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ELOVL1 as a Potential Biomarker Associated with Poor Prognosis in Glioma

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Abstract: Seven elongases (ELOVL1-7) exist within the human body, exhibiting distinct tissue expression patterns and substrate specificities. ELOVL1 serves as the primary rate-limiting enzyme for the synthesis of very long-chain fatty acids (VLCFAs), regulating the rate and direction of this process. Accumulating research demonstrates a close association between ELOVL1 and tumorigenesis and progression; however, its specific function in glioma remains incompletely understood. In this we utilized data from The Cancer Genome Atlas (TCGA), the Genotype-Tissue Expression (GTEx) database, and the Chinese Glioma Genome Atlas (CGGA) to investigate the association between ELOVL1 expression and the clinicopathological/molecular characteristics of glioma patients, as well as its correlation with patient prognosis. Our findings reveal that high ELOVL1 expression is significantly associated with poor patient prognosis. Further analysis of the biological role of ELOVL1 in glioma indicates its involvement in multiple biological processes implicated in glioma development, including immune responses, inflammatory responses, and the regulation of defense responses within the immune system. Immune infiltration analysis using the CIBERSORT database uncovered correlations between high ELOVL1 expression and the infiltration of various immune cell types, as well as immune checkpoints, in glioma. In summary, ELOVL1 may serve as a promising potential biomarker for the clinical diagnosis and treatment of glioma.

Keywords: *ELOVL1, Glioma, Immune, Prognosis*

1. Introduction

Glioma represents the most common primary brain tumor, classified according to histological and molecular characteristics defined by the World Health Organization (WHO) classification system [1]. This classification reflects the tumor's aggressiveness and malignant potential, with grades ranging from slow-growing low-grade gliomas to highly aggressive forms. Among these, glioblastoma multiforme (GBM) constitutes the most severe and rapidly progressive subtype, representing the most prevalent form of aggressive brain cancer in adults. It is characterized by rapid growth and high invasiveness, typically leading to poor prognosis despite patients receiving aggressive treatment [2, 3]. Although the standard treatment for GBM includes maximal surgical resection, temozolomide (TMZ) chemotherapy, and radiotherapy, the 5-year survival rate remains only 6%, with a median overall survival of approximately 15 months [4, 5]. This underscores the urgent need for more effective therapies to improve patient outcomes. Therefore, an in-depth analysis of the molecular mechanisms underlying glioma development and progression, screening for key driver genes and signaling pathways, and the identification of potent therapeutic targets hold significant clinical value for improving patient prognosis.

To date, seven ELOVL family genes (ELOVL1-7) have been identified in humans [6, 7]. Multiple members of the ELOVL family, including ELOVL1, -3, -4, -5, and -6, are expressed in cells of the central nervous system (CNS), with their expression levels varying across distinct brain regions [8, 9]. ELOVL enzymes are widely distributed in various tissues such as the testes, brain, and adrenal glands. Studies have indicated that several genes within the ELOVL family are significantly upregulated or downregulated during the development of cancers including breast cancer, renal cancer, and prostate cancer [10]. ELOVL1 (Elongase of Very Long Chain Fatty Acids 1), the primary rate-limiting enzyme

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for the synthesis of VLCFAs, exhibits elevated expression in colorectal cancer and breast cancer. This overexpression may contribute to carcinogenesis and is associated with malignancy [11]. However, the clinical significance and role of ELOVL1 in glioma remain unclear. Therefore, a better characterization of these proteins may provide novel insights for glioma treatment.

In this study, we revealed the overexpression of ELOVL1 in glioma. Its expression level was significantly associated with malignant tumor phenotypes and poor patient prognosis. Through differential expression gene enrichment analysis and immune cell infiltration analysis, we discovered that high ELOVL1 expression is closely linked to the biological progression of glioma. Collectively, our findings indicate that ELOVL1 not only serves as a potential biomarker for glioma diagnosis but may also represent a novel target for therapeutic intervention.

2. Materials and methods

2.1. Data Collection

We obtained glioma patient clinical information and RNA sequencing data from The Cancer Genome Atlas (TCGA; http://cancergenome.nih.gov/)[12] and the Chinese Glioma Genome Atlas (CGGA; http://www.cgga.org.cn/)[13] databases. Gene expression data for normal brain tissue were acquired from the Genotype-Tissue Expression (GTEx;https://xenabrowser.net/datapages/)[14] database.

2.2. Differential Expression Analysis

We utilized the GEPIA2 analysis tool (http://gepia2.cancer-pku.cn/) to evaluate differential mRNA expression levels of ELOVL1 across various malignancies [15]. Furthermore, we employed the Human Protein Atlas (HPA; https://www.proteinatlas.org) database to compare ELOVL1 protein expression levels in different parts of the brain and to obtain immunohistochemical images depicting glioma versus normal brain tissue [16, 17].

2.3. Clinical Prognostic Analysis

We employed the 'limma' R package, the 'survival' R package, and the 'survminer' R package to perform survival analysis and generate Kaplan-Meier survival curves. The 'timeROC' R package was used to plot Receiver Operating Characteristic (ROC) curves assessing the association of ELOVL1 expression with 1-year, 3-year, and 5-year survival rates.

2.4. Protein-Protein Interaction Prediction

We utilized the STRING protein-protein interaction network database (https://cn.string-db.org/) to analyze proteins interacting with ELOVL1 and perform functional enrichment analysis of these interactions [18].

2.5. GO Enrichment and KEGG Pathway Analysis

We employed the 'clusterProfiler' R package to conduct Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis for ELOVL1. Terms with an adjusted *p*-value < 0.05 were considered statistically significant.

2.6. Immune Infiltration Analysis

Infiltration data for immune cells in glioma were obtained from the CIBERSORT database (http://cibersort.stanford.edu/) [19]. Differences in immune cell infiltration levels between glioma samples with high and low ELOVL1 expression were assessed using the Wilcoxon rank-sum test. Spearman's correlation analysis was performed to calculate the correlation coefficients (ρ) between ELOVL1 expression levels and the infiltration levels of different immune cell types; a*p*-value < 0.05 was considered statistically significant. Subsequently, Pearson correlation analysis was applied to identify immune checkpoints significantly associated with ELOVL1 expression, using a threshold of *p* < 0.001.

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3. Results

3.1. Overexpression of ELOVL1 in Glioma

To investigate the differential expression of ELOVL1 across various cancers and their corresponding normal tissues, we utilized the GEPIA2 online platform to integrate data from the TCGA and GTEx databases, assessing ELOVL1 expression in tumor tissues. The results demonstrated that ELOVL1 expression was significantly upregulated in GBM, low-grade glioma (LGG), hepatocellular carcinoma (LIHC), ovarian serous cystadenocarcinoma (OV), and pancreatic adenocarcinoma (PAAD) (Fig. 1A). Furthermore, GEPIA2 analysis revealed significantly elevated ELOVL1 mRNA levels in both GBM and LGG compared to normal brain tissue (Fig. 1B).

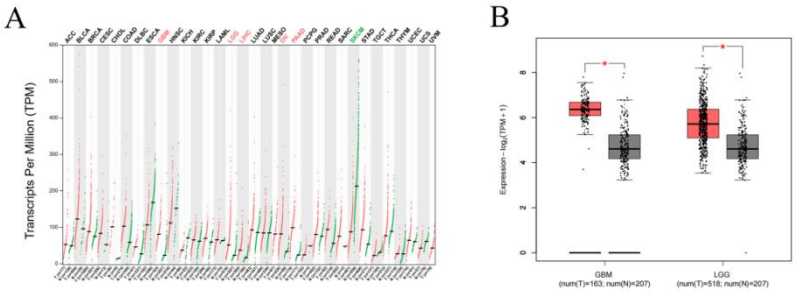

Figure 1: ELOVL1 Transcriptional Expression in 33 Types of Cancers (GEPIA 2 Database)

*A: Analysis of pan-cancer ELOVL1 expression in TCGA and GTEx databases using the GEPIA2 online platform. B: Differential ELOVL1 expression in GBM and LGG via GEPIA2 online analysis. (*p* < 0.05, **p* < 0.01, ***p* < 0.001, ****p* < 0.0001)*

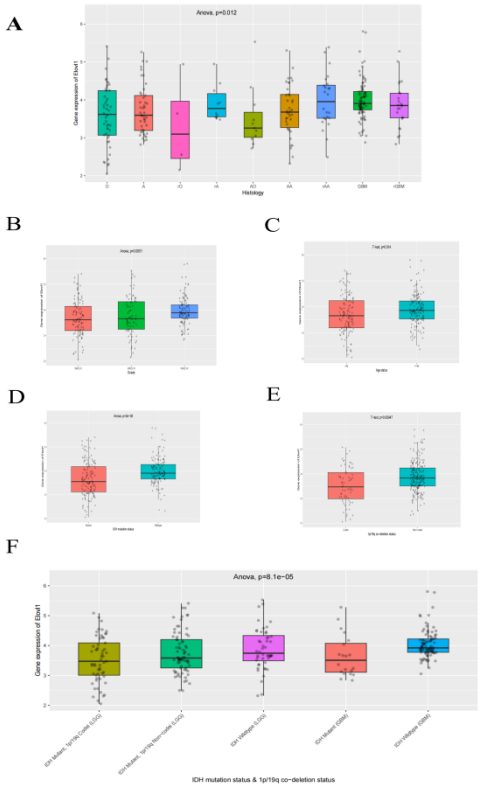

Figure 2: Relationship between ELOVL1 mRNA Expression and Cancer Staging and genetic alterations in GBM and LGG Patients (CGGA database).

*A-B: Association between ELOVL1 expression levels and glioma histology/WHO grade in the CGGA database. C: Correlation of ELOVL1 expression with patient age. D-F: Relationship between ELOVL1 expression and genetic alterations (IDH mutation, 1p/19q codeletion).(*p* < 0.05, **p* < 0.01, ***p* < 0.001, ****p* < 0.0001)*

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3.2. ELOVL1 Overexpression is Significantly Associated with Glioma Clinical and Molecular Features

Given the aberrantly high expression of ELOVL1 in glioma tissues, we subsequently analyzed its correlation with clinical and molecular characteristics of glioma. Analysis of ELOVL1 expression across different glioma grades within the CGGA database revealed a positive correlation between ELOVL1 expression levels and both histological grade and WHO classification (Fig. 2A, B). Furthermore, ELOVL1 expression levels also exhibited a positive correlation with patient age (Fig. 2C). Previous studies have established that IDH mutation and 1p/19q codeletion are critical molecular alterations in glioma development, closely associated with patient prognosis [20]. Consequently, we evaluated these genetic alterations in glioma patients from the CGGA database. We found that ELOVL1 expression levels were significantly lower in the IDH-mutant group and the 1p/19q codeleted group compared to their respective wild-type groups (Fig. 2D, E, F). These results suggest that ELOVL1 may be closely associated with malignant progression, treatment resistance, and poor prognosis in glioma.

3.3. ELOVL1 Overexpression is Associated with Poor Prognosis in Glioma Patients

To investigate the impact of high ELOVL1 expression on patient prognosis in glioma, we collected clinical data for glioma patients from the TCGA and CGGA databases. Patients were stratified into high-expression and low-expression groups based on ELOVL1 expression levels. Within the TCGA database, patients with high ELOVL1 expression exhibited significantly shorter overall survival (OS) and disease-free survival (DFS) compared to the low-expression group ($p < 0.001$, log-rank test; Fig. 3A, B). Furthermore, in the CGGA database, both primary and recurrent glioma patients in the low ELOVL1 expression group demonstrated significantly longer survival times than those in the high-expression group ($p < 0.05$, log-rank test; Fig. 3D, E). These findings indicate that elevated ELOVL1 expression is associated with poor patient prognosis. To further evaluate the predictive value of ELOVL1 expression levels for glioma patient prognosis, we constructed ROC curves for 1-year, 3-year, and 5-year survival and calculated the corresponding area under the curve (AUC) values. In the TCGA cohort, the AUC values for 1-year, 3-year, and 5-year survival all exceeded 0.7 (Fig. 3C), demonstrating significant predictive accuracy of high ELOVL1 expression for patient outcome risk.

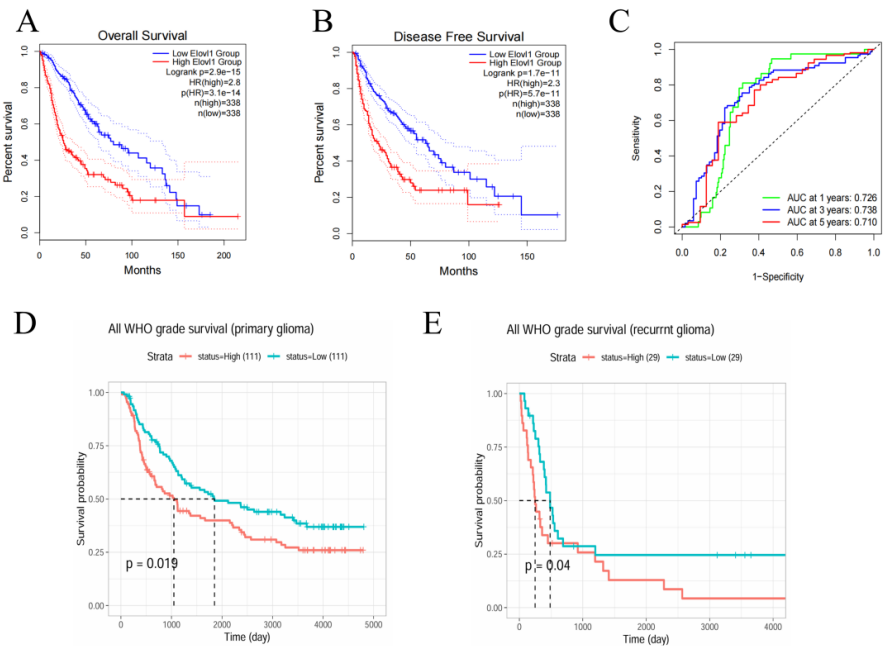

Figure 3: Prognostic Value of ELOVL1 mRNA Expression in Cancer (GEPIA 2, TCGA, CGGA Database).

*A-C: Survival curves depicting OS and DFS, along with ROC curves, were generated for glioma patients based on data from the TCGA database.D-E: Correlation between ELOVL1 expression levels and patient survival in primary and recurrent gliomas from the CGGA database. (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001)*

ISSN 2618-1584 Vol. 7, Issue 4: 22-29, DOI: 10.25236/FMSR.2025.070403

3.4. Protein-Protein Interaction Network and Protein Level of ELOVL1

We constructed a Protein-Protein Interaction (PPI) network for ELOVL1 to investigate its associations with related proteins. This analysis revealed interactions between ELOVL1 and ELOVL3, ELOVL4, ELOVL7, ABCD1, CERS2, CERS3, SCD, HSD17B12, and AWAT1. These interacting genes constitute a metabolic network for VLCFAs, suggesting that ELOVL1 may participate in regulating cell membrane structure and signal transduction (Fig 4A). We further analyzed ELOVL1 mRNA expression levels in human brain tissues using the HPA database. The results demonstrate consistently high expression of ELOVL1 mRNA across brain tissues (Fig 4B). Consequently, we hypothesize that ELOVL1 plays a significant role in the pathogenesis and progression of glioma. Analysis of ELOVL1 protein levels via the HPA database revealed elevated expression in both LGG and GBM tissues compared to corresponding normal tissues (Fig 4C). This finding suggests that ELOVL1 could serve as a potential tumor biomarker.

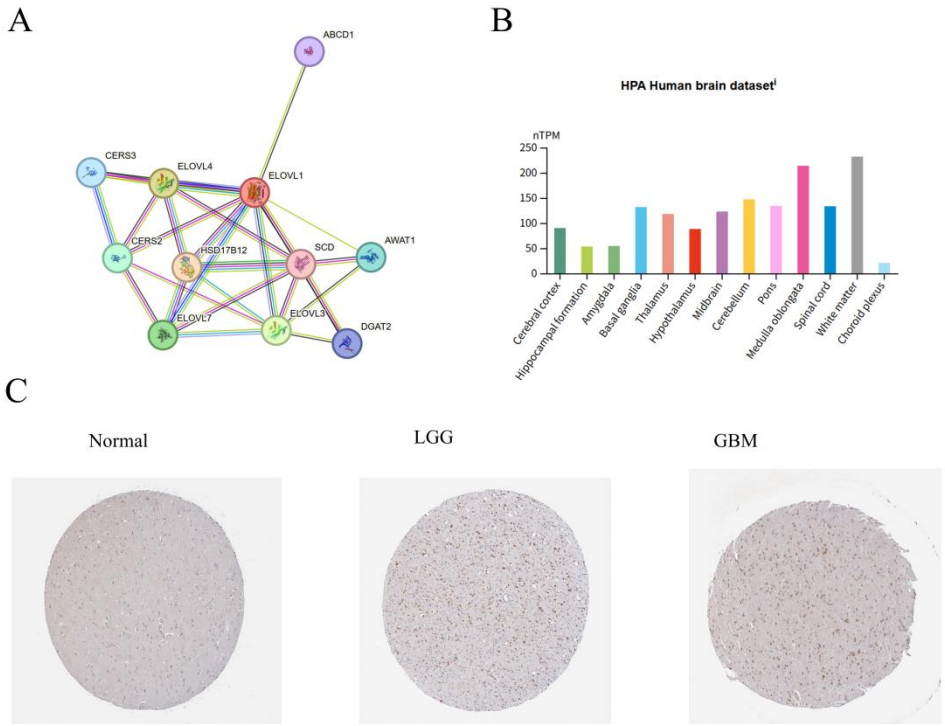

Figure 4: PPI network and protein level of ELOVL1.(STRING, HPA Database).

A: Protein-protein interaction (PPI) network of ELOVL1. Each node represents a protein. Edges are color-coded: azure for database annotations, magenta for experimentally validated interactions; green, red, and navy blue represent gene neighborhood, gene fusion, and gene co-occurrence relationships, respectively; lime green indicates text mining results, black denotes co-expression, and light blue represents protein homology. B: Expression levels of ELOVL1 in various subregions of brain tissue based on the HPA database. C: Representative immunohistochemical staining results of ELOVL1 protein in tumor tissues (LGG & GBM) versus normal tissues from the HPA database.

3.5. Potential Functional Analysis of ELOVL1

We employed Pearson correlation analysis to screen for 50 significant genes whose expression was strongly correlated with ELOVL1 expression, visualized via a heatmap. Among these, NINJ2, TRIM59, and SLC31A2 exhibited significantly positive correlations with ELOVL1 expression, whereas RRN3, TTC3, and RNASEN showed significantly negative correlations with ELOVL1 expression (Figs 5A, B, C). These results suggest that ELOVL1 exerts a broad influence on transcriptional regulation. Based on ELOVL1 expression levels in gliomas, samples from the TCGA database were stratified into high-expression and low-expression groups. Differential expression analysis between these groups was performed using R software, identifying differentially expressed genes (DEGs) associated with ELOVL1. To investigate the biological pathways linked to these DEGs, GO enrichment analysis was

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conducted. This analysis revealed significant enrichment of these genes in multiple biological processes, including immune response, inflammatory response, and regulation of immune system defense response (Fig 5D). Furthermore, KEGG pathway enrichment analysis was performed. The results indicated that the DEGs were primarily enriched in pathways such as cytokine-cytokine receptor interaction and extracellular matrix (ECM)-receptor interaction (Fig 5E). Collectively, these analyses provide crucial molecular mechanistic insights for further understanding the functional role of ELOVL1 in glioma.

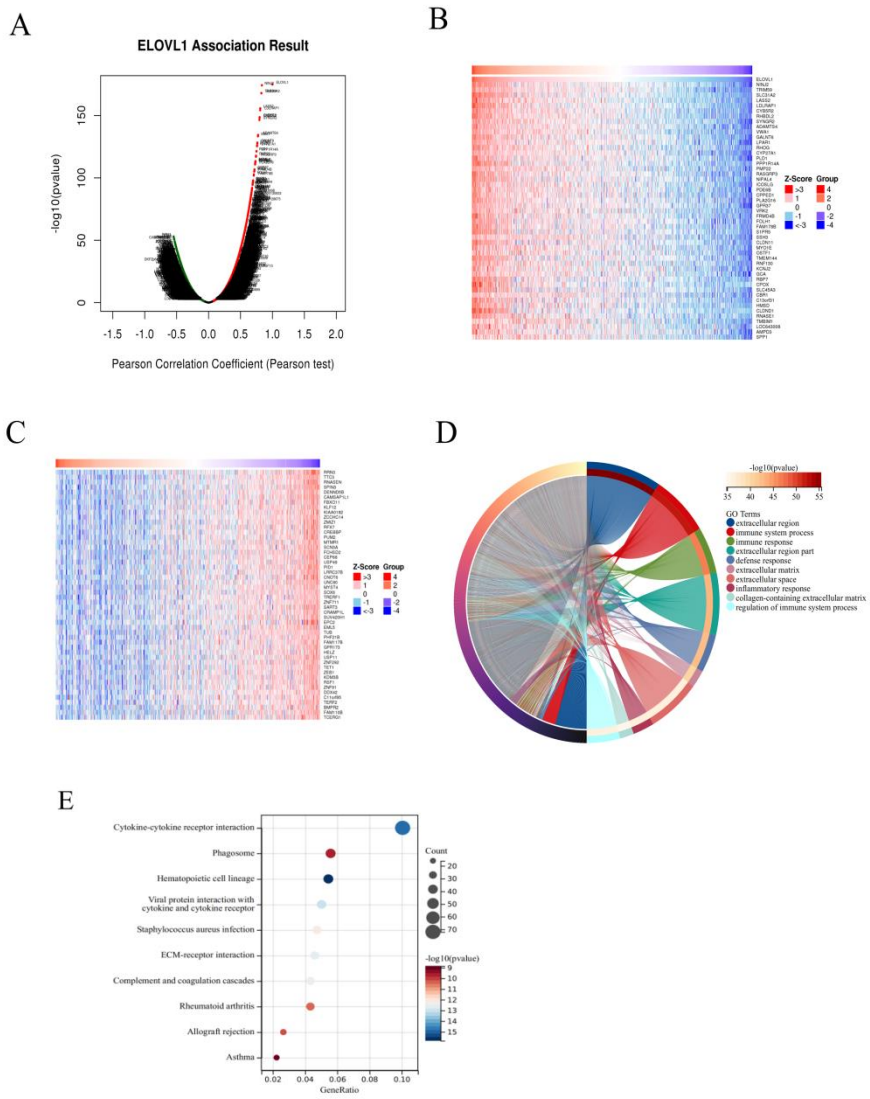

Figure 5:Functional Enrichment Analysis of ELOVL1 (LinkedOmics database).

A-C: Genes co-expressed with ELOVL1 in the LinkedOmics online database. D: GO analysis of DEGs. E: KEGG analysis of DEGs.

3.6. ELOVL1 Expression Levels Influence Immune Cell Infiltration in Glioma

We further analyzed the distribution differences of 22 types of immune cells between the high ELOVL1 expression group and the low ELOVL1 expression group in glioma. The results demonstrated that the infiltration levels of macrophages, CD8+ T cells, and γδ T cells were significantly positively correlated with ELOVL1 expression. Conversely, the infiltration levels of activated mast cells, activated natural killer (NK) cells, and monocytes were significantly negatively correlated with ELOVL1 expression (Fig 6A). Given the critical role of immune checkpoint molecules in regulating immune cell responses against tumor cells, we investigated the correlation between ELOVL1 expression levels and these molecules. We found that ELOVL1 expression showed significant positive correlations with the majority of immune checkpoint molecules examined (such as PD-1, CTLA-4,

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IDO1, etc.) (Fig 6B). These findings reveal a potential role for ELOVL1 in modulating the infiltration of specific immune cell subsets and suggest its influence on tumor sensitivity to immune checkpoint inhibitor therapy.

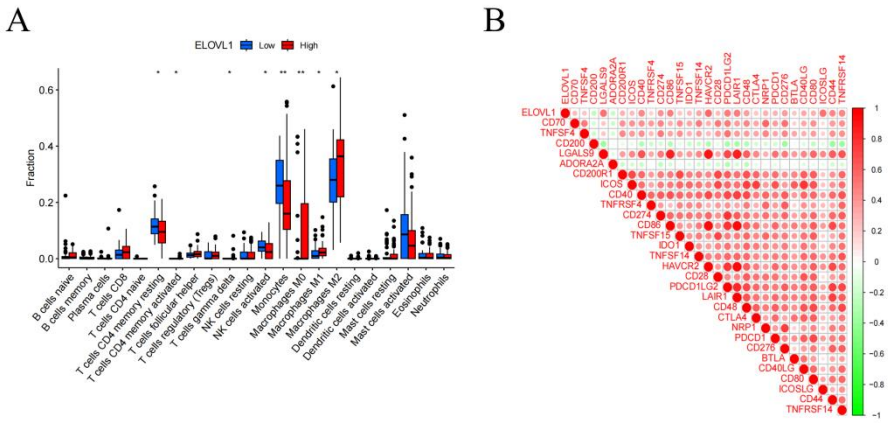

Figure 6: Correlation between ELOVL1 Transcriptional Expression and Immune Infiltrating Cells/Immune Checkpoint Molecules

*A: Infiltration differences of 22 tumor-infiltrating immune cells between the high ELOVL1 expression group and the low ELOVL1 expression group. B: Correlation between ELOVL1 and immune checkpoint genes. (Green denotes negative correlation; red denotes positive correlation. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001).*

4. Discussion

Gliomas remain among the most challenging malignancies due to their complex and adaptable tumor microenvironment. Despite advances in surgical techniques, radiation therapy, and the frontline chemotherapeutic agent TMZ, the prognosis for patients with GBM remains poor. This lack of effective long-term therapeutic options underscores the urgent, unmet clinical need for novel treatment strategies to improve patient outcomes.

ELOVL1, a fatty acid elongase, is highly expressed in colorectal and breast cancers, where it may promote cancer progression and is associated with malignancy levels [11]. Our study demonstrated that ELOVL1 is significantly upregulated in glioma tissues and showed significant associations with tumor stage, molecular genetic features, and poor prognosis in glioma patients. Tumor immune escape represents a critical mechanism by which tumors evade immune surveillance [21]. We further explored the immunomodulatory function of ELOVL1 in gliomas, revealing its involvement in multiple immune response processes and significant correlations with immune cell infiltration patterns and immune checkpoint molecule expression within the glioma microenvironment.

While our current study provides some insights into the relationship between ELOVL1 and glioma, certain limitations remain. Firstly, the precise mechanisms underlying ELOVL1's immunomodulatory role in glioma require further investigation. Secondly, our findings lack support from clinical sample information, limiting the comprehensiveness of interpreting ELOVL1's prognostic significance in glioma. Future research will focus on elucidating these aspects to gain deeper insights into ELOVL1's role in glioma development, thereby providing more robust evidence for its potential as a therapeutic target or prognostic biomarker in glioma.

5. Conclusions

Our study demonstrates that ELOVL1 overexpression correlates with clinicopathological and molecular characteristics of glioma and predicts poor prognosis in glioma patients. Consequently, ELOVL1 could serve as a potential biomarker for glioma diagnosis and a novel therapeutic target for treatment.

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