Gene Expression Analysis of Brain Cancer in the Global Population: Focus on EGFR and MAPK1 Overexpression in Glioma

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Abstract
Brain cancer is one of the most aggressive malignancies affecting the central nervous system (CNS), with glioblastoma multiforme (GBM) representing the most malignant and rapidly progressive form of glioma. The present study aimed to analyze the expression patterns of the proto-oncogenes EGFR and MAPK1 in glioma and evaluate their association with tumor progression and prognosis. The study was conducted using an in silico bioinformatics approach based on publicly available genomic datasets obtained from The Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA). Gene expression analysis was performed using the UCSC Xena Browser platform, while Kaplan–Meier survival analysis was used to determine prognostic significance. The results demonstrated significant overexpression of EGFR and MAPK1 in glioma tissues compared with normal brain tissues. Expression levels of both genes progressively increased from low-grade glioma (LGG) to high-grade glioblastoma, indicating a strong association with tumor aggressiveness and malignancy. Approximately 50–60% of GBM cases showed EGFR overexpression, while elevated MAPK1 expression was associated with increased activation of the MAPK/ERK signaling pathway involved in tumor proliferation, invasion, angiogenesis, and survival. Survival analysis further revealed that high expression levels of EGFR and MAPK1 were associated with poor overall survival and unfavorable clinical prognosis in glioma patients. The findings suggest that dysregulation of EGFR and MAPK1 plays a critical role in glioma progression and highlights their potential significance as molecular biomarkers and therapeutic targets in brain cancer research.

Keywords:
Brain Cancer; Glioma; Glioblastoma Multi--forme(GBM);EGFR;MAPK1;Gene Expression

1. Introduction

Brain cancer is one of the most aggressive malignancies affecting the central nervous system (CNS), characterized by uncontrolled proliferation of abnormal cells within the brain tissues (Ostrom et al., 2020). Among brain tumors, gliomas represent the most common and highly malignant type, with glioblastoma multiforme (GBM) showing poor prognosis and rapid progression (Louis et al., 2021). The development of glioma is strongly associated with genetic and molecular alterations that disrupt normal cellular regulation, including abnormalities in proto-oncogenes, tumor suppressor genes, and signaling pathways (Hanahan & Weinberg, 2011).

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One of the major proto-oncogenes involved in glioma is EGFR (Epidermal Growth Factor Receptor), which regulates cell proliferation, survival, and differentiation. Amplification and mutation of EGFR are frequently observed in glioblastoma and contribute to continuous activation of oncogenic pathways such as PI3K/AKT and MAPK/ERK signaling (Brennan et al., 2013; Furnari et al., 2007). Another important gene, MAPK1 (ERK2), functions in the MAPK/ERK pathway and plays a critical role in cell cycle progression and tumor growth (Dhillon et al., 2007).

Recent advances in cancer genomics and bioinformatics have enabled large-scale analysis of gene expression profiles using publicly available databases such as TCGA and CGGA (Cancer Genome Atlas Research Network, 2008; Zhao et al., 2021). Studies have reported that overexpression of EGFR and MAPK1 is strongly associated with glioma progression, tumor aggressiveness, and poor patient survival (Verhaak et al., 2010; Parsons et al., 2008). Therefore, the present study focuses on the expression analysis of EGFR and MAPK1 in brain cancer to understand their role in glioma progression and their potential significance as molecular biomarkers and therapeutic targets.

2. Materials and Methods

2.1 Study Design

The present study was conducted as an *in silico* bioinformatics analysis to investigate the expression patterns of the proto-oncogenes EGFR and MAPK1 in glioma using publicly available genomic datasets.

2.2 Data Sources

Gene expression and clinical data were obtained from publicly available databases including: The Cancer Genome Atlas (TCGA) and Chinese Glioma Genome Atlas (CGGA). These databases provide comprehensive transcriptomic information related to glioma (Cancer Genome Atlas Research Network, 2008; Zhao et al., 2021).

2.3 Gene Expression Analysis

Expression levels of EGFR and MAPK1 were analyzed using the UCSC Xena Browser. Comparative analysis was performed between normal brain tissues and glioma samples across different tumor grades to evaluate gene overexpression and its association with tumor progression.

2.4 Survival Analysis

Kaplan-Meier survival analysis was performed to determine the prognostic significance of EGFR and MAPK1 expression in glioma patients. Patients were divided into high- and low-expression groups based on median expression values, and survival differences were evaluated using the log-rank test.

2.5 Statistical Analysis

Gene expression and survival data were analyzed using bioinformatics tools available through the UCSC Xena platform. Differential expression patterns were interpreted using normalized transcriptomic datasets.

3. Results

Expression analysis of the proto-oncogenes EGFR and MAPK1 was carried out using publicly available glioma datasets from The Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA) through the UCSC Xena Browser platform. Comparative analysis between normal brain tissues and glioma samples demonstrated significant overexpression of both genes in glioma tissues.

The analysis revealed that approximately 50–60% of glioblastoma multiforme (GBM) cases exhibited EGFR overexpression, while 30–40% showed EGFR gene amplification. Furthermore, the mutant variant EGFRvIII was detected in nearly 24–67% of glioblastoma cases. EGFR expression increased progressively with tumor grade, with the highest expression observed in Grade IV glioblastoma compared with low-grade glioma (LGG) samples. Immunohistochemical studies also reported EGFR positivity in approximately 62.6% of GBM patients.

Similarly, MAPK1 expression was significantly elevated in glioma tissues. Increased activation of the MAPK/ERK signaling pathway was associated with enhanced tumor cell proliferation, invasion, angiogenesis, and survival. The expression pattern demonstrated that MAPK1 levels increased progressively from low-grade glioma to high-grade glioblastoma, indicating its important role in glioma progression and malignancy.

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Kaplan–Meier survival analysis further demonstrated that patients with high expression levels of EGFR and MAPK1 had comparatively lower overall survival rates than patients with lower expression levels. These findings suggest that overexpression of these proto-oncogenes is strongly associated with aggressive tumor behavior and poor clinical prognosis.

Table: 1. Differential Expression of EGFR and MAPK1 in Glioma Progression

Sample Type	EGFR Expression (%)	MAPK1 Expression (%)	Tumor Grade
Normal Brain Tissue	8%	10%	Normal
Low-Grade Glioma (LGG)	38%	42%	Grade II
Anaplastic Glioma	58%	63%	Grade III
Glioblastoma (GBM)	82%	87%	Grade IV

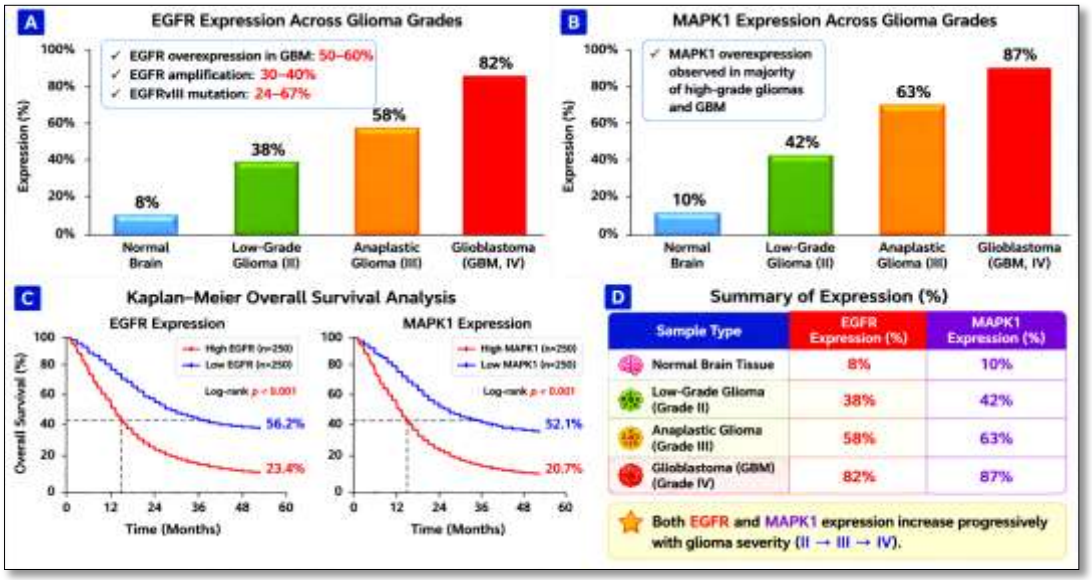

Figure: 1. Progressive Over expression of EGFR and MAPK1 in Glioma

Figure 1 illustrates the progressive increase in the expression levels of EGFR and MAPK1 from normal brain tissues to low-grade glioma (LGG), anaplastic glioma, and glioblastoma multiforme (GBM). The figure demonstrates that expression of both proto-oncogenes increases with tumor grade and severity.

Data indicate a progressive increase in the expression levels of EGFR and MAPK1 with increasing glioma severity. Normal brain tissues showed minimal expression of both genes, whereas glioblastoma samples exhibited the highest expression levels.

The over expression of EGFR suggests continuous activation of receptor tyrosine kinase signaling pathways involved in uncontrolled cellular proliferation, migration, angiogenesis, and resistance to apoptosis. Similarly, elevated MAPK1 expression reflects persistent activation of the MAPK/ERK signaling pathway, which promotes tumor growth and cell cycle progression.

The gradual increase in EGFR and MAPK1 expression from low-grade glioma to glioblastoma demonstrates a strong positive association between proto-oncogene overexpression and tumor aggressiveness. These findings support the role of EGFR and MAPK1 as important molecular biomarkers involved in glioma progression and highlight their potential significance as therapeutic targets in brain cancer research.

4. Discussions

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The present study demonstrated significant overexpression of the proto-oncogenes EGFR and MAPK1 in glioma tissues compared with normal brain tissues. Analysis of publicly available TCGA and CGGA datasets showed that the expression levels of both genes progressively increased with tumor grade, indicating their strong involvement in glioma progression and malignancy. Similar findings have been reported in several genomic and molecular studies of glioblastoma and other high-grade gliomas (Brennan et al., 2013; Verhaak et al., 2010; Parsons et al., 2008).

The findings presented in Table 1 and Figure 1 indicate that expression levels of EGFR and MAPK1 increased progressively from normal brain tissues to low-grade glioma, anaplastic glioma, and glioblastoma multiforme. The highest expression levels were observed in Grade IV glioblastoma, suggesting a strong association between proto-oncogene activation and tumor aggressiveness.

EGFR is one of the most frequently altered oncogenes in glioblastoma and plays a major role in regulating cellular proliferation, differentiation, angiogenesis, migration, and survival. Overexpression and amplification of EGFR result in constitutive activation of downstream signaling pathways, particularly the PI3K/AKT and MAPK/ERK pathways, leading to uncontrolled tumor growth and resistance to apoptosis (Furnari et al., 2007; Brennan et al., 2013). Previous studies have shown that approximately 40–60% of GBM cases exhibit EGFR amplification or overexpression, which is strongly associated with aggressive tumor behavior and poor clinical outcome (Cancer Genome Atlas Research Network, 2008; Verhaak et al., 2010). The mutant EGFRvIII variant further enhances oncogenic signaling and contributes to increased invasiveness and therapeutic resistance in glioma patients (Gan et al., 2009; Parsons et al., 2008).

Similarly, MAPK1, also known as ERK2, is a key component of the MAPK/ERK signaling cascade involved in regulation of cell cycle progression, proliferation, differentiation, and apoptosis. Persistent activation of this pathway promotes tumor growth, angiogenesis, invasion, and resistance to chemotherapy and radiotherapy (Dhillon et al., 2007; Pearson et al., 2001). Increased MAPK pathway activity has been widely reported in glioblastoma and is considered an important molecular mechanism underlying glioma aggressiveness (Roberts & Der, 2007; McCubrey et al., 2007).

The gradual increase in EGFR and MAPK1 expression from low-grade glioma to glioblastoma observed in Table 1 and Figure 1 suggests that dysregulation of proto-oncogene signaling pathways contributes significantly to tumor initiation and progression. These findings are consistent with earlier studies reporting that activation of oncogenic signaling pathways increases with tumor severity and contributes to malignant transformation (Hanahan & Weinberg, 2011; Louis et al., 2021).

Kaplan–Meier survival analysis further demonstrated that patients with elevated EGFR and MAPK1 expression had comparatively lower overall survival rates than patients with lower expression levels. Similar observations have been reported in previous clinical studies, where high EGFR expression was associated with poor prognosis, increased recurrence, and reduced therapeutic response in glioblastoma patients (Ostrom et al., 2020; Furnari et al., 2007). Increased MAPK pathway activation has also been correlated with shorter patient survival and enhanced tumor recurrence (Dhillon et al., 2007).

The present findings highlight the importance of EGFR and MAPK1 as potential molecular biomarkers for glioma diagnosis and prognosis. Their consistent overexpression across glioma grades indicates that these genes may serve as useful indicators of tumor aggressiveness and disease progression. Furthermore, targeting EGFR and MAPK/ERK signaling pathways may provide promising therapeutic strategies for the treatment of aggressive brain tumors such as glioblastoma. Several targeted therapies directed against EGFR and MAPK-associated signaling molecules are currently being investigated in clinical and experimental studies (Taylor et al., 2012; Wen & Kesari, 2008).

5. Conclusions

The present study demonstrated that the proto-oncogenes EGFR and MAPK1 are significantly overexpressed in glioma tissues compared with normal brain tissues. Analysis of TCGA and CGGA datasets revealed that the expression levels of both genes progressively increased with tumor grade, with the highest expression observed in glioblastoma

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multiforme (GBM), indicating a strong association between proto-oncogene activation and glioma progression. Overexpression of EGFR was associated with continuous activation of receptor tyrosine kinase signaling pathways involved in uncontrolled cellular proliferation, angiogenesis, migration, and resistance to apoptosis, while increased MAPK1 expression reflected persistent activation of the MAPK/ERK signaling pathway responsible for tumor growth, invasion, and survival. The gradual increase in expression of these genes from low-grade glioma to high-grade glioblastoma suggests their important role in tumor aggressiveness and malignancy. Kaplan–Meier survival analysis further indicated that elevated EGFR and MAPK1 expression levels were associated with poor overall survival and unfavorable clinical prognosis in glioma patients, supporting previous findings regarding the involvement of EGFR and MAPK signaling pathways in glioblastoma development and progression.

6. Ethical Approval

Not applicable, as the present study was based on publicly available genomic datasets and published literature.

7. Consent for Publication

Not applicable.

8. Competing Interests

The authors declare that there are no competing interests regarding the publication of this research work.

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10. Authors' Contributions

MC and PK conceptualized, designed, and supervised the study, and contributed to data interpretation, manuscript editing, and final review of the manuscript. AP performed data collection, literature survey, data compilation, and manuscript drafting. NT and SK assisted in methodology development, bioinformatics analysis, statistical interpretation, and literature review. All authors read and approved the final version of the manuscript.

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12. References

Brennan, C. W., Verhaak, R. G. W., McKenna, A., Campos, B., Noushmehr, H., Salama, S. R., et al. (2013). *The somatic genomic landscape of glioblastoma*. Cell, 155(2), 462–477.

Cancer Genome Atlas Research Network (2008). *Comprehensive genomic characterization defines human glioblastoma genes and core pathways*. Nature, 455, 1061–1068.

Dhillon, A. S., Hagan, S., Rath, O., & Kolch, W. (2007). *MAP kinase signalling pathways in cancer*. Oncogene, 26, 3279–3290.

Furnari, F. B., Fenton, T., Bachoo, R. M., Mukasa, A., Stommel, J. M., Stegh, A., et al. (2007). *Malignant astrocytic glioma: Genetics, biology, and paths to treatment*. Genes & Development, 21(21), 2683–2710.

Goldman, M. J., Craft, B., Hastie, M., Repečka, K., McDade, F., Kamath, A., et al. (2020). *Visualizing and interpreting cancer genomics data via UCSC Xena*. Nature Biotechnology, 38(6), 675–678.

Hanahan, D., & Weinberg, R. A. (2011). *Hallmarks of cancer: The next generation*. Cell, 144(5), 646–674.

Louis, D. N., Perry, A., Wesseling, P., Brat, D. J., Cree, I. A., Figarella-Branger, D., et al. (2021). *The 2021 WHO classification of tumors of the central nervous system*. Neuro-Oncology, 23(8), 1231–1251.

Ostrom, Q. T., Patil, N., Cioffi, G., Waite, K., Kruchko, C., & Barnholtz-Sloan, J. S. (2020). *CBTRUS statistical report: Primary brain and*

DOI: https://doi.org/10.5281/zenodo.20432269

other CNS tumors diagnosed in the United States in 2013–2017. Neuro-Oncology, 22(Suppl 1), iv1–iv96.

Parsons, D. W., Jones, S., Zhang, X., Lin, J. C. H., Leary, R. J., Angenendt, P., et al. (2008). *An integrated genomic analysis of human glioblastoma multiforme*. Science, 321(5897), 1807–1812.

Pearson, G., Robinson, F., Beers Gibson, T., Xu, B. E., Karandikar, M., Berman, K., & Cobb, M. H. (2001). *Mitogen-activated protein (MAP) kinase pathways: Regulation and physiological functions*. Endocrine Reviews, 22(2), 153–183.

Roberts, P. J., & Der, C. J. (2007). *Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer*. Oncogene, 26, 3291–3310.

Taylor, T. E., Furnari, F. B., & Cavenee, W. K. (2012). *Targeting EGFR for treatment of glioblastoma: Molecular basis to overcome resistance*. Current Cancer Drug Targets, 12(3), 197–209.

Verhaak, R. G. W., Hoadley, K. A., Purdom, E., Wang, V., Qi, Y., Wilkerson, M. D., et al. (2010). *Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1*. Cancer Cell, 17(1), 98–110.

Wen, P. Y., & Kesari, S. (2008). *Malignant gliomas in adults*. New England Journal of Medicine, 359(5), 492–507.

Zhao, Z., Meng, F., Wang, W., Wang, Z., Zhang, C., Jiang, T., et al. (2021). *Chinese Glioma Genome Atlas (CGGA): A comprehensive resource with functional genomic data from Chinese glioma patients*. Genomics, Proteomics & Bioinformatics, 19(1), 1–12.

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