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The Role Of Microrna In The Development And Progression Of Glioblastoma Multiforme

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Abstract
Glioblastoma Multiforme (GBM) Is A Malignant Brain Tumour That Can Be Categorised Into Primary And Secondary Types With Several Subtypes.Recent Advancements In Genomics And Proteomics Have Enabled Researchers To Identify Various Molecular Biomarkers Which Are Typically Collected Via Biopsy Or Bodily Fluid Samples And Quantitatively Analysed Using Polymerase Chain Reaction And Computational Technologies. This Review First Highlights Several Biomarkers Including O6-Methylguanine-DNA Methyltransferase, Epidermal Growth Factor Receptor Viii, Isocitrate Dehydrogenase Mutation, And Others, Which Are Expressed Differently Across Various Types And Subtypes Of GBM. However, There Is A Particular Focus On Micrornas (Mirnas) As Both A Biomarker And Therapeutic Target Due To Their Various Roles In The Cell Cycle. Mirnas Play A Large Role In Cell Growth, And Cell Division. Specific GBM-Related Mirnas With Promising Prognostic Values Are Discussed, Along With Their Roles In Tumorigenesis. Understanding The Mechanisms And Effects Of Biomarkers In GBM Is Crucial For The Development Of Effective Therapies. Thus, This Review Also Discusses The Potential Of Biomarkers As Drug Targets And The Possibility Of Combining Different Biomarkers To Develop Innovative GBM Therapies.

Keywords *:Biomedical And Health Sciences; Immunology; Microrna; Glioblastoma Multiforme; Upregulation; Downregulation*

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I. Introduction

Glioblastoma multiforme (GBM) is a highly malignant primary brain tumour that arises from the supportive cells of the brain, called glial cells. It is an infiltrative tumour that can occur in any part of the brain and is characterised by its rapid growth and resistance to treatment. GBM is the most common and aggressive form of primary brain cancer, accounting for approximately 50% of all primary brain tumours. (Sasmita et Al.)

The symptoms of GBM are often related to the location of the tumour and can include headache, seizures, changes in behaviour or personality, weakness or numbness in the limbs, and difficulty speaking or understanding language.

The aetiology of GBM is not fully understood, but genetic predisposition, radiation exposure, and environmental factors have been implicated as potential risk factors. (Sasmita et Al.)

Treatment of GBM typically involves a combination of surgical resection, radiation therapy, and chemotherapy. However, the prognosis for patients with GBM is poor, with a median survival rate of only 15 months even with aggressive treatment. Due to the highly invasive nature of GBM, complete surgical resection is often not possible, and tumour recurrence is common. (Rezaei et Al.)

As of now, the treatments for GBM include surgical resection, radiation therapy, chemotherapy, targeted therapy, and immunotherapy. Surgical resection aims to remove as much of the tumour as possible, while radiation therapy and chemotherapy target the remaining cancer cells. Targeted therapy is designed to specifically inhibit molecular pathways involved in tumour growth, while immunotherapy harnesses the immune system to recognize and attack cancer cells. Despite the various ongoing treatments, GBM remains a challenging disease with limited treatment options and a poor prognosis. This research aims to explore the use of microRNA as biomarkers for their therapeutic uses associated with GBM. (Grochans et Al.)

In order to create effective treatments, an understanding of the molecular and biological underpinnings of GBM is necessary. Various computational methods have been utilised in numerous studies to observe genetic changes and protein expression patterns in GBM, which have resulted in the creation of a vast database of biomarkers belonging to different categories. The validation of a particular biomarker presents a significant challenge in terms of its effectiveness. Since GBM is an extremely aggressive tumour, accurate tests are crucial for diagnosing patients correctly. The ultimate aim is to develop potential therapies that can reverse the effects of cancerous growth or impede disease progression. (Sasmita et Al.) Some of the biomarkers include:

O6-methylguanine-DNA methyltransferase (MGMT)

The MGMT gene is located on chromosomal position 10q26 and produces proteins that are involved in repairing DNA by removing alkyl groups from guanine at its O6 position. The expression of MGMT is regulated by various transcription factors, such as nuclear factor kappa B and specificity protein 1, which activate the MGMT promoter and increase MGMT expression. Methylation of the MGMT gene has been found to enhance the effectiveness of the chemotherapy drug temozolomide (TMZ) when used in combination with radiation therapy. According to another study, patients with MGMT promoter methylation have better outcomes when receiving TMZ treatment, with a median overall survival of 18.2 months compared to a significantly lower 12.2 months for patients without methylation. (Sasmita et Al.)

Epidermal Growth Factor Receptor (EGFR)

GBM often exhibits EGFR amplification and genetic rearrangement (EGFRvIII) in around 40-50% of cases, especially in the classical subtype and primary GBM. EGFR is a tyrosine kinase receptor encoded by a gene of the same name, which is specific to certain growth factors. The mutation of EGFR, caused by histone modifications on its gene enhancer at chromosome 7p12, results in the formation of EGFRvIII. EGFR mutations and amplifications are classified as prognostic biomarkers since they are prevalent in GBM samples. (Sasmita et Al.)

Platelet-derived Growth Factor Alpha Receptor

Similar to EGFR, PDGFRA is a receptor that responds to specific growth factors and overexpression of this receptor can cause abnormal and uncontrolled cell growth. Gliomas, including GBM, have various types of PDGFRA receptors and ligands, with PDGFRA and PDGFRB being the first ones discovered. Changes in the expression and abundance of PDGFRA are prognostic biomarkers for GBM, particularly for the proneural subtype. (Sasmita et Al.)

Isocitrate Dehydrogenase (IDH)

The IDH enzyme is produced by genes located on chromosome 2 and its main job is to facilitate the oxidative decarboxylation process in the Krebs cycle. However, when mutations occur in the IDH gene, the enzyme's function changes and it becomes responsible for producing 2-hydroxyglutarate (2-HG), a substance that promotes the development of tumours. 2-HG competes with alpha-ketoglutarate in activating enzymes that aid in DNA demethylation, leading to hypermethylation in cancer cells and ultimately causing the formation of tumours. (Sasmita et Al.)

Loss of heterozygosity (LOH) of chromosome 10

LOH is a common occurrence in cancerous tumour cells, where it affects tumour suppressor genes and weakens the body's protection against tumorigenesis. Microsatellites and PCR are used to analyse LOH in GBM patients. (Sasmita et Al.)

Tumour Protein 53

The p53 gene encodes a well-known tumour suppressor protein called p53, which is responsible for various roles in suppressing tumour formation and progression. Mutations in the TP53 gene are more common in secondary GBM (90%) than primary GBM (30%) and may occur early in the development of gliomas and accumulate as the tumour progresses. One proposed mechanism for TP53 mutation in GBM progression is the regulation of the mevalonate (MVA) pathway. The activity of the MVA pathway is higher in R273H cells (mutant TP53) than in U343 cells (wild-type TP53), and TP53 mutation is correlated with the activation of the MVA pathway through the upregulation of enzymes that promote tumorigenesis, including MVA kinase and 3'-hydroxy-3'-methylglutaryl-coenzyme A reductase. (Sasmita et Al.)

Circulating Tumour Cells

GBM, like other types of cancer, produces circulating tumour cells (CTCs) that can potentially cause the disease to spread and metastasize. CTCs in GBM have prognostic value and can be used to monitor patients. These cells are easily obtained from bodily fluids, such as blood samples, and can be analysed through telomerase assays or amplification of EGFR. (Sasmita et Al.)

MicroRNAs

MicroRNAs, or miRNAs, are small RNA transcripts of approximately 22 nucleotides in length, produced by RNA polymerase II and converted to precursor miRNA by the enzyme Drosha. In the cytoplasm, the precursor miRNA is processed by the enzyme Dicer, producing a 22 nucleotide duplex that interacts with an AGO family protein. One strand is retained as the mature miRNA and binds to target mRNA sequences, leading to the cleavage

of these transcripts. Dysregulation of miRNAs has been observed in multiple cancer types and can result from genomic changes in coding genes, abnormal transcription regulation, epigenetic modifications, or abnormalities in the miRNA synthesis machinery. These small transcripts play a role in carcinogenesis by affecting cell proliferation, response to growth suppressors, apoptosis, invasive behaviour, and angiogenesis. The involvement of miRNAs in the pathogenesis of glioblastoma is well documented through various pieces of research. (Sasmita et Al.)

MicroRNAs (miRNAs) play a critical role in the modulation of gene expression within the organism. These small, non-coding RNA transcripts interact with complementary sequences in messenger RNA (mRNA) transcripts, leading to the repression or degradation of the mRNA, which regulates the expression of multiple genes and frequently results in the suppression of protein synthesis. MiRNAs are involved in a multitude of biological pathways such as metabolism, proliferation, apoptosis, etc. (Rezaei et Al.)

Specifically, miRNAs are important in GBM because they play a role in regulating gene expression and cellular processes that are involved in the development and progression of this cancer. Firstly, miRNAs can regulate genes involved in cell growth and division, and play a role in the uncontrolled cell division that is characteristic of cancer cells. Secondly, they can regulate genes involved in apoptosis, which is prevented in GBM which results in the accumulation of abnormal cells and the development of cancer. Thirdly, miRNAs can regulate genes involved in angiogenesis, which is a crucial process for the growth and progression of GBM. Fourthly, they can regulate genes involved in the immune response, and have been shown to play a role in the evasion of the immune system by cancer cells. And lastly, miRNAs can regulate various molecular signalling pathways that are involved in the development and progression of GBM. (Rezaei et Al.)

II. Discussion and Limitations

Upregulated miRNAs

In terms of miRNA seen in GBM, there are multiple types which are dysregulated to aid its progression and development. In GBM, certain miRNAs are upregulated where its expression or activity could increase resulting in a decrease of the protein that gene encodes for. Such miRNAs explored in this paper are miR-21, miR-196a, miR-10b, miR-17-5p, and miR-221/222.

First, one of the most critical overexpressed miRNA in GBM is miR-21. miR-21 is a small non-coding RNA molecule that functions as a negative regulator of gene expression through binding to complementary target mRNAs leading to their degradation or repression of protein synthesis. miR-21 has been implicated in a multitude of cellular processes such as cellular proliferation, differentiation, and apoptosis. In the context of pathological states, miR-21 has been found to be aberrantly expressed, where it has been shown to act as an oncogenic driver, promoting tumorigenesis and progression. Research has shown that silencing a specific microRNA, miR-21, in laboratory studies can trigger the activation of a process called apoptosis and inhibit the growth of tumours. This suggests that over-expression of miR-21 may contribute to the development of GBM by suppressing pro-apoptotic genes. Further studies in living organisms and in the lab have supported the idea that miR-21 plays a role in the oncogenesis of glioblastoma. For example, reducing the amount of miR-21 in xenograft models of GBM has been shown to inhibit tumour growth and alter the expression of genes and pathways related to cancer. Additionally, large-scale studies have revealed that silencing miR-21 can change the expression of 169 different genes, further emphasising its importance in regulating genes related to cancer. (Rezaei et Al.)

Second, miR-196a is a small non-coding RNA molecule that serves as a negative regulator of gene expression by binding to complementary target mRNAs leading to degradation or repression of protein synthesis. miR-196a has been demonstrated to play a role in various biological processes, including embryonic development, cellular differentiation, and neoplasia. In the context of GBM, miR-196a has been implicated in tumorigenesis. In the context of GBM, elevated expression of miR-196a has been documented and is believed to contribute to the pathogenesis and progression of this malignant brain neoplasm. Elevated miR-196a expression has been demonstrated to modulate the expression of genes associated with cellular proliferation, differentiation, and apoptosis, resulting in a pro-oncogenic effect and contributing to the formation and growth of GBM tumours. Additionally, miR-196a has been implicated in facilitating tumour cell invasion and angiogenesis. (Rezaei et Al.)

Third, overexpression of miR-10b has been implicated in the development and progression of GBM, a type of brain cancer. miR-10b has been shown to promote cell proliferation, invasion, and angiogenesis, and to suppress tumour suppressor genes in GBM cells, leading to the aggressive behaviour of these tumours. The precise mechanism by which miR-10b contributes to GBM development and progression is still under investigation, but targeting miR-10b or its downstream targets may have therapeutic potential for treating GBM. The fact that miR-10b is not expressed in the brain yet is markedly increased in some subtypes of glioma is noteworthy information. It was discovered that the expression of miR-10b positively linked with two invasive factors, RhoC and urokinase-type plasminogen activator receptor (uPAR). MiR-10b expression levels were shown to be substantially correlated with multifocal tumours using magnetic resonance imaging (MRI), which suggests that miR-10b contributes to the extremely invasive character of glioma cells. It was discovered that miR-10b directly targets BCL2L11,

TFAP2C, CDKN1A, and CDKN2A, among other cell growth regulators. According to research, blocking miR-10b caused the restoration of the aforementioned genes, which reduced the proliferation of glioma cells by triggering death and cell cycle arrest. (Grochans et Al.)

Fourth, miR-17-5p is a microRNA that acts as a post-transcriptional regulator of gene expression. MiR-17-5p is known to be involved in the regulation of diverse biological processes, including cell proliferation, differentiation, and apoptosis. Furthermore, its dysregulation has been linked to the development and progression of several diseases, including cancer, cardiovascular disease, and neurological disorders. MiR-17-5p has been found to have both oncogenic and tumour suppressor roles depending on the type of cancer and the specific target genes involved. MiR-17-5p's role in glioblastoma is still being actively investigated, and there is no consensus on its specific role. While some studies suggest that it may act as an oncogene by promoting GBM cell proliferation, migration, and invasion, other studies have suggested that it may act as a tumour suppressor by inhibiting these processes. One study found that miR-17-5p was upregulated in GBM cells and that its expression correlated with patient survival, suggesting a potential role as a prognostic biomarker. Other studies have found that miR-17-5p can promote GBM cell proliferation and invasion by targeting key genes involved in these processes, including PTEN and TP53. However, additional studies have found that miR-17-5p may also have tumour-suppressive effects in GBM by inhibiting the expression of oncogenes such as CDK6 and HMGA2. (Rezaei et Al.)

Last, miR-221 and miR-222 are microRNAs that mediate regulation of gene expression through post-transcriptional repression. These microRNAs are frequently referred to collectively due to their high sequence homology, indicative of functional similarity. miR-221/222 have been implicated in multiple physiological processes, including cellular proliferation, differentiation, and apoptosis, and are associated with various pathological conditions, such as neoplasia and cardiovascular disease. Aberrant expression of miR-221/222 has been implicated in the development and progression of cancer, rendering these microRNAs promising therapeutic targets in cancer treatment strategies. By targeting the cell cycle inhibitors (p27 and p57) through its increased expression in glioblastoma, miR-221/222 can promote S-phase entrance, and miR-221/222 knockdown significantly inhibited tumour growth in vivo. In human glioma cells, upregulation of miR-221/222 reduces cell death through targeting PUMA. Additionally, miR-222/221 overexpression in glioblastoma can encourage cell migration and development by suppressing the activity of the protein tyrosine phosphatase (PTP). Additionally, it was discovered that miR-221/222 could control the ability of glioma cells to invade by specifically targeting TIMP3. According to other studies, plasma levels of the miR-221/222 family were discovered to be significantly upregulated in glioma patients, and high plasma levels of the miR-221 and miR-222 family were both correlated with a low survival rate, suggesting the need for a new additional tool to more accurately define glioma. (Grochans et Al.)

Downregulated miRNAs

Certain miRNAs are also downregulated where its expression or activity decreases resulting in an increase of the protein that gene encodes for. Such miRNAs explored in this paper are miR-124, miR-137, miR-34a, miR-338-3p, and miR-124-3p.

In terms of the various miRNA which are down-regulated in GBM, one of the imperative ones is miR-124. miR-124 is a microRNA that modulates gene expression via post-transcriptional repression through binding to cognate mRNAs and promoting their degradation or hindering their translation. miR-124 is one of the most abundant and evolutionarily conserved microRNAs within the central nervous system and is implicated in the regulation of several crucial processes related to neuronal development and function, including neural proliferation, differentiation, migration, and synaptogenesis. Studies have established that miR-124 is significantly down-regulated in GBM in comparison to normal brain tissue, and this down-regulation has been correlated with unfavourable patient outcomes. The exact mechanisms responsible for miR-124 down-regulation in GBM have yet to be fully elucidated, but are suspected to involve genetic and epigenetic alterations, such as promoter methylation and chromosomal aberrations. The down-regulation of miR-124 in GBM has been demonstrated to impact several key cellular processes, including cell cycle progression, apoptosis, and oxidative stress response regulation. (Rong et Al.). Additionally, down-regulation of miR-124 has been linked to the activation of oncogenic signalling pathways, such as PI3K/Akt and MAPK, which are considered to be critical in the development and progression of GBM. Given the crucial role of miR-124 in gene expression regulation and its down-regulation in GBM, it is a promising target for the design of new therapeutic strategies aimed at treating this cancer. The aim of these strategies would be to reestablish normal expression levels of miR-124 to restore normal cellular processes and to disrupt the malignant phenotype of GBM cells. (Rezaei et Al.)

Second, miR-137 is a microRNA which is involved in several crucial biological processes, including the development of the central nervous system, the regulation of synaptic plasticity, and the control of cell proliferation and differentiation. Down-regulation of miR-137 in glioblastoma multiforme (GBM) has been documented and is believed to be associated with genetic and epigenetic changes such as promoter methylation and chromosomal alterations. This down-regulation has been observed to impact cellular processes such as cell

cycle progression, apoptosis, migration, and invasion. Additionally, down-regulation of miR-137 has been linked to the activation of oncogenic signalling pathways including PI3K/Akt and MAPK, which play a crucial role in the development and progression of GBM. Thus, the re-establishment of normal miR-137 expression levels in GBM cells is being explored as a potential therapeutic strategy through the use of miR-137 mimetics or antagomirs. In summary, the down-regulation of miR-137 in GBM is a major concern as it is associated with poor patient outcomes and a more malignant phenotype of GBM cells. Further investigations are needed to comprehend the underlying mechanisms and to devise effective therapeutic approaches targeting this microRNA. (Rong et Al.)

Third, miR-34a is a microRNA which has been demonstrated to exert a significant influence on the control of fundamental cellular behaviours, including cell proliferation, differentiation, and programmed cell death or apoptosis. This microRNA also participates in the modulation of various signalling pathways, crucial for multiple cellular processes, such as cellular ageing, stress response, and DNA repair. Notably, miR-34a has been linked to several pathological conditions, encompassing cancer, cardiovascular disease, and neurodegenerative disorders, signifying its pivotal role in the aetiology of these diseases. Multiple research studies have demonstrated that the expression of miR-34a in cells affected by glioblastoma multiforme (GBM) is frequently diminished, suggesting its potential tumour suppressive characteristics. MiR-34a can exert its anti-tumor properties by targeting a variety of key genes that are involved in the proliferation, survival, and invasion of cells, such as c-Met, Notch-1, Bcl-2, CD44, and Myc. The downregulation of these genes by miR-34a leads to the inhibition of cell growth and invasion and promotes programmed cell death or apoptosis in GBM cells. Furthermore, miR-34a has been linked to the regulation of cancer stem cells (CSCs), a particular subpopulation of cells that are responsible for initiating and relapsing of GBM. MiR-34a can suppress the ability of CSCs to self-renew and induce tumorigenesis while encouraging their differentiation, ultimately resulting in the reduction of the stemness and malignancy of GBM. (Grochans et Al.)

Fourth, miR-338-3p is a microRNA that plays a key regulatory role in multiple biological processes, including neuronal differentiation, neurogenesis, and neural plasticity. It can modulate the expression of various genes that are associated with neuronal signalling, such as GABA receptor subunits, NMDA receptor subunits, and ion channels, thereby indicating its probable involvement in synaptic transmission. Besides its role in the nervous system, miR-338-3p has also been implicated in the control of cancer cell proliferation and invasion. In several studies, miR-338-3p has been shown to downregulate the expression of various oncogenes, including BMI-1 and c-Met, and inhibit the growth and invasion of cancer cells, indicating its potential anti-tumor effects. The function of miR-338-3p in GBM is currently an area of active investigation. While its precise role in this context is still unclear, a growing body of evidence suggests that it may exert tumour suppressor effects. Several studies have shown that miR-338-3p is frequently downregulated in GBM cells, and that decreased levels of miR-338-3p expression are associated with poor patient prognosis. Notably, overexpression of miR-338-3p in GBM cells has been found to significantly reduce cell proliferation, migration, and invasion, and to promote cell death. These observations suggest that miR-338-3p has anti-tumor activity in GBM. (Rezaei et Al.).

Last, MiR-124-3p is a microRNA that is expressed at high levels in neurons and is known to play a significant role in the development and function of the nervous system. Research has demonstrated that miR-124-3p functions as a key regulator of neuronal differentiation and maturation, and is critical for the proper formation and function of neural networks. Moreover, miR-124-3p has also been implicated in the regulation of other biological processes, such as cell proliferation, differentiation, and apoptosis. Furthermore, miR-124-3p has been found to be dysregulated in a variety of diseases, including cancer, cardiovascular disease, and neurological disorders. Studies have indicated that miR-124-3p may have a protective role in some types of cancer by inhibiting tumour cell growth and invasion, and may also play a role in the regulation of cardiovascular function. Studies have demonstrated that miR-124-3p plays a crucial role as a tumour suppressor in glioblastoma multiforme (GBM), a highly malignant and aggressive form of brain cancer. Research has shown that miR-124-3p is frequently downregulated in GBM cells, and its restoration can impede cell proliferation, migration, and invasion while promoting cell death. The antitumor effects of miR-124-3p are mainly mediated by its ability to target several key genes involved in cell proliferation, migration, and invasion, such as CDK6, EZH2, and SNAI2. By repressing the expression of these genes, miR-124-3p impedes the growth and invasion of GBM cells. Moreover, miR-124-3p has been implicated in the regulation of CSCs, which are responsible for tumour initiation and recurrence in GBM. MiR-124-3p attenuates the self-renewal and tumorigenicity of CSCs and promotes their differentiation, thus reducing the stemness and malignancy of GBM. (Rezaei et Al.)

Now, miRNAs are looked at in the field of medicine for therapeutic treatments for GBM. One approach is to inhibit the expression of oncogenic miRNAs, which are often overexpressed in glioblastoma and contribute to tumour growth and therapy resistance. Anti-miRNA oligonucleotides can specifically target these oncogenic miRNAs, reduce tumour growth, and sensitise cancer cells to other therapies. Another approach is to deliver tumour suppressor miRNAs to the cancer cells, which are often downregulated in glioblastoma. This can inhibit tumour growth and sensitise the cancer cells to other therapies. (Rong et Al.)

Furthermore, combining miRNA-based therapies with traditional therapies such as chemotherapy or radiation therapy can enhance their effectiveness. For example, miRNAs can be used to sensitise glioblastoma cells to radiation therapy, resulting in reduced radiation doses and increased efficacy.

Personalised medicine is another potential application of miRNA-based therapies for glioblastoma. The expression levels of specific miRNAs can vary between individual patients, and miRNA-based therapies can be tailored to each patient's unique needs. Overall, miRNA-based therapies hold great promise in the treatment of glioblastoma. However, further research is needed to fully understand their mechanisms of action, optimise their efficacy, and ensure their long-term safety. (Rong et Al.)

III. Conclusion

To conclude, glioblastoma is a highly malignant brain tumour with poor prognosis and its pathogenesis involves complex molecular mechanisms. This research paper answers the therapeutic role of miRNAs in terms of GBM. miRNAs, small non-coding RNA molecules that regulate gene expression, have been shown to play crucial roles in glioblastoma development and progression. Dysregulation of specific miRNAs has been linked to the activation of oncogenic pathways and inhibition of tumour suppressor pathways, contributing to glioblastoma tumorigenesis. Additionally, miRNAs have been implicated in glioblastoma stem cell maintenance and differentiation, indicating their potential as therapeutic targets. Various approaches to miRNA-based therapy are currently under investigation, including miRNA replacement therapy and delivery of miRNA inhibitors via nanoparticles. However, further research is needed to better understand the mechanisms underlying miRNA dysregulation in glioblastoma and to develop effective miRNA-based therapies for this devastating disease.

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