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The Inflammatory Characteristics of Symptomatic Glioma Associated With Poor Prognosis and Chemoresistance via Tumor Necrosis Factor Signaling Pathway

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Background Among gliomas, the most common primary malignant brain tumor, incidental gliomas account for 2.5%–5% of cases. The controversy over whether to pursue immediate treatment or adopt a wait-and-see approach remains, and more molecular and immunological evidence is needed for definitive treatment decisions.

Methods Total RNA sequencing (RNA-seq) data and single cell RNA sequencing (scRNA-seq) data were retrospectively analyzed to compare the molecular and immunological tumor microenvironment differences between incidental glioma and symptomatic glioma samples. These were classified using symptom data from The Cancer Genome Atlas (TCGA) and public dataset.

Results RNA-seq analysis of the GBMLGG dataset identified 343 genes upregulated in symptomatic glioma and 118 in incidental glioma, with 104 common genes upregulated in symptomatic glioma across both the TCGA and Chinese Glioma Genome Atlas (CGGA) datasets. Enrichment analysis revealed that these 104 genes in symptomatic glioma were significantly associated with immunological pathways. scRNA-seq analysis of glioma revealed 11 cell types, including T cells, myeloid cells, and oligodendrocytes, with the tumor necrosis factor (TNF) signaling pathway strongly influencing other cell types, particularly myeloid cells. Enrichment and survival analyses showed that TNF signaling is associated with temozolomide resistance and poorer prognosis in glioma patients.

Conclusion The findings suggest that symptomatic glioma enhances inflammatory responses linked to poor prognosis and chemoresistance. This supports the hypothesis that immediate treatment of incidental glioma may improve patient outcomes over a wait-and-see approach.

Keywords Glioma; Incidental discovery; Prognosis; Drug resistance; Neuroinflammation; Tumor necrosis factor.

INTRODUCTION

Glioma is the most common primary malignant intracranial tumor, accounting for approximately 80% of cases [1]. Its incidence was 6.0 per 100,000 population from 2010 to 2014 in the United States [2]. Symptoms usually appear depending on the location of tumor, but seizure and headache are most common [3]. Gliomas are typically diagnosed through MRI followed by surgical resection [4]. However, molecular diagnosis using a next-generation sequencing panel, which in-

cludes the detection of IDH1 mutation, has become increasingly important according to 2021 WHO Classification of Tumors of the Central Nervous System [5].

In adult-type diffuse gliomas, IDH-mutant tumors are classified as astrocytoma or oligodendrogliomas, while IDH-wildtype gliomas are classified as glioblastomas [5]. Appropriate treatment strategies include concomitant chemoradiation or independent radiation therapy [5]. Chemotherapy using adjuvant procarbazine, carmustine, vincristine (PCV) or temozolomide is often selected based on molecular testing results [6]. However, as these molecular tests rely on biospecimens obtained after surgical resection, the clinical approach to incidentally discovered adult-type diffuse gliomas remains unresolved.

Incidentally discovered adult-type diffuse gliomas, incidental gliomas, are diagnosed unexpectedly, such as during a medical check-up following an unrelated event like a motorbike accident or a headache that is not specifically indicative of glioma [7,8]. Incidental gliomas account for about 2.5%−5% of glioma cases, and their incidence has increased over time due to advancements in radiological diagnostic technique, which can now detect smaller tumor lesion [9]. Despite this, the clinical management of incidental gliomas remains controversial, with debate between adopting a wait-and-see approach until seizure or neurological deficits appear versus initiating immediate treatment upon diagnosis [10,11].

Although previous studies suggest that incidental gliomas have a more favorable prognosis than symptomatic gliomas, molecular evidence remains insufficient to definitively support either approach [3,7,12,13]. Our prior research demonstrated that symptomatic gliomas exhibit greater malignancy and chemoresistance to PCV and temozolomide [14]. In this study, we further investigate the nature of incidental gliomas from an immunological and molecular perspective, as the immunological landscape of gliomas has gained increasing importance.

MATERIALS AND METHODS

The Cancer Genome Atlas data and Cancer Dependency Map data

The analysis was conducted with GBMLGG dataset, which includes clinical, survival, and RNA-seq data generated from The Cancer Genome Atlas (TCGA; https://www.cancer.gov/tcga). These data were downloaded from Gliovis (gliovis.bioinfo.cnio.es/), and 441 samples were selected after excluding those with missing symptom data. Forty-two incidental glioma samples were classified as having no symptoms or only headaches, while 399 samples were classified as symptomatic gliomas. Additional cancer cell line drug sensitivity data and RNA-seq expression data from Dependency Map (DepMap; https://depmap.org/portal/) were used to investigate correlations between gene expression and drug sensitivity in IDH wildtype cell lines. Drug sensitivity data were obtained from the PRISM Repurposing Primary Screen, and RNA-seq expression data were from the 21Q4 release.

Differentially expressed gene analysis

Differentially expressed gene (DEG) analysis between incidental glioma and symptomatic glioma were conducted using the DESeq2 package [15] in R (R Foundation for Statistical Computing, Vienna, Austria). Genes with a log2 fold-change >1 and a Benjamini-Hochberg adjusted p-value <0.05 were considered significantly differentially expressed.

Gene set enrichment analyses (GSEA) and single sample GSEA

GSEA was conducted using Gene Ontology (GO) biological process (https://geneontology.org/), Kyoto Encyclopedia of Genes and Genomes (KEGG) (https://www.genome.jp/kegg/), Reactome (https://reactome.org/), and Hallmark (https://www.gsea-msigdb.org/gsea/msigdb) curated database using ShinyGO software (https://bioinformatics.sdstate.edu/go/). Significantly enriched results were selected with false discovery rate (FDR) correction <0.05 were extracted using ShinyGO v. 0.741, and top 20 terms were visualized sorted by fold enrichment value. Single sample GSEA (ssGSEA) was conducted to score each sample with Hallmark curated database using ssGSEA module from GenePattern (https://www.genepattern.org/) with default settings.

Single cell RNA-seq analysis

Single-cell RNA sequencing (scRNA-seq) analysis was carried out on the GSE256493 dataset (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE256493) using Seurat V5 [16], including around 20,000 cells. Cells were filtered out if they had fewer than 200 or more than 5,500 detected genes, or if their mitochondrial gene content exceeded 5%. After filtering, default settings were used for data processing, with Find Neighbors and Find Clusters functions run on 20 principal components and a resolution of 0.25. Dimensionality reduction and visualization were performed using Uniform Manifold Approximation and Projection (UMAP), revealing 11 distinct clusters. These clusters were annotated based on established markers for specific cell types. Furthermore, pathway network analysis was conducted using the CellChat package (v1.5.0) [17] to explore intercellular communication between the identified cell types. Single cell GSEA was conducted to calculate the score of every cell.

Survival analysis

Survival analysis was conducted using the R package Survival (v3.2) and visualized by Survminer (v0.4.8). Log-rank test was also conducted to calculated *p*-value between two groups devided by ssGSEA score.

Statistical analyses

Student t-test was conducted to compare age between incidental glioma and symptomatic glioma. Fisher exact test was performed to compare the proportion of gender and IDH status between incidental and symptomatic glioma. Pearson method was used to investigate correlation of temozolomide resistance and gene expression. The Venn diagram was visualized by Venny (v2.1.0; https://bioinfogp.cnb.csic.es/tools/venny/).

RESULTS

Comparison of clinical and molecular characteristics between incidental and symptomatic gliomas

A total of 441 samples from the TCGA GBMLGG dataset and 39 cell line data from DepMap dataset were selected for total RNA-seq analysis and about 20,000 cells were selected for scRNA-seq analysis in this study (Fig. 1). The clinical characteristics of both incidental and symptomatic gliomas, including tumor location, gender, age at initial diagnosis, and IDH mutation status, were compared, revealing no significant differences between the two groups (Table 1).

To investigate molecular characteristics, DEGs were extracted using RNA-seq data from the GBMLGG dataset. Genes with an adjusted *p*-value of <0.05 and an absolute value of log2 fold change greater than 1 were selected. Among them, 343 genes were found to be upregulated in symptomatic glioma and 118 genes in incidental glioma (Fig. 2A). The results of analysis using Chinese Glioma Genome Atlas (CGGA) data was used to validate these findings, identifying 104 genes commonly upregulated in the symptomatic gliomas across both datasets (Fig. 2B) [18].

Enrichment analysis was performed with 104 genes com-

Table 1. The clinical characteristics of incidental and symptomatic gliomas

	Incidental glioma (n=42)	Symptomatic glioma (n=399)	*p*-value
Gender			0.0519
Male	18	197	
Female	23	155	
NA	1	47	
Average age (yr) at initial diagnosis	43.5	43.4	0.2411
IDH status			0.7311
Wildtype	6	74	
Mutant	36	323	
NA	-	2	
Tumor location			0.8961
Supratentorial, frontal lobe	28	234	
Supratentorial, occipital lobe	-	5	
Supratentorial, parietal lobe	2	37	
Supratentorial, temporal lobe	12	111	
Posterior fossa, brain stem	-	1	
Posterior fossa, cerebellum	-	2	
Supratentorial, not otherwise specified	-	8	
NA	-	1	

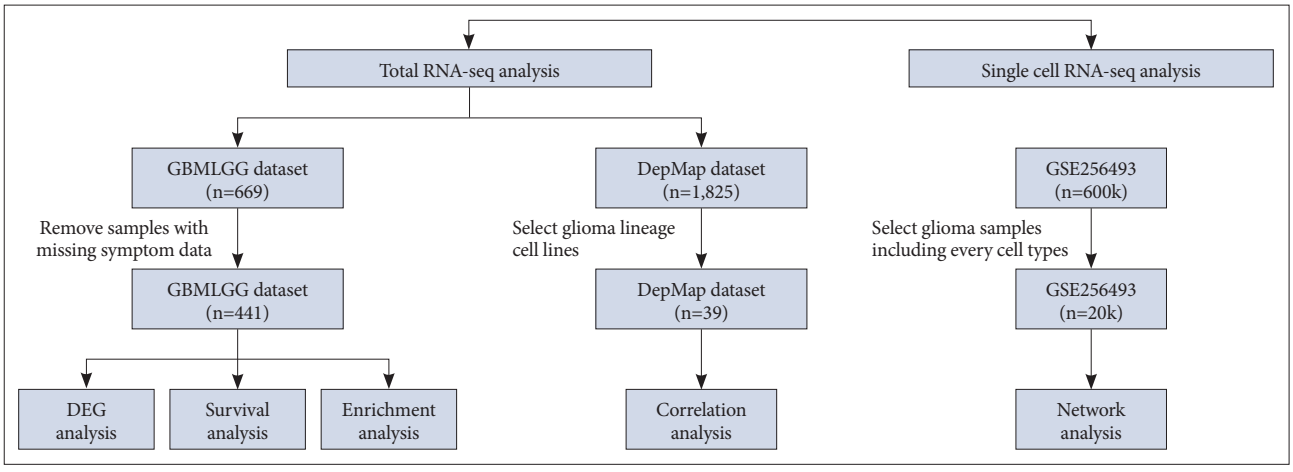

Fig. 1. The flowchart of this study. DEG, differentially expressed gene.

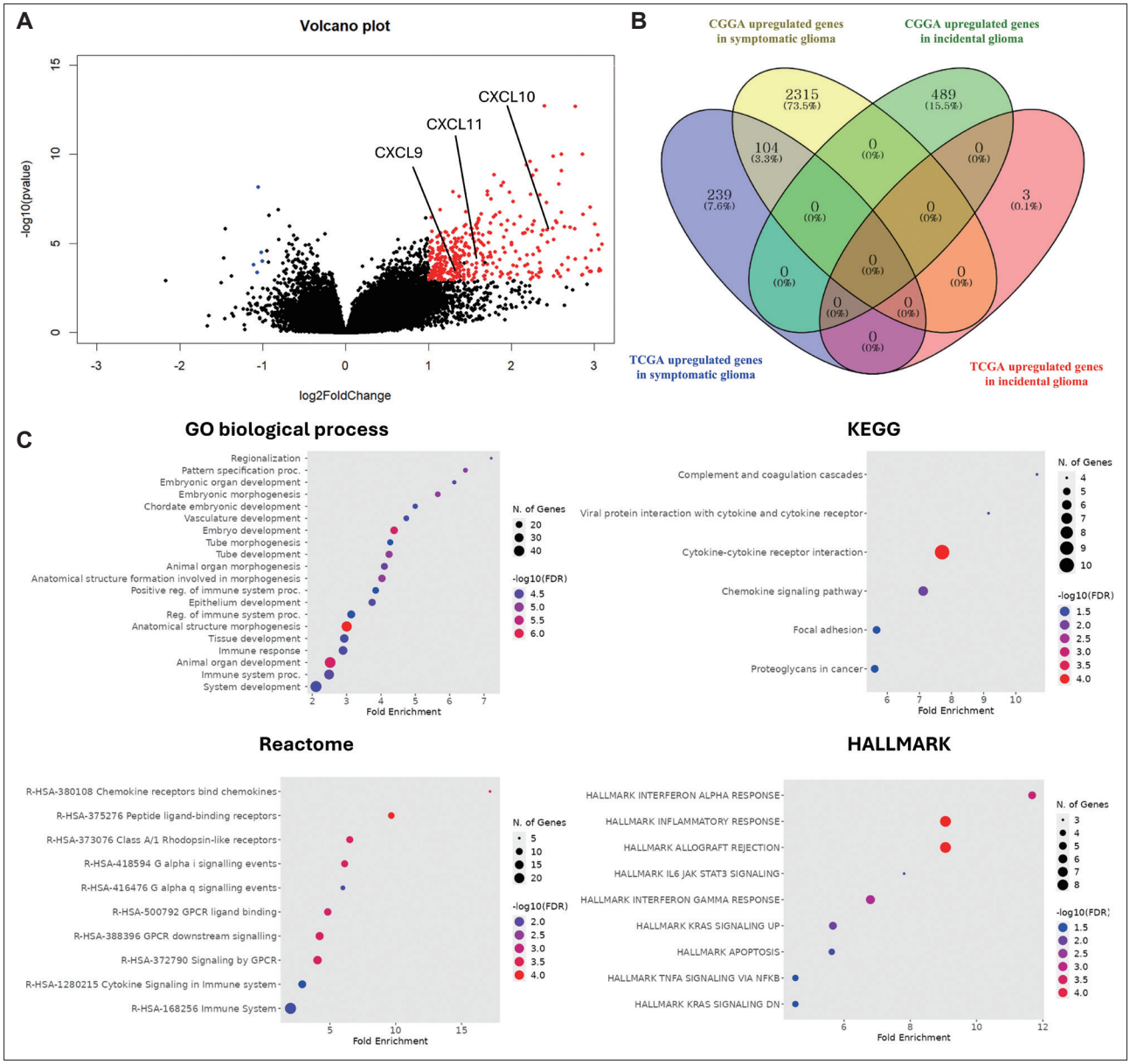

Fig. 2. The result of DEG analysis. A: The volcano plot based on the result of DEG analysis. Blue is genes whose *p*-value is lower than 0.05, red is 0.01. B: The venn diagram based on significantly upregulated genes in symptomatic and incidental glioma with TCGA and CGGA data set. C: The dot plot of gene set enrichment analysis with commonly upregulated genes in symptomatic glioma. DEG, differentially expressed gene; TCGA, The Cancer Genome Atlas; CGGA, Chinese Glioma Genome Atlas; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

monly upregulated in symptomatic gliomas using the GO biological process, KEGG, Reactome, and Hallmark databases to explore the biological significance. The terms that positive regulation of immune system process and immune response in GO biological process, cytokine-cytokine receptor interaction and chemokine signaling pathway in KEGG, chemokine receptors bind chemokine and cytokine signaling in immune system in Reactome, interferon responses, inflammatory response, and TNF-α signaling pathway via NF-kB in Hallmark is significantly enriched in symptomatic glioma (Fig. 2C).

Association of immune microenvironment and poor prognosis in gliomas

Given the association between symptomatic gliomas and immunological pathways, scRNA-seq analysis was performed to investigate the actions and effects in glioma immune microenvironment in perspective of immune response, signaling pathway, and cell-to-cell interactions. Using well-known markers, we identified 11 distinct cell types, including T cells, myeloid cell and oligodendrocytes (Fig. 3A). The single cell GSEA scores of significantly upregulated four Hallmark immuno-

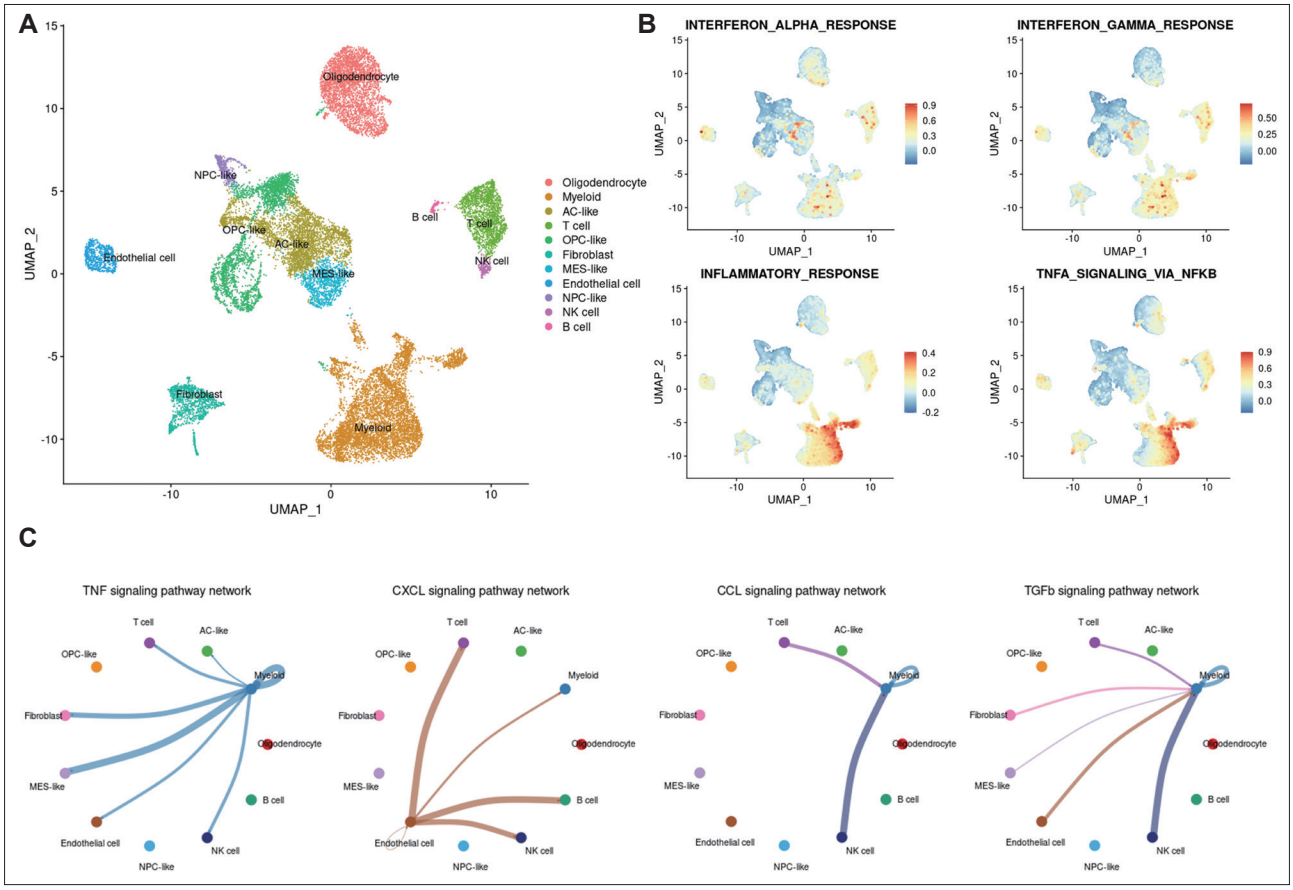

Fig. 3. Immunological landscape of glioma. A: The uniform manifold approximation and projection (UMAP) plot as result of scRNA-seq analysis. AC-like is astrocyte like cells, OPC-like is oligodendrocyte progenitor cell like cells, MES-like is mesenchymal like cells, NPC-like is neural progenitor cell like cells. B: The feature plot of single cell gene set enrichment analysis (GSEA) score of four selected hallmark immunological terms. C: The result of significant immunological cell-to-cell interaction network.

logical terms suggested in Fig. 2C were high in the most of immune cells, but other cell types also contained some high scoring cells (Fig. 3B). A cell-to-cell interaction network analysis was subsequently conducted to determine the immunological interactions between these cell types, revealing four key immunological signaling pathways. Notably, the TNF signaling pathway had a substantial influence on other cell types, especially those derived from myeloid lineage cells, while TGF-β signaling affected myeloid cells from other cell types (Fig. 3C).

Interestingly, TNF signaling pathways are consistently identified during enrichment analysis using four databases, and genes with moderate to strong positive correlation with temozolomide resistance were found to be involved in TNF signaling (Fig. 4A). To further investigate the association between the TNF signaling pathway and prognosis, we conducted a survival analysis. Each TCGA sample was scored using ssGSEA based on genes involved in the Hallmark inflammatory response and TNF-α signaling via the NF-kB pathway. The group with higher scores had significantly poorer prognosis (Fig. 4B).

DISCUSSION

This study compares the molecular and immunological microenvironments of incidental and symptomatic gliomas and explores how these differences impact prognosis and resistance to chemotherapy. Our findings reveal that immunologically significant genes are upregulated in symptomatic gliomas, with myeloid cells exerting significant influence on other cell types via the TNF signaling pathway. This pathway was also positively correlated with temozolomide resistance and poorer prognosis.

Our previous research demonstrated that symptomatic gliomas show increased malignancy at the transcriptome level compared to incidental gliomas, with a greater number of mutations in key glioma-related genes [14]. Symptomatic gliomas also exhibited higher resistance to PCV and temozolomide [9]. In contrast to our previous findings, which focused on the malignancy of tumor cells themselves, this study emphasizes the importance of the tumor microenvironment, particularly the neuroinflammatory response, and its poten-

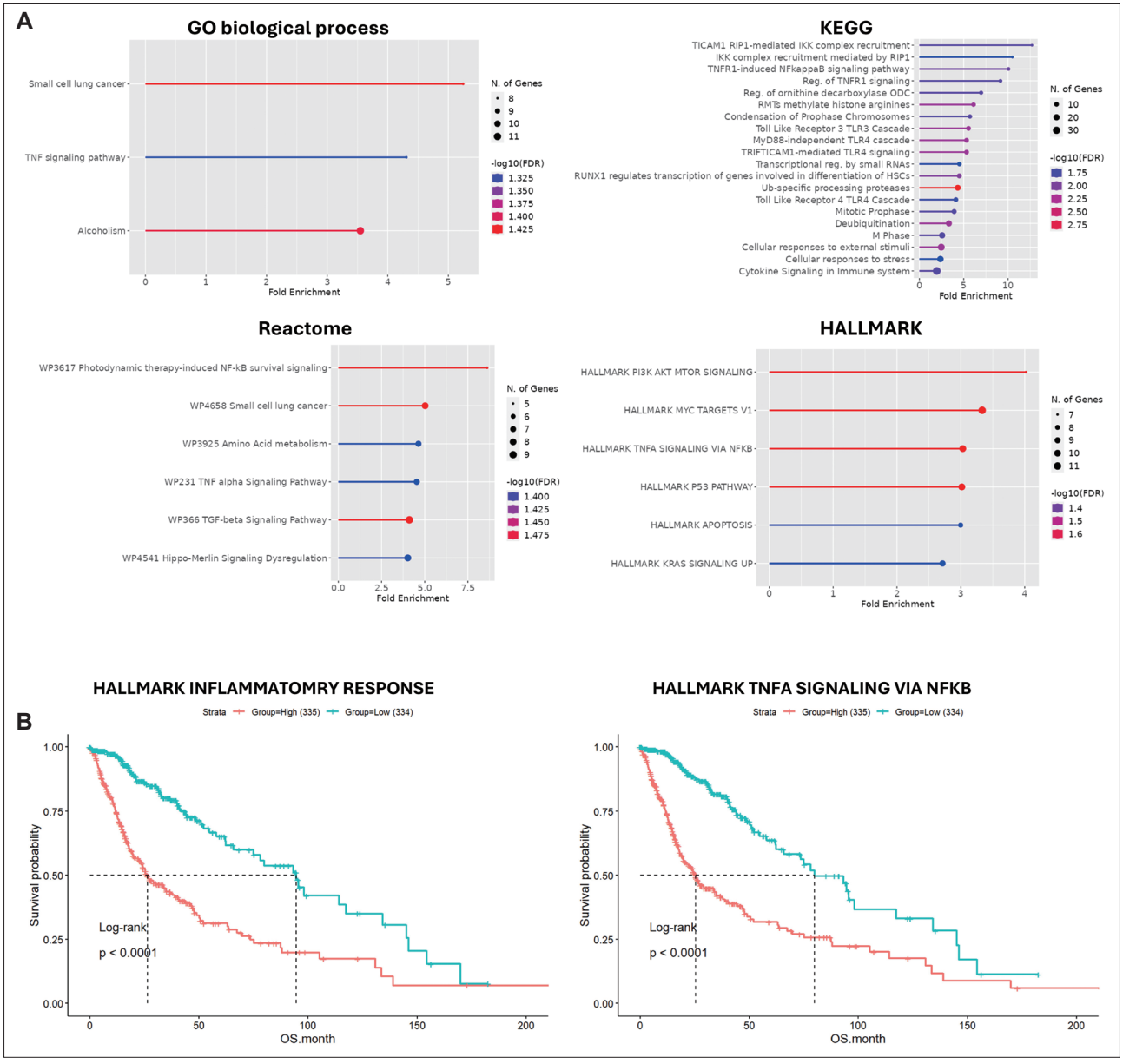

Fig. 4. The association of TNF signaling pathway and poor prognosis of glioblastoma. A: The dot plot of significantly enriched pathways with genes whose expression is positively correlated with temozolomide resistance. B: The Kaplan-Meier curve of two groups divided by ssGSEA score. TNF, tumor necrosis factor; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; OS, overall survival; ssGSEA, single sample gene set enrichment analysis.

tial to predict prognosis.

With the advance of scRNA-seq technology, studies examining the tumor microenvironment in gliomas are becoming increasingly common [19,20]. Our results align with growing evidence that inflammation in gliomas is positively correlated with malignancy [21-28]. This suggests that glioma inflammation may serve as a critical indicator for determining treatment strategies and predicting outcomes in adult-type diffuse gliomas.

Despite the relatively small sample size and lack of experimental validation, our study suggests that symptomatic gliomas increase tumor-associated inflammation, which is linked to poorer prognosis and chemoresistance [29,30]. This supports the argument that, among the two debated strategies for treating incidental gliomas, immediate treatment may improve patient outcomes more than a wait-and-see approach.

Ethics Statement

This retrospective study was performed abiding by the Helsinki Declaration, and the data collected remain anonymous under the principles of human research ethics.

Availability of Data and Material

The datasets generated or analyzed during the current study are available in the Gliovis repository, http://gliovis.bioinfo.cnio.es/.

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Conflicts of Interest

Jaejoon Lim, an associate editor of *Brain Tumor Research and Treatment*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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