The Predictive and Therapeutic Role of Complement in Gliomas

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Abstract

Background

The human complement system plays an essential role in innate immunity in the tumor microenvironment. However, the exact function of complement in gliomas progress is still ambivalent and unclear.

Methods

A total of 194 complement genes were included in our study to build a risk score model based on the CGGA database and was verified by the validation database and our sequencing data. Kaplan-Meier analysis was used to compare survival differences between groups. CIBERSORT and ESTIMATE algorithms were applied to explore immune infiltrates in the tumor microenvironment. The biological processes and functions were identified by GO and KEGG analysis.

Results

We build a risk score model using univariate and multivariate Cox regression analysis based on the CGGA database and verified in the TCGA database. Patients with gliomas in the low-risk group have a better prognosis and were associated with low grade, 1p19q codeletion, IDH mutant status, MGMT promoter methylation. In addition, the low-risk group is prone to have more infiltration of CD4 naive T cells and monocytes. Patients with gliomas in the low-risk group exhibit temozolomide sensitivity. Moreover, we explored several vital pathways that were associated with complement genes in this study.

Conclusion

Complement-related gene signature can predict the malignancy and outcome of patients with gliomas and was related to temozolomide sensitivity, which might act as a promising target for gliomas therapy in the future.

Introduction

Gliomas are the most common type of central nervous system cancers and have high mortality and mortality among young adults[1, 2]. They are heterogeneous primary brain tumors that differ in grade, histology, and genomic characteristics[3]. The 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System grouped gliomas into different subtypes based on 1p/19q codeletion, IDH mutation, MGMT promoter methylation[4, 5]. Unfortunately, even with current standard therapies, including surgical resection, radiation, and chemotherapy, the prognosis of gliomas is still unsatisfied[6, 7]. Especially in patients with glioblastoma (GBM), the overall survival (OS) of GBM is still a

disappointing 10–12 months, and less than 5% of patients can survive than five years following diagnosis[8, 9].

The tumor microenvironment (TME), composed of cytokines, chemokines, extracellular matrix, malignant and transformed cells, plays a vital role in tumorigenesis, progression, metastasis, recurrence, and drug resistance[10, 11]. Increasing evidence indicates that the complement system as an irreplaceable part of the innate immune system is related to the immune surveillance and inflammatory processes in TME[12–14]. There are three traditional complement activation pathways: the lectin pathway (LP), the alternative pathway (AP), and the classical pathway (CP). Both stromal and tumor cells in the TME can secrete complement during tumorigenesis and progression[15, 16]. Furthermore, studies found that the expression levels of complement and key-proteins of complement activation pathways were upregulated in gliomas microenvironment[17, 18]. However, the influence of the complement system on gliomas' pathology remains unclear.

This study selected complement genes from the GSEA-MSIGDB database and built a risk model based on the CGGA database. We found that patients in the low-risk group were prone to have more favorable gliomas clinicopathologic features and a better outcome. We also explored the immune infiltration in TME between high-risk and low-risk groups. Moreover, the reliability of this risk model was verified by the TCGA database and our sequencing data from gliomas. In addition, we found that patients in high-risk groups exhibit temozolomide (TMZ) resistance which might provide a new direction for treating gliomas with TMZ.

Materials And Methods

Sample and clinical data

The clinical and RNA sequencing (RNA-seq) data from CGGA (<http://www.cgga.org.cn/download.jsp>) [19, 20] was selected as our training cohort, and data from TCGA (<http://cancergenome.nih.gov>) was used as our validating cohort. Meanwhile, a total of 24 clinical and RNA sequencing (RNA-seq) data from adult glioma patients who underwent neurosurgery at the Department of Neurosurgery, Xiangya Hospital, were included in the study, of which 18 received temozolomide (TMZ) treatment after surgery. Informed consent of all subjects has been obtained in this study.

Gene signature building

The complement gene list was downloaded from the GSEA-MSIGDB database (<http://www.gsea-msigdb.org/gsea/msigdb/index.jsp>). The risk score model was built by Univariate Cox analysis first with genes' P values less than 0.1. Multivariable Cox proportion hazard regression models were then used to investigate the relationship between risk scores with clinicopathologic features. Next, we grouped these samples into the low-risk and high-risk groups according to their risk scores in the CGGA database. The risk score was expressed as: gene 1 (expression × coefficient) + gene 2 (expression × coefficient) + gene 3 (expression × coefficient).

Related characteristics analysis

The log-rank test's Kaplan-Meier (KM) analysis compares patients' overall survival (OS) in low-risk and high-risk groups. CIBERSORT[21] and ESTIMATE[22] algorithms were applied to explore immune infiltrate in the tumor microenvironment. The Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases were applied to examine the enrichment pathways. R(version: 4.0.4) was used to study the clinicopathologic features (grade, IDH1 mutant status, glioma subtype, 1p19q codeletion, and MGMT promoter methylation) between low-risk and high-risk groups.

Statistical analysis

A log-rank test was performed to compare OS between different groups. Meanwhile, the student's t-test was applied to compare two groups, and ANOVA analysis was used to compare multiple groups. All statistical tests were two-sided, and $p < 0.05$ was considered a significant difference. All analyses were performed under the R language.

Results

Build risk model based on the expression of complement genes in the CGGA database and verified in the TCGA database

First, a total of 194 complement genes was chosen from the GSEA-MSIGDB database to construct gene signature (Supplement Table 1). Then we build a gene-based risk model from the CGGA database using univariate and multivariate regression analysis. Consequently, an eight-gene signature was selected, and the risk score as follows: $(-2.670 \times \text{GPD2 expression}) + (-0.297 \times \text{LGMN expression}) + (-0.391 \times \text{KCNIP3 expression}) + (-0.002 \times \text{ANXA5 expression}) + (-0.003 \times \text{C1R expression}) + (0.029 \times \text{RAF1 expression}) + (0.061 \times \text{GNAI3 expression}) + (-0.124 \times \text{ZEYVE20 expression})$. The Kaplan–Meier curve for the CGGA database indicated that patients in the low-risk group from the CGGA database had a significantly longer OS than high-risk group patients in the WHO low-grade glioma (LGG), GBM, and glioma (Fig. 1A). The consistency of results was validated for the TCGA database in the GBM and glioma (Fig. 1B). Then, we analyzed the relationship between complement gene signature and clinicopathological characteristics, including WHO grade, IDH1 mutation, MGMT promoter methylation, 1p19q codeletion, tumor subtypes in the CGGA database (Fig. 2A) and TCGA database (Fig. 2B). Results showed that glioma patients with higher risk scores are prone to have a higher WHO grade, 1p19q non-codeletion, IDH WT status, classical and mesenchymal subtypes both in the CGGA (Fig. 2C) and TCGA (Fig. 2D) databases.

The immune landscapes of patients in low-risk and high-risk groups from the CGGA and the TCGA databases

Next, we explored the tumor purity, estimate score, stromal score, tumor score, and immune cells infiltration in the TME in low-risk and high-risk groups from the CGGA and the TCGA databases (Fig. 3). Patients in the high-risk group from the CGGA database have a lower tumor purity and a higher estimate

score, stromal score, tumor score than the low-risk group (Fig. 3A). The consistency of results was also validated in the TCGA database (Fig. 3B). CIBERSORT algorithm revealed fewer M0 macrophages and more CD4 naive T cells and monocytes in the low-risk group from the CGGA database (Fig. 3C). In addition, the results from the TCGA database indicated the expression of several immune cells such as naive B cells, plasma cells, CD8 T cells, CD4 T cells, NK Cells et al. were also significantly different from low-risk and high-risk groups (Fig. 3D).

The immune aspects in the tumor microenvironment from our sequencing data and enrichment pathways related to the complement genes

Then, to test the reliability of the risk score model, we validation the immune results using our sequencing data (Fig. 4). The data showed that patients in the high-risk group from our sequencing data have a higher estimate score, stromal score, tumor score than the low-risk group (Fig. 4A-C). Moreover, the patients in the high-risk group exhibit TME resistance (Fig. 4D). In addition, patients in the high-risk group have more infiltration of follicular helper T cells, monocytes, M2 macrophages, and less infiltration of memory resting CD4 T cells, M0 macrophages in the TME (Fig. 4E).

To investigate the function of the complement genes in gliomas, we analyzed the biological process, cellular component, molecular function, and enrichment pathways from the GO and KEGG databases (Supplement Fig. 1). The KEGG enrichment analysis indicated that the top five enrichment pathways were complement and coagulation cascades, Kaposi sarcoma-associated herpesvirus infection, pertussis, chemokine signaling, tuberculosis (Supplement Fig. 1A). In addition, the GO enrichment analysis showed that the most biological processes were coagulation, regulation of body fluid levels, blood coagulation, hemostasis, and regulation of inflammatory response (Supplement Fig. 1B); the cellular components were enriched mainly in the extracellular matrix, collagen-containing extracellular matrix, secretory granule lumen, cytoplasmic vesicle lumen and vesicle lumen (Supplement Fig. 1C); the most related molecular function were endopeptidase activity, serine-type peptidase activity, serin hydrolase activity, serine-type endopeptidase activity and enzyme activator activity (Supplement Fig. 1D).

Discussion

This study discussed the relationship between the expression of complement genes and clinicopathologic characteristics in gliomas. First, we analyzed the clinical prognosis and immune aspects of complement genes and then build a risk-score model based on the CGGA database and validated it in the TCGA database and our sequencing data. The results indicated that a higher risk score was significantly related to worse clinicopathologic features, including higher gliomas WHO graded, 1p19q non-codeletion, IDH WT status, and was more common in classical and mesenchymal subtypes both in the CGGA and TCGA databases. Meanwhile, patients in the high-risk group have a higher estimate, stromal, and tumor scores than the low-risk group in the public database and our sequencing data. Significantly, the patients in the high-risk group are prone to show TMZ resistance. These results

demonstrated that complement genes played a vital role in the malignancy of gliomas and were associated with TMZ sensitivity, which might provide a promising target for gliomas in the future.

Both highly malignant tumor cells and their resistance to the immune system contribute to the unfavorable prognosis of patients with gliomas. Extracellular matrix components and stromal cells, including microglia/macrophages, T cells, B cells, neurons, endothelial cells, and B cells, construct a micro-environment that connects glioma cells [23, 24]. These cells produce various kinds of cytokines and immunoglobulins. The complement system is an essential immune suppressor that prohibits gliomas cells from being cleared by the innate immune system. The complement system in the brain has become a key regulator in CNS hemostasis, especially in the progress of neurogenesis and synaptic pruning [25, 26]. Various cells in the CNS were found to produce complement proteins, such as astrocytes, neurons, microglia/macrophages, oligodendrocytes, and ependymal cells [27]. Activation of the complement system is involved in many CNS diseases, including Alzheimer's disease, brain inflammation, tumor, and brain injury [17, 28]. Tumor-associated macrophages (TAMs) in the tumor micro-environment also can secrete various complement proteins, which led to immunosuppression and thus promoting glioma cell proliferation. In a recent study, Alessandro Mangona et al. found that the expression levels of C1q synthesized by CD68 and CD163 positive infiltrating macrophages synthesized in the tumor microenvironment contribute to a poor outcome in LGG [29].

In addition, the complement system has a close relationship with the immune checkpoints in the tumor micro-environment. Pentraxin-related protein 3 (PTX3) exhibits a tumor suppressor role by interacting with C1q and inhibiting complement activation, resulting in lower C5a expression, immune cells infiltration, and angiogenesis [30]. Antibody blocking C5a receptor significantly prohibits the infiltration of myeloid-derived suppressor cells and the expression of immune suppressors ARG1, CTLA-4, LAG3, and PD-L1 [31], which impaired tumor growth. Thus, blockages targeting the complement pathway in the tumor microenvironment have become a promising therapeutic method in many cancers [32, 33] [34]. TMZ-based chemotherapy has provided survival benefits in the treatment of patients with gliomas [35]. However, studies indicated that more than 60% of patients with GBM exhibit no help from the treatment with TMZ [36]. TMZ resistance remained a significant limitation in the treatment of gliomas and led to the unsatisfied outcome [37, 38]. In this study, we build an eight complement genes-based risk model and found the effect of TMZ treatment was significantly increased in the low-risk group. This result shows that these genes are involved in mechanisms affecting TMZ sensitivity, which might provide a new direction for in-depth study on the signaling pathways of TMZ resistance.

There are several limitations to this study. Firstly, our study is still far from clarifying the relationship between these gene expressions and TMZ sensitivity; more studies need to be included in the future. Secondly, this study does not reveal the actual function and signaling pathways involved in complement activation in the TME. Thirdly, the role of complement genes in regulating immune infiltration has not been explored through in vivo and in vitro studies.

In conclusion, our study explored the expression and clinical features of complement genes in gliomas. It provided a promising prognostic predict risk model for patients with gliomas based on complement-related gene signature. This study will also contribute to thoroughly clarifying the complement system's fundamental role in the gliomas microenvironment and provide novel immunotherapy targets against gliomas in the future.

Abbreviations

CGGA: ; Chinese Glioma Genome Atlas; TCGA: The Cancer Genome Atlas; GO: Gene Ontology Term Enrichment; KEGG: Kyoto Encyclopedia of Genes and Genomes; IDH: Isocitrate dehydrogenase; MGMT: O6-Methylguanine-DNA Methyltransferase; GBM: Glioblastoma; OS: Overall survival; WHO: World Health Organization; TME: Tumor microenvironment; TAMs: Tumor-associated macrophages; TMZ: Temozolomide; KM: Kaplan-Meier; CNS: Central nervous system; LGG: Low-grade glioma; PTX3: Pentraxin 3; ARG1: Arginase 1; CTLA-4: Cytotoxic T-Lymphocyte associated protein 4; LAG3: Lymphocyte activating 3; PD-L1: Programmed death-ligand 1; LP: lectin pathway; AP: alternative pathway; CP: classical pathway.

Declarations

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Availability of data and materials: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest: none

Ethical approval and ethical standards: The study with human data was approved by the ethics committee of the Xiangya Hospital, Central South University. The procedures with human data were performed following the ethical standards of the ethics committee and the Helsinki Declaration of 1975 and its later amendments.

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Figures

Figure 1

Overall survival status of glioma patients based on gene signature risk score in CGGA and TCGA datasets. Kaplan–Meier overall survival curve among low- and high-risk groups in the CGGA (A) and TCGA (B) databases.

Figure 2

Expression of eight risk-related genes and gliomas clinicopathologic features in training and validating cohorts. Complement gene signature is associated with gliomas clinicopathological features in CGGA (A and C) and TCGA (B and D) databases. *** $p < 0.001$.

Figure 3

Correlation of risk-related genes and immune landscapes in gliomas microenvironment from the training and validating cohorts. The relationship of risk-related genes and tumor purity, estimate score, immune score, stromal score in the CGGA (A) and TCGA (B) databases. The immune cells infiltration in gliomas microenvironment from the CGGA (C) and TCGA (D) databases. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ns: no significant differences.

Figure 4

Correlation of risk-related genes and immune landscapes in the glioma microenvironment from our sequencing data. The relationship of risk-related genes and estimate score (A), stromal score (B), immune score (C), TMZ sensitivity (D) from our sequencing data. The immune cells infiltration in the gliomas microenvironment from our sequencing data (E). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ns: no significant differences.

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