Original Article

Expression analysis of human glioma susceptibility gene and *P53* in human glioma and its clinical significance based on bioinformatics

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Background: The exact mechanism of glioblastoma multiforme (GBM) remains unclear. This study was to clarify the expression of *P53* in glioma and its molecular mechanism, and to explore the possibility of *P53* as a potential therapeutic target of glioma and its clinical application value, so as to provide a new theoretical basis for the treatment of glioma.

Methods: Firstly, a dataset was established to analyze the expression of *P53* in different stages of glioma and its relationship with prognosis by using The Cancer Genome Atlas (TCGA) database, RNA-seq data, and survival data of glioma and normal control samples in gene expression profiling and interactive analysis (GEPIA). The genes co-expressed with *P53* were screened out, their differential expression between glioma and normal control group was analyzed, and their functions were analyzed by enrichment analysis. The TGGA database was used for data verification and analysis. The correlation between *P53* expression and clinicopathological parameters was analyzed. Kaplan-Meier survival analysis was used to analyze the relationship between *P53* expression and overall survival (OS) and progression-free survival (PFS) of glioma patients, and Cox regression analysis was used to analyze the independent factors affecting OS and PFS of glioma patients.

Results: The results of TCGA data analysis were as follows: The expression level of *P53* was different from that of different stages of glioma, namely, the expression level of *P53* between grade II and grade III, grade III and grade IV, and grade II and grade IV were significantly different ($P<0.05$). The results of *P53* gene-related survival analysis showed that KNL1 high expression and low expression were significantly different in OS, and the high expression group was associated with poor prognosis ($P<0.05$).

Conclusions: The *P53* expression can be an effective biological indicator of poor prognosis of glioma.

Keywords: Glioma; *P53*; TCGA database; gene; prognosis

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Introduction

Glioma is the most common primary intracranial tumor in adults, accounting for 46–70% of all central nervous system (CNS) tumors (1-3). Epidemiological investigation has shown that the incidence of glioma is increasing year by year, and males are more commonly affected than females. The prognosis of glioma varies with age and pathological type. The 5-year survival rate is low, especially in glioblastoma multiforme (GBM) and elderly patients. The World Health Organization (WHO) has classified gliomas of the CNS as low-grade and high-grade (4). According to this classification, low-grade gliomas are classified into grade I and grade II (5). Grade I tumors are benign and slow-growing gliomas, whereas grade II tumors have the potential to develop into high-grade gliomas. High-grade gliomas can be classified as grade III and IV. Grade III tumors have increased tumor cells and high rates of metastasis and recurrence (6-8). Grade IV glioma has the highest malignant degree, showing high proliferation, metastasis, vasculogenesis, and necrosis. The WHO tumor grade is one of the prognostic factors of treatment outcome. Other factors include the age of the patient, the location of the tumor, the extent of surgical resection, and the proliferation index. The survival rates of patients with grade II and III tumors is 5 years and 2–3 years, respectively (9). Patients with grade IV cancer die of the disease within one year, depending on the effective protocols available (9).

The pathogenesis of glioma is complex, involving risk factors such as ionizing radiation, hereditary syndromes, family history of brain tumors, and immunosuppression (10). However, genetic factors are thought to be the main cause of cancer. P53 gene is the most studied tumor suppressor gene at present, which has powerful functions of regulating cell cycle, repairing DNA after damage and inducing cell apoptosis. As one of the most common mutation genes in brain glioma, the inactivation of p53 gene plays an important role in the progress of brain glioma. A recent study had revealed several major molecular alterations typical for different types of tumors, such as IDH1/IDH2 mutations in diffuse invasive gliomas, TP53 and ATRX mutations in astrocytomas in oligodendrocytomas, mutations in the TERT promoter in oligodendroglioma and IDH wild-type, and BRAF mutations or fusions in astrocytomas, especially in children (10). Identifying those abnormalities in tumors and several other genetic abnormalities is therefore clinically important to help clinicians to determine the right treatment strategy and predict prognosis (11).

At present, the treatment of glioma is mainly surgical resection of the tumor, combined with radiotherapy, chemotherapy, and other comprehensive treatment methods (12). It is recommended that the operation should be safe and achieve the maximum extent of tumor resection. Radiotherapy can kill or inhibit the residual tumor cells and prolong the survival time of patients (13). Glioma has the characteristics of recurrence *in situ*, and 90% of the recurrence occurs within 2 cm from the primary lesion (14). Therefore, optimization of the local radiotherapy regimen is the focus of treatment. Chemotherapy is an effective treatment for glioma. Temozolomide (TMZ) combined with concurrent radiotherapy, followed by 6 cycles of TMZ adjuvant chemotherapy, can prolong the survival time of patients with GBM, increasing the median survival time to 14.6 months. TMZ concurrent radiotherapy combined with adjuvant chemotherapy has become the standard treatment for newly diagnosed GBM. At present, molecular biology, immunotherapy, molecular targeted therapy, and other new therapies are gradually applied in the treatment of glioma (15-17). Molecular targeted therapy is a new therapeutic concept proposed in recent years. Many targeted drugs have been developed for different target molecules. So far, only targeted therapies against angiogenesis have had some effect. For example, it is used alone or in combination for the treatment of lung cancer, esophageal cancer, breast cancer, and other malignant tumors. Among them, bevacizumab is the most common treatment at present. The efficacy of bevacizumab on recurrent GBM is limited to a few phase II clinical trials, but strong clinical data to validate the efficacy is still lacking (18).

Highlight box

Key findings

- The P53 expression can be an effective biological indicator of poor prognosis of glioma.

What is known and what is new?

- The inactivation of p53 gene plays an important role in the progress of brain glioma.
- KNL1 high expression and low expression were significantly different in OS, and the high expression group was associated with poor prognosis.

What is the implication, and what should change now?

- We confirmed that P53 expression can be an effective biological indicator of poor prognosis of glioma. The study of miRNA or lncRNA regulating the P53 was needed.

Co-expression analysis helps to identify genes in the network that lead to disruption of regulatory mechanisms. Gene expression data analysis is widely used in transcriptomic studies to understand the function and intermolecular interactions of intracellular molecules. Co-expression analysis investigated disease and phenotypic variation and found that the co-expression patterns of gene modules varied under different conditions (19). Over the past few years, numerous studies have been conducted to explore the underlying molecular mechanisms, genetics, and developmental pathways of GBM. However, the exact mechanism of GBM remains unclear. In recent years, bioinformatics analysis has attracted extensive attention and made consistent breakthroughs in the search for oncogenes (20). A variety of biomarkers have been discovered for cancer diagnosis and prognosis to better understand the underlying molecular mechanisms of GBM and to search for new potential therapeutic targets. Moreover, the correlation between *P53* expression and clinicopathological parameters and prognosis was poorly studied. Therefore, this study provides more research evidence for GBM based on bioinformatics. Immunohistochemistry (IHC) was used to further observe the expression of *P53* in glioma and its influence on clinical features, pathology, and prognosis. We present the following article in accordance with the STREGA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5646/rc).

Methods

Data download

We downloaded 2 groups of RNA-seq data and clinical data from The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/). The dataset comprised a total of 173 samples which were categorized as patients with GBM (n=156) and normal samples (n=5), and other samples were grouped into unknown groups. In addition, a total of 523 samples were diagnosed as grade II and III gliomas. The data was downloaded in August 2022 (details at: http://www. cgga.org.cn/about.jsp). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data preprocessing

RNA-seq data for the disease in TCGA data were downloaded using the R software TCGAbiolinks in R (The R Foundation for Statistical Computing, Vienna, Austria). The ENSEMBL ID in RNA-seq is re-annotated using the GTF annotation file in GENCODE (https://www.gencodegenes.org/) to obtain the corresponding gene symbol. At the same time, messenger RNAs (mRNAs) in the data were screened out according to the information in the annotation file. Since multiple ENSEMBL IDs in the data may correspond to the same gene symbol, its average value was obtained as the unique expression value corresponding to the mRNA. Disease survival information and clinical data were obtained from cBioPortal (https://www.cbioportal.org/).

P53 expression and different cancer stages

The R software GGPUBR package was used to a draw violin map of *P53* gene expression in glioma samples according to clinical information, and to mine the expression of *P53* in different cancer stages of WHO grade (Grade II-IV). The glioma samples were grouped and plotted separately. If WHO grade clinical data of cancer stage are missing from a sample, the sample was not included in the figure for that stage type.

Gene-related survival analysis

The Kaplan-Meier survival curve is one of the promising methods for predicting survival and prognostic value. An online database containing microarray data sets. According to the expression level of *P53* among samples, the total samples were divided into 2 groups: high expression samples and low expression samples. Secondly, according to the downloaded survival data, R and survival were used to analyze the survival of *P53* gene and low-grade glioma (LGG) + GBM samples. The Kaplan-Meier survival curve was drawn, and the log-rank test was performed to determine whether there was any difference between groups.

Gene regulatory network

The Pathway Commons Network Visualizer (PCViz) is an efficient public network visualization tool online platform which can be used to link targets to interacting genes. We used the PCViz website (http://www.pathwaycommons.org/pcviz/) to construct a regulatory network including the *P53* gene and the genes interacting with it. By inputting the

name of the *P53* gene, we could obtain all of its interacting genes. The top 50 genes were selected to construct the final gene regulatory network. The network also included the following types of functions: regulating protein state changes, regulating gene expression, and regulating phosphorylation in the same protein complex.

Gene co-expression analysis of the regulatory network

Based on the calculation method of Spearman's correlation coefficient, the co-expression relationship between *P53* and other genes in the regulatory network was analyzed. The correlation coefficient r>0.75 and P<0.05 were used as the threshold of the screened co-expression relationship. The ggpubr package (https://cran.rproject.org/web/packages/ggpubr/index.html) was applied to draw the correlation map of gene expression.

Differential analysis of co-expressed genes

Co-expression analysis is increasingly used to study the global transcriptional mechanisms underlying phenotypic changes. There were not enough blank samples in TCGA to test whether co-expressed genes were differentially expressed in GBM samples versus normal samples and LGG samples versus normal samples, so gene expression profiling interactive analysis (GEPIA) was used (http://gepia.cancer-pku.cn/detail.php). The database was used to screen the differentially co-expressed genes in the 2 comparison groups. GEPIA provides the normal sample data of TCGA as well as the normal samples in Genotype-Tissue Expression (GTEx). The process was as follows: select *P53* gene, set $|\log_2 FC| = 1.585$ (fold change =3), P=0.05, select LGG and GBM for datasets, and obtain the corresponding box line diagram of *P53*. The genes were replaced with other genes co expressed with *P53*, and the corresponding box plots were drawn respectively.

Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analysis

We used the following databases to extract the biological functions of many genes: Database for Annotation, Visualization and Integrated Discovery (David), GO, and the KEGG. The R software cluster profiler package was used to analyze the enrichment of KEGG and GO biological process (BP) of P53 and the above differentially co-expressed genes and a bubble chart was used to display the results. On the basis of KEGG pathway/GO terms, all GO terms involved in *P53* were displayed. A P value <0.05 represented the significance of GO or pathway entries. The significantly enriched functional analysis results were visualized by David.

Statistical analysis

The statistical software SPSS 23.0 was used for data analysis. Chi square test was used for the expression of *P53* in glioma and normal tissues; the correlation between *P53* expression and clinicopathological parameters in glioma specimens was tested by chi square test; the correlation with Ki-67 in tumor tissue was analyzed by Spearman rank correlation analysis. Kaplan-Meier survival analysis was used to observe the effect of *P53* expression on progression-free survival (PFS) and overall survival (OS) of malignant glioma patients during the follow-up period, and log rank analysis was used to compare the significant differences between the groups; Cox regression model was constructed to analyze the relationship between *P53* protein expression level, general clinical factors, and patient prognosis (PFS and OS). The difference was considered statistically significant when P<0.05.

Results

P53 gene expression and different cancer stages

Among the data downloaded from TCGA, 60,483 probes were aligned to ensemblID. When the annotation file was used, a total of 19,600 mRNAs were found in the dataset, and a total of 19,579 different genes were screened. The amount of *P53* expression was grouped using the glioma grade (grade II-IV, not included in grade I) in the clinical information (*Figure 1*).

P53 gene-related survival analysis

The Kaplan-Meier plotter (http://www.kmplot.com) was used to evaluate the relationship between *P53* gene expression and GBM clinical prognosis. LGG and GBM samples were divided into a high expression group and low expression group according to the median expression value of *P53*. From the survival curve, it can be seen that there was a significant difference between high expression *P53* and low expression *P53* in the OS period, and the high expression group was associated with poor prognosis

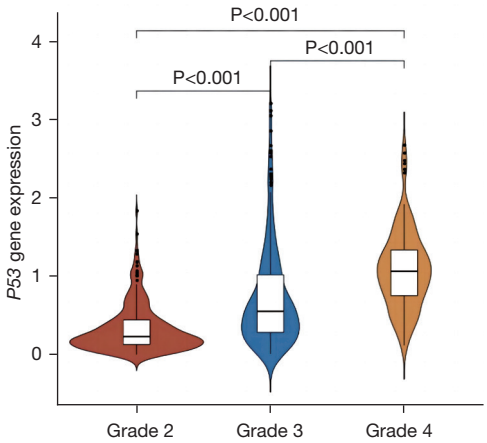

Figure 1 Violin plot to compare the relationship between *P53* expression and glioma grade (it showed that *P53* expression increased with the increase of grade).

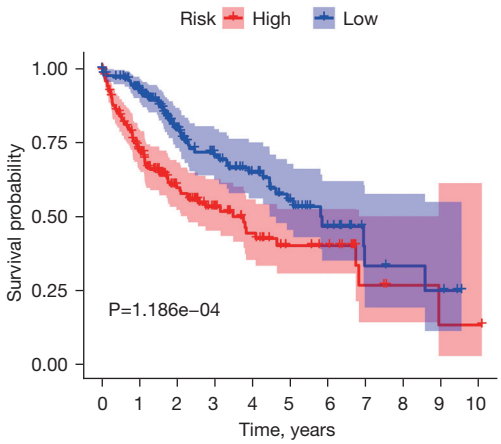

Figure 2 *P53* survival curve analysis. There was a significant difference between high expression *P53* and low expression *P53* in the OS period. OS, overall survival.

(P<0.05) (*Figure 2*).

Gene regulatory network

A total of 172 genes and 8,422 interaction relationships were obtained by inputting the *P53* gene into the PCViz website. The first 50 closely related genes were selected to display the *P53* family related regulatory network. The gene regulatory network contains 3 relationships with *knl1*, for example, *INS*, *CREB1*, and other genes can regulate the expression of *knl1* gene. It was shown that *CDK1*, *CDC42*, and *CCNB1* can regulate the state change of *P53* (*Figure 3*).

Gene co-expression analysis in the regulatory network

In order to confirm the relationship between *P53* and the genes in the above regulatory network, Spearman's test was performed to analyze the co-expression of 50 genes in all regulatory networks. With P<0.05, |R|>0.75 as the screening threshold, a total of 4 genes co-expressed with *P53* were obtained: *ZWIN*, *PLK1*, *NDC80*, and *MAD2L1*, and it was found that the screened genes were positively correlated with the expression of *P53* (*Figure 4*).

KEGG and GO enrichment analysis

In order to further learn the role of *P53* in glioma, KEGG enrichment analysis and GO BP were performed on the 17 differentially expressed genes (DEGs). The most significant KEGG pathway was cell cycle and oocyte meiosis; however, *knl1* was not enriched to any KEGG pathway. GO BP terms with significant enrichment of co-expressed DEGs included chromosome aggregation, mitotic sister chromatid aggregation. The mitotic sister chromatid aggregation term contained 14 proteins, including *P53* (*Figure 5*).

Heat map analysis

In the first part of the article, the authors systematically studied the relationship between the pathological characteristics of glioma such as WHO grade, IDH status, co-deletion status, and EMT, because previous studies had shown that *P53* is closely related to the malignant degree of glioma. Relevant studies have considered the possible relationship between lymphocyte infiltration and tumor prognosis. Most of the cells infiltrating the tumor are T cells, and the degree of lymphocyte infiltration in the primary tumor is positively correlated with tumor metastasis (*Figure 6*).

Correlation analysis of immune infiltrating cells

Tumor immune cell infiltration refers to the infiltration of immune cells from the blood to the tumor tissue, which can be separated from the tumor tissue. The infiltration of immune cells in tumors is closely related to clinical outcomes. The infiltrated immune cells in tumors are most likely to be used as drug targets to improve the survival rate of patients (*Figure 7*).

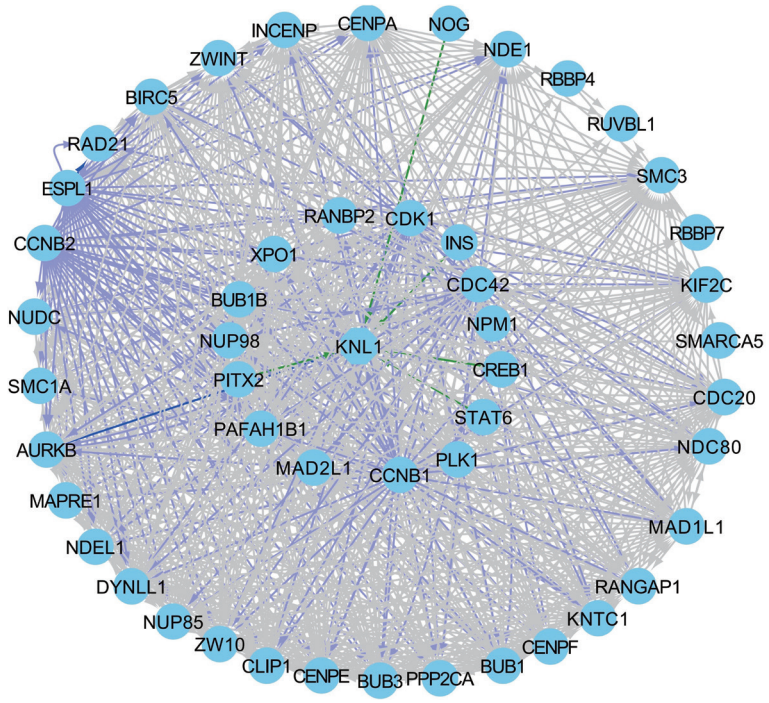

Figure 3 *P53* gene regulatory network. It showed that *CDK1*, *CDC42*, and *CCNB1* can regulate the state change of *P53*.

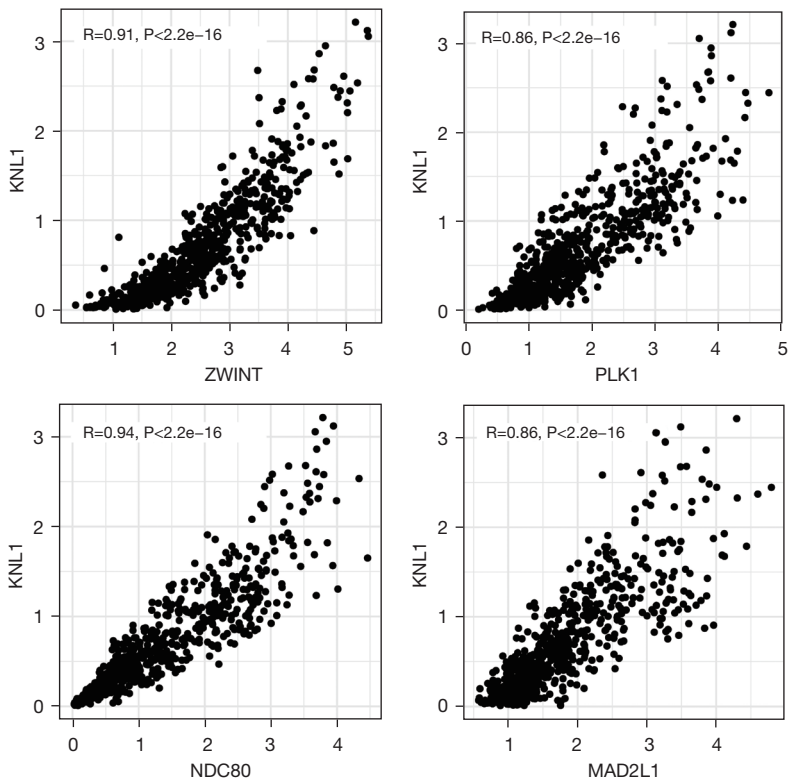

Figure 4 Correlation analysis of *P53* and co expressed genes in regulatory network. Four genes co-expressed with *P53* were obtained: *ZWIN*, *PLK1*, *NDC80*, and *MAD2L1*, and it was found that the screened genes were positively correlated with the expression of *P53*.

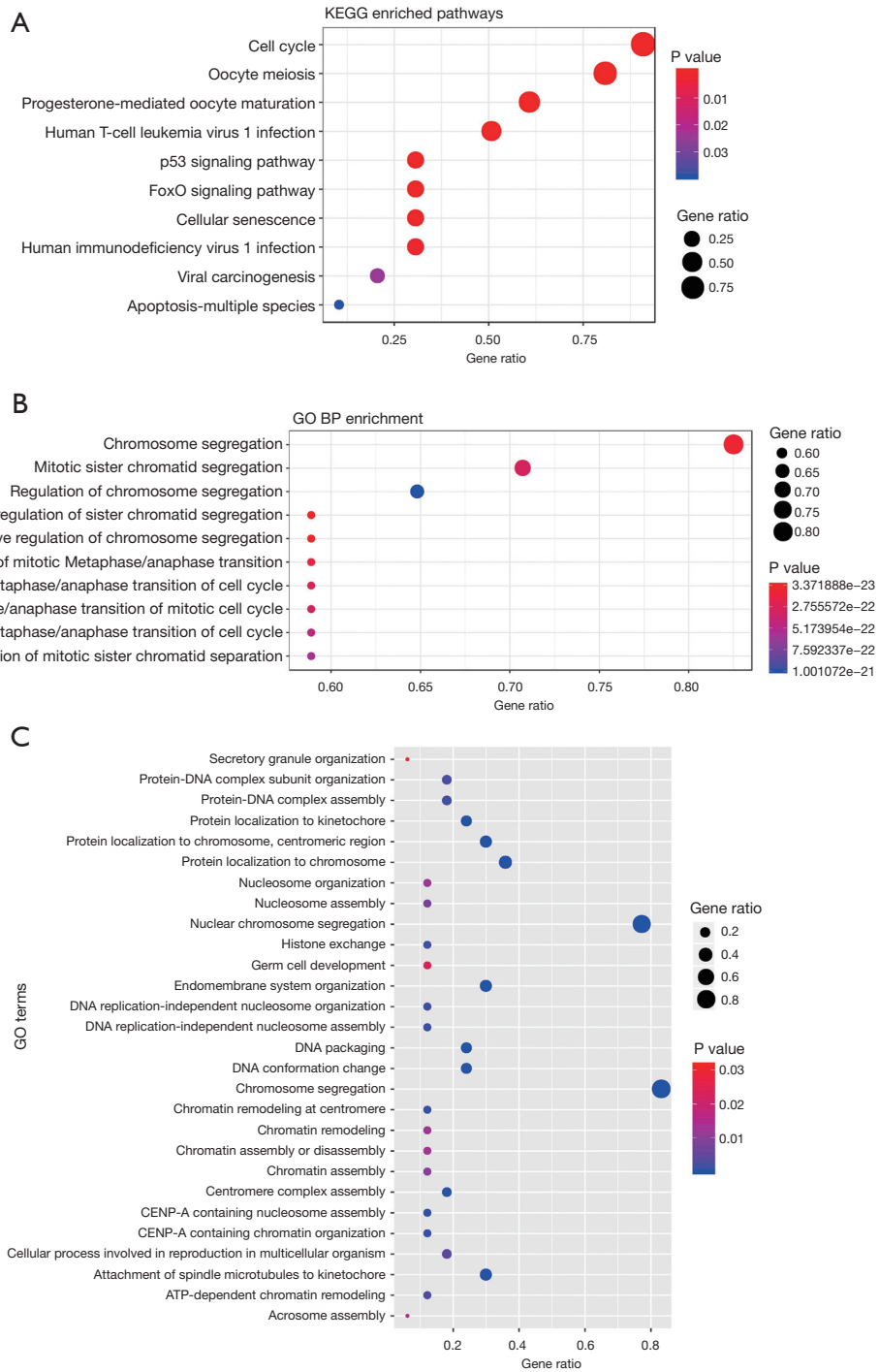

Figure 5 Enrichment analysis of differentially co-expressed genes within *P53* and other regulatory networks. (A) KEGG enrichment analysis results, showing the pathway of top 10. (B) GO BP enrichment analysis results, showing the GO terms of top 10. (C) *P53*-related GO term enrichment results. KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, Gene Ontology; BP, biological process.

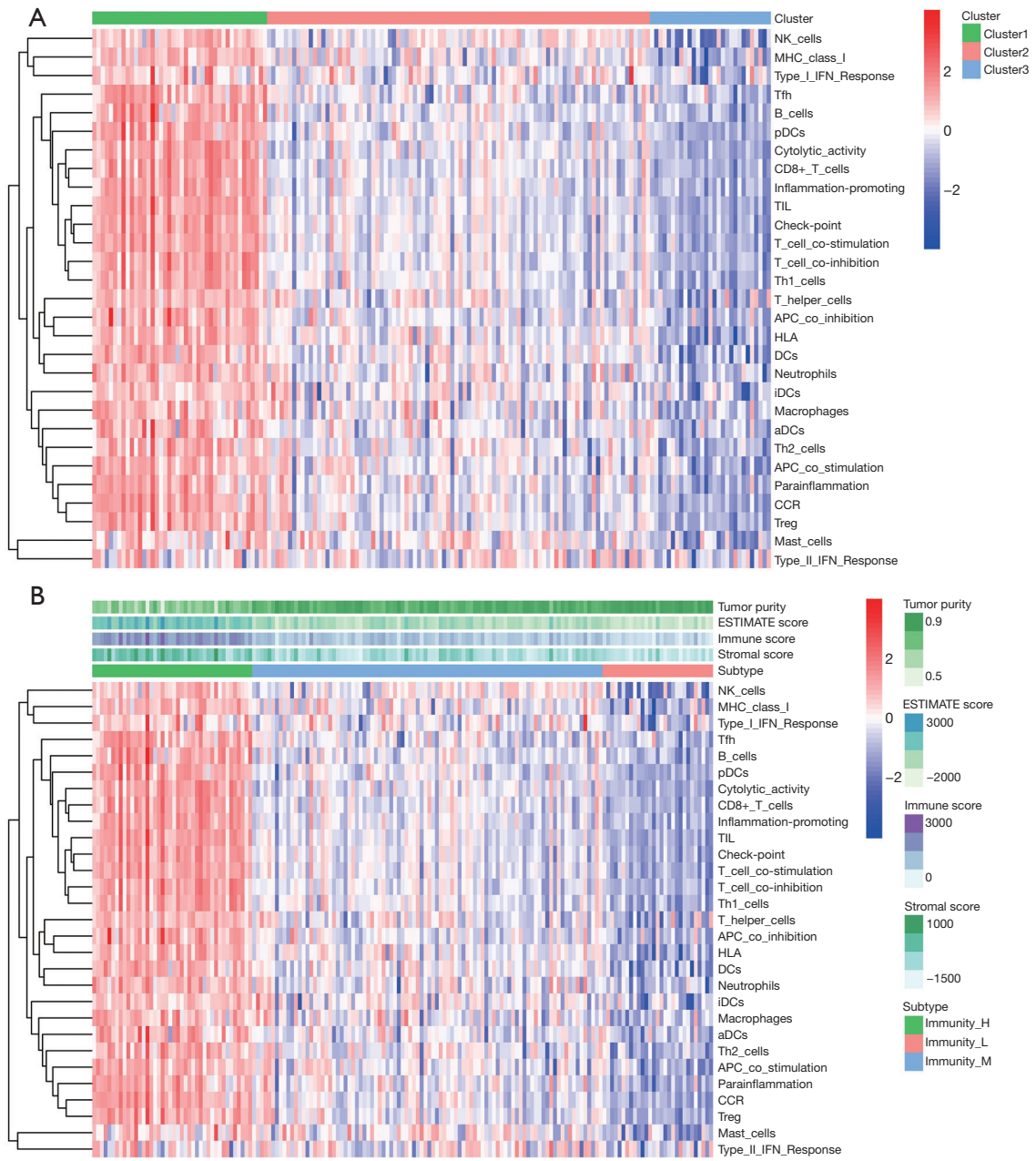

Figure 6 Heat map analysis. Most of the cells infiltrating the tumor are T cells, and the degree of lymphocyte infiltration in the primary tumor is positively correlated with tumor metastasis.

GSEA analysis

The input of GSEA is a gene expression matrix, in which the samples are divided into 2 groups: A and B. First, all genes are sorted. In a simple summary, GSEA is designed to sort from large to small according to the difference multiplier value after treatment, which is used to indicate the change trend of gene expression between the 2 groups. The top of the sorted gene list can be regarded as the up-regulated DEGs, and the bottom is the down-regulated

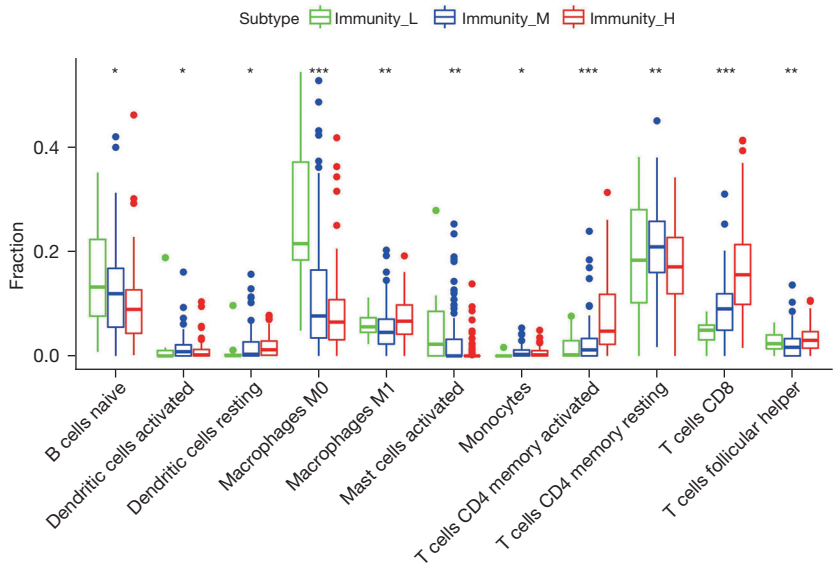

Figure 7 Analysis of the relationship between tumor and immune cell infiltration. The infiltration of immune cells in tumors is closely related to clinical outcomes; *, P<0.05; **, P<0.01; ***, P<0.001.

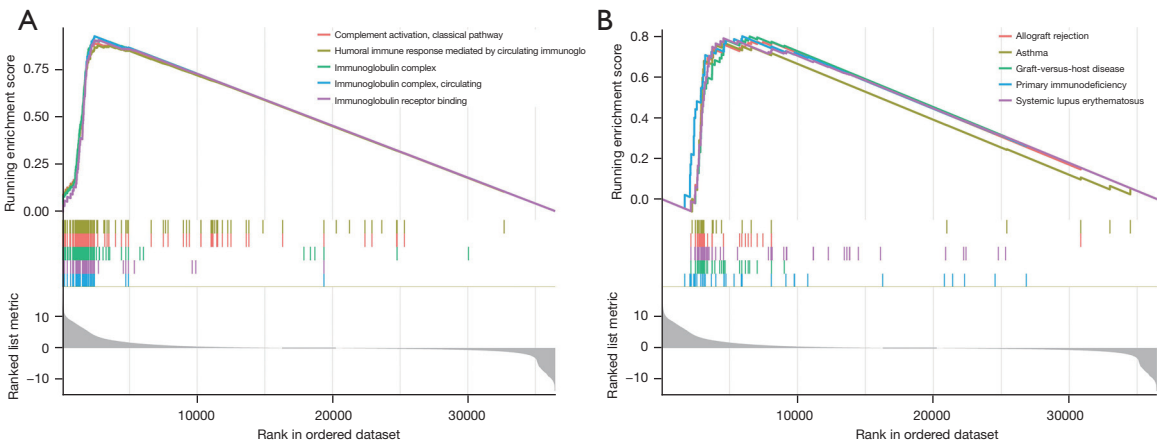

Figure 8 GO of GSEA analysis (A); KEGG of GSEA analysis (B). The top of the sorted gene list can be regarded as the up-regulated DEGs, and the bottom is the down-regulated DEGs. GO, Gene Ontology; GSEA, gene set enrichment analysis; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes.

DEGs (*Figure 8*).

Discussion

Glioma is the most common brain tumor in adults, accounting for about 40–60% of primary intracranial tumors (21). The incidence rate shows a trend of further increase, with an annual growth rate of about 1–2%. Astrocytes, oligodendrocytes, and ependymal gliomas account for more than 70% of all brain tumors (22). Among all malignant gliomas, GBM is the most common and malignant tissue type, with a higher incidence in males than females. It is more common in the elderly, followed by diffuse astrocytes (23). At present, the main treatment for glioma is surgery combined with radiotherapy and chemotherapy, which can prolong the survival period to a certain extent. However, due to the characteristics of rapid recurrence and drug resistance of high-grade glioma, the

one-year survival rate is about 30% (24). In recent years, some new therapies have been widely developed, such as immunotherapy, gene therapy, and targeted therapy, which have brought new hope to the treatment of glioma; however, the effect has not reached the expectation and the prognosis remains very poor. Therefore, it is of great significance to study the mechanism of glioma and explore the possible therapeutic targets for clinical treatment and improving prognosis (25). At present, the occurrence and development of glioma are driven by the dynamic changes of gene pathway activity and connectivity. Revealing these dynamic events is necessary for understanding the pathological mechanism of glioma and developing effective therapeutic methods (26). The mutation rate of *p53* gene in malignant glioma is 35–60%. The aim of this study was to investigate the abnormal genes closely related to the occurrence of gliomas and to determine whether the expression of *P53* is significantly different with different cancer stages (27).

Thanks to the rapid development of bioinformatics (28), a previous study has found that the high expression of *P53* is closely related to the progression and prognosis of lung cancer, colorectal cancer, and gastric cancer (29). Through IHC, we found that the expression of *P53* in glioma was higher than that in normal brain tissue. A total of 74 cases (62.18%) of glioma cells showed positive expression. However, in the control group, there were 2 cases (10%) of *P53* positive expression. There was a significant difference in the expression between the glioma group and the control group. The expression of *P53* was also different in different grades of gliomas (30). The positive expression of *P53* in high grade gliomas was higher than that in low grade gliomas. Our results were consistent with these findings. However, the correlation between *P53* expression and clinicopathological parameters and prognosis was not further studied. Therefore, *P53* expression was also analyzed in this study. There were differences between the positive and negative expression of *P53* in Karnofsky performance scale (KPS) score, WHO grade, and age of patients. This indicated that the positive expression of *P53* was higher than the negative expression in KPS, WHO grade, and age ($P<0.05$) (31-33). In addition, we analyzed whether there was a correlation between the expression of *P53* and the prognostic molecule Ki-67. The results showed that the poorly differentiated gliomas had a high expression of Ki-67, and the gliomas with P53 positive expression had a significant correlation with the high expression of Ki-67 (34). In the evaluation of prognosis, Kaplan-Meier was first applied to analyze the relationship between the expression of P53 and the PFS and OS of glioma patients. We found that the positive expression of P53 was closely related to the clinical prognosis of glioma patients (35). Glioma is one of the most immunosuppressive solid tumors. The ability of glioma to cause severe systemic T cell defects is one of its most prominent and earliest reported immune effects. We also found that the infiltration of immune cells in tumors was closely related to clinical outcomes.

Limitations

This study also had some limitations: (I) the sample size of this study is small, and the time to analysis of pathological tissue was long. The staining effect may have been distorted or flaked, leading to the possibility that the expression rate of P53 protein was low. It was a single center study, and the conclusion needs further confirmation; (II) the occurrence, development, and mechanism of P53 in gliomas were not studied in this study, which needs to be further explored in the future. Therefore, P53 as a prognostic indicator and potential immunotherapeutic target in glioma deserves further study; (III) we failed to study the miRNA or lncRNA regulating the P53; (IV) finally, in vivo and in vitro experimental were also needed to confirm these findings.

Conclusions

The innovation of this study is to propose the correlation between P53 expression level and clinicopathological parameters and prognosis of glioma for the first time, and confirm that P53 expression can be an effective biological indicator of poor prognosis of glioma. At the same time, P53 related indicators may also become new therapeutic targets.

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Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5646/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.

amegroups.com/article/view/10.21037/atm-22-5646/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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