt activation, and cell proliferation. Oncogene. 2018;37(21):2890-2902.
36. Nikolova E, Laleva L, Milev M, Spiriev T, Stoyanov S, Ferdinandov D, et al. miRNAs and related genetic biomarkers according to the WHO glioma classification: From diagnosis to future therapeutic targets. Noncoding RNA Res. 2023;9(1):141-152.
37. Wolter M, Werner T, Malzkorn B, Reifenberger G. Role of microRNAs Located on Chromosome Arm 10q in Malignant Gliomas. Brain Pathol. 2016;26(3):344-358.
38. Huse JT, Brennan C, Hambardzumyan D, Wee B, Pena J, Rouhanifard SH, et al. The PTEN-regulating microRNA miR-26a is amplified in high-grade glioma and facilitates gliomagenesis in vivo. Genes Dev. 2009;23(11):1327-1337.
39. Jiang L, Mao P, Song L, Wu J, Huang J, Lin C, et al. miR-182 as a prognostic marker for glioma progression and patient survival. Am J Pathol. 2010;177(1):29-38.
40. Schneider B, William D, Lamp N, Zimpfer A, Henker C, Classen CF, et al. The miR-183/96/182 cluster is upregulated in glioblastoma carrying EGFR amplification. Mol Cell Biochem. 2022;477(9):2297-2307.
41. Angom RS, Nakka NMR, Bhattacharya S. Advances in Glioblastoma Therapy: An Update on Current Approaches. Brain Sci. 2023;13(11):1536.
42. Ge X, Pan MH, Wang L, Li W, Jiang C, He J, et al.. Hypoxia-mediated mitochondria apoptosis inhibition induces temozolomide treatment resistance through miR-26a/Bad/Bax axis. Cell Death Dis. 2018;9(11):1128.
43. Wang C, Kang L, Wang X, Liu Y, Zhao X. Expression of miR-200a and chemotherapeutic treatment efficacy of glioma. Oncol Lett. 2018;15(4):5767-5771.
44. Kouri FM, Ritner C, Stegh AH. miRNA-182 and the regulation of the glioblastoma phenotype - toward miRNA-based precision therapeutics. Cell Cycle. 2015;14(24):3794-800.
45. Bhere D, Tamura K, Wakimoto H, Choi SH, Purow B, Debatisse J, et al. microRNA-7 upregulates death receptor 5 and primes resistant brain tumors to caspase-mediated apoptosis. Neuro Oncol. 2018;20(2):215-224.
46. Mahinfar P, Mansoori B, Rostamzadeh D, Baradaran B, Cho WC, Mansoori B. The Role of microRNAs in Multidrug Resistance of Glioblastoma. Cancers (Basel). 2022;14(13):3217.
47. Li Y, Xu J, Zhang J, Zhang J, Zhang J, Lu X. MicroRNA-346 inhibits the growth of glioma by directly targeting NFIB. Cancer Cell Int. 2019;19:294.