Identification of Prognostic Biomarkers and Immunotherapeutic Targets with CXC Chemokines in Glioblastoma Multiforme Using Integrated Bioinformatic Analysis

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Abstract

Background Glioblastoma multiforme (GBM) is the most malignant central nervous system tumour bearing a dismal prognosis. The study aimed to explore the potential biomarkers and therapeutic targets with CXC chemokines in GBM by integrated bioinformatics analysis.

Methods Differentially expressed CXC Chemokines were identified in GBM using GEPIA and UALCAN databases, and Kaplan–Meier analyses were performed by GEPIA subsequently. Protein–protein interaction (PPI) network was established in STRING database. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways analysis were utilized to analyze differentially expressed CXC Chemokines and their similar genes gained from GEPIA. Then, we conducted transcription factors, kinase targets, and immune cells infiltration using TRRUST, LinkedOmics, and TIMER, respectively.

Results The mRNA expression levels of CXCL3/5/6/9/10/11/12/13/16 in GMB were significantly elevated compared to normal tissues. GBM patients with higher transcriptional levels of *CXCL5/6* were significantly associated with worse disease-free survival, while higher transcriptional levels of *CXCL3/5/8* were significantly related to worse overall survival. The functions of CXC chemokines were enriched in Chemokine signaling pathway, Cytokine-cytokine receptor interaction, IL-17 signaling pathway, et.al. *RELA* and *NFKB1* were key transcription factors of CXC chemokines. The kinase targets of CXC chemokine contained *CDK1*, *CDK2*, *PRKCD*, *MAPK14*, *ATM*, *LCK*, *MTOR*, and *GRK3*, which are involved in oncogenesis, migration, and survival. Moreover, we revealed significant correlations between the expression of CXC chemokines and the infiltration immune cells, especially for dendritic cells.

Conclusion The significant CXC chemokines and related pathways may provide a novel possibility for prognostic biomarkers and immunotherapeutic treatment in GMB.

Short title: CXC Chemokines with prognosis in GBM

1. Background

Glioblastoma multiforme (GBM) is the most malignant central nervous system tumour with dismal prognosis. Despite incremental advances in diagnostics and therapeutics including surgery, radiation, and chemotherapy, the 5-year survival rate of GBM patients is less than 15%¹. The cross-talk between cancer cells and immune cells is a crucial part in cancer growth, metastasis, and treatment effects, which is mediated in part by CXC chemokines in the tumor microenvironment². Immunotherapy becomes an effective method of targeted therapy in tumors³. Recently, rapid progress in immunotherapy, such as immune-checkpoint inhibitors and cell-based vaccines have contributed to glioblastoma treatment⁴. However, it is still in the clinical trial, more molecular approaches contributing to clinically applicable biomarkers and therapeutic targets are needed.

Chemokines are small chemotactic cytokines including CXC-chemokines, CCchemokines, Cchemokines, and CX3C-chemokines according to the position of their first two cysteine residues, which were expressed by tumour cells, immune cells, and stromal cells. It involved in leucocyte trafficking, angiogenesis, tumor growth, invasion, metastasis, and survival⁵. A complex chemokine network between immune-cell and leukocyte infiltration exists in tumor, which was related to tumour cell proliferation, migration, and survival⁶. Previous studies revealed that CXC-chemokines were associated with GBM angiogenesis, proliferation, and migration⁷. However, identifying suitable CXC chemokines as prognostic biomarkers and therapeutic targets for GBM is elusive. Thus, a compelling attention to molecular basis and analysis is needed to extensively identify genomic abnormalities underlying GBM.

With the advent of next-generation sequencing technologies and the establishment of various public databases, comprehensive bioinformatics analysis of the expression of CXC chemokines in GBM has become possible. Our study using integrated bioinformatics analysis of the expression of CXC chemokines might provide valuable information for exploring potential new molecular biomarkers and therapeutic targets for GBM.

2. Materials And Methods

UALCAN

UALCAN (<http://ualcan.path.uab.edu/analysis.html>), is an interactive web-portal to perform analyses of The Cancer Genome Atlas (TCGA) level 3 RNA-seq and clinical data from 31 cancer types⁸. In the study, we gained the data of CXC chemokines in GBM using the “TCGA Analysis” module of UALCAN and the “GBM” dataset, and then performed a differential mRNA expression analysis of GBM and normal tissues. The p-value was explored with Student’s t-test and the cutoff was 0.05.

GEPIA

GEPIA (<http://gepia.cancer-pku.cn/index.html>) is a web-based tool with extensively customize the visualization to deliver functionalities including differential expression analysis, profiling plotting, correlation analysis, patient survival analysis, similar gene detection and dimensionality reduction analysis based on TCGA and GTEx data⁹. In the study, we performed a differential mRNA expression analysis of tumor and normal tissues with the “GBM” dataset of GEPIA. Then we used GEPIA server to analyze the prognostic significance of differentially expressed CXC chemokines in GBM. The prognostic analysis was performed using a Kaplan-Meier curve. Data of “similar gene detection” were extracted to evaluate the interaction of CXC chemokines in GBM. Student’s t-test was used to analyze the differentially expressed of CXC chemokines in GBM. The p-value cutoff was 0.05.

cBioPortal

cBioPortal (www.cbioportal.org), a comprehensive web resource, provides mutation data, copy number alterations, microarray-based and RNA sequencing-based mRNA expression changes based on the TCGA-

derived data¹⁰. We explored the genetic alteration of differentially expressed CXC chemokines with cBioPortal.

STRING

STRING (<https://string-db.org/>) is a web resource available online to construct the protein-protein interaction (PPI) network¹¹. We explored gene coexpression with STRING. Moreover, we established a PPI network analysis of differentially expressed CXC chemokines to explore the interactions among genes in STRING database. A value of $P < .05$ was seen to be statistically significant.

R software

Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways involving differentially expressed CXC chemokines and their similar genes were conducted using R software to analyze the function enrichment among the genes. A value of $P < .05$ was seen to be statistically significant.

TRRUST

TRRUST (<https://www.grnpedia.org/trrust/>) is a versatile database for the study of the transcriptional regulation, consisting of 8444 regulatory interactions for 800 transcription factors (TFs) in humans¹². We gained the TF of CXC chemokines in GBM.

LinkedOmics

LinkedOmics (<http://www.linkedomics.org/>) is an open source portal available online, and provides a stage for biologists and clinicians to access, analyze and compare cancer multi-omics data within and across tumor types from The Cancer Genome Atlas (TCGA) project¹³. We used the "LinkInterpreter module" transforms identified associations into biological understanding through the pathway and network analysis of CXC chemokines in GBM.

TIMER

TIMER (<https://cistrome.shinyapps.io/timer/>) is a visual tool to comprehensively investigate molecular characterization of tumor-immune interactions¹⁴. In our study, we used "Gene module" to evaluate the correlation between CXC chemokines level and the infiltration of immune cells, including CD4 + T cells, CD8 + T cells, B cells, Macrophages, Neutrophils, and Dendritic cells, while we used "Survival module" to evaluate the correlation among clinical outcome and the infiltration of immune cells based on the GBM data from TCGA database.

3. Results

Aberrant expression of CXC chemokines in GBM vs normal tissue.

Sixteen CXC chemokines except CXCL15 in GMB were conducted on the UALCAN database. We screened out nine increased mRNA expression levels for CXCL3, CXCL5, CXCL6, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL16 in GMB patients compared to normal tissues. The results are presented in Fig. 1. Meanwhile, based on the database of GEPIA, the transcriptional levels of CXCL2, CXCL3, CXCL8, CXCL9, CXCL10, CXCL11, and CXCL16 in GBM tissues were significantly elevated compared to normal tissue (Fig. 2). All the differential expression gene were elevated. Combining the data from two databases of UALCAN and GEPIA, we gained eleven differentially expressed CXC chemokines in GBM totally (CXCL2, CXCL3, CXCL5, CXCL6, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, and CXCL16). CXC chemokines of CXCL1, CXCL4, CXCL7, and CXCL14 were excluded because of similar levels in GBM compared to normal tissue.

The prognostic value of CXC chemokines in GBM

We conducted Kaplan–Meier analysis of differentially expressed CXC chemokines and clinical outcome using GEPIA to assess the value of CXC chemokines in the prognosis of GMB. GBM patients with higher transcriptional levels of CXCL5 ($p = 0.0086$) and CXCL6 ($p = 0.017$) were significantly associated with worse disease-free survival (Fig. 3). Meanwhile, we found that GBM patients with higher transcriptional levels of CXCL3 ($p = 0.021$), CXCL5 ($p = 0.0046$), and CXCL8 ($p = 0.049$) were significantly associated with worse overall survival (Fig. 4).

The molecular characteristics, similar Gene, and PPI network analysis of CXC chemokines in patients with GBM

We conducted an overall analysis of the molecular characteristics of differentially expressed CXC chemokines, including genetic alteration and gene coexpression. We gained the genetic alterations of differentially expressed CXC chemokines using cBioPortal, and found CXCL2, CXCL3, CXCL5, CXCL6, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, and CXCL16 were altered in 13%, 6%, 4%, 6%, 33%, 7%, 21%, 8%, 6%, 5% and 0% in patients with GBM, respectively (Fig. 5A), which suggested high mRNA expression was the most common alteration. And then we explored the potential coexpression of the differentially expressed CXC chemokines with STRING (Fig. 5B). According to the coexpression scores, we revealed high correlation among CXCL9/10, CXCL9/10, CXCL8/2, and CXCL9/11, followed by CXCL3/8 and CXCL9/13. With the “similar gene detection” module of GEPIA, we identified additional genes with expression features similar to the differential expression CXC chemokines. The top five similar genes of each CXC chemokines were selected, which including ZC3H12A, TACSTD2, IGFL3, RP11-154H12.2, LSM1P1, BIRC3, BIRC4, BIRC5, BIRC6, BIRC7, CXCL6, OR8G3P, SERPINB2, RN7SKP65, RP1-209B9.2, CXCL5, OR8G3P, PF4V1, CTB-158D10.3, RPS27P23, BCL2A1, RP11-84C10.2, RNASE2, CXCL3, CCL20, ZBED2, CCL17, RP13-461N9.2, RN7SKP266, USP9YP8, CXCL9, TRAV12-3, PLA2G2D, TRBV20-1, CCL17, IDO1, CXCL10, RP11-44K6.4, CXCL9, DUTP8, TMEM150B, TIMD4, TRIM50, AQP9, SLAMF8, MMP13, CYCSP20, RP11-723G8.1, SSXP3, FAM218BP, ZMYND15, CD37, DOCK2, SPI1, and VAV1. Using STRING, we conducted a PPI network analysis of differentially expressed CXC chemokines, which contained 11 nodes and 55

edges (Fig. 5C). The function of these differentially expressed CXC chemokines enriched in chemokine signaling pathway and inflammatory and immune response pathway.

Functional enrichment analysis of the differentially expressed CXC chemokines and their similar genes in patients with GBM

GO and KEGG enrichment analysis were used to explore the potential function of the differentially expressed CXC chemokines and their similar genes with R software (Fig. 6). GO analysis demonstrated that the differentially expressed CXC chemokines and their similar genes were mostly enriched in BP (biological processes) category (response to chemokine, cellular response to chemokine, neutrophil migration, and et.al.) and MF (molecular function) category (chemokine activity, chemokine receptor binding, cytokine activity, and et.al.). CC category (cellular components) was absent. In addition, KEGG pathway analyses demonstrate that the top ten most significant pathways contained Chemokine signaling pathway, Viral protein interaction with cytokine and cytokine receptor, Cytokine-cytokine receptor interaction, IL-17 signaling pathway, Rheumatoid arthritis, TNF signaling pathway, NF-kappa B signaling pathway, Apoptosis - multiple species, Toll-like receptor signaling pathway, and Legionellosis.

Transcription factor targets and kinase targets of CXC chemokines in patients with GBM

To understand the context of CXC chemokines, we revealed possible transcription factor targets and kinase targets of the differentially expressed CXC chemokines with the resource of TRRUST and LinkedOmics respectively.

Query genes of CXCL2, CXCL5, CXCL8, CXCL10, CXCL12 included in TRRUST. Our data revealed two transcription factors (RELA and NFKB1) were the key regulators for gene targets of CXCL2, CXCL5, CXCL8, CXCL10, and CXCL12 (Table 1). We selected the top two kinase targets of CXC chemokines except CXCL8/16 with LinkedOmics database. Kinase-target network of CXCL2 is related to PRKCD and MAPK14, while network of CXCL3 and CXCL9 is correlated to CDK2 and ATM. CDK2 and CDK1 were suggested as targets for CXCL5, CXCL6, CXCL11, and CXCL13 kinase-target network. CXCL10 kinase-target network were generally associated with LCK and MTOR, and CXCL12 is related to PRKCD and GRK3 (Table 2).

Table 1
Results of candidate key regulators from TRRUST.

Key TF	description	Regulated targets	P value	FDR
RELA	v-rel reticuloendotheliosis viral oncogene homolog A (avian)	CXCL2/5/8/10/12	4.26e-07	4.4e-07
NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	CXCL2/5/8/10/12	4.4e-07	4.4e-07
TF: transcription factor				

Table 2
Enriched kinase targets of CXC chemokines from LinkerOmics.

CXC chemokines	Enriched kinase target	Description	Leading Edge Number	P Value
CXCL2	Kinase_PRKCD	protein kinase C delta	31	0
	Kinase_MAPK14	mitogen-activated protein kinase 14	27	0.004
CXCL3	Kinase_CDK2	cyclin dependent kinase 2	75	0
	Kinase_ATM	ATM serine/threonine kinase	60	0
CXCL5	Kinase_CDK2	cyclin dependent kinase 2	118	0
	Kinase_CDK1	cyclin dependent kinase 1	104	0
CXCL6	Kinase_CDK1	cyclin dependent kinase 1	123	0
	Kinase_CDK2	cyclin dependent kinase 2	107	0
CXCL9	Kinase_CDK2	cyclin dependent kinase 2	89	0
	Kinase_ATM	ATM serine/threonine kinase	48	0
CXCL10	Kinase_LCK	LCK proto-oncogene, Src family tyrosine kinase	19	0
	Kinase_MTOR	mechanistic target of rapamycin	19	0
CXCL11	Kinase_CDK2	cyclin dependent kinase 2	83	0
	Kinase_CDK1	cyclin dependent kinase 1	79	0
CXCL12	Kinase_PRKCD	protein kinase C delta	28	0
	Kinase_GRK3	G protein-coupled receptor kinase 3	24	0
CXCL13	Kinase_CDK1	cyclin dependent kinase 1	104	0
	Kinase_CDK2	cyclin dependent kinase 2	99	0

Immune cell infiltration of CXC chemokines in patients with GBM

To systematical analysis of immune infiltrates across GBM, we use “Gene module” module of TIMER to explore the correlation between differentially expressed CXC chemokine (not including CXCL8) and abundance of immune infiltrates (B cells, CD4 + T cells, CD8 + T cells, Neutrophils, Macrophages, and Dendritic cells). CXCL2 expression was negatively associated with the infiltration of CD8 + T cells (Cor = -0.148, p = 0.002), and positively associated with the infiltration of neutrophils (Cor = 0.203, p = 2.76E-05) and dendritic cell (Cor = 0.400, p = 1.67E-17) (Fig. 7A). CXCL3 expression was negatively associated with the infiltration of B cells (Cor = -0.102, p = 0.036) and macrophage (Cor = -0.130, p = 0.007), and positively associated with the infiltration of neutrophils (Cor = 0.122, p = 0.012) and dendritic cell (Cor = 0.389, p =

1.31E-16) (Fig. 7B). CXCL5 expression was negatively associated with the infiltration of B cells (Cor = -0.109, $p = 0.024$) and CD8 + T Cell (Cor = -0.154, $p = 0.001$), and positively associated with the infiltration of dendritic cell (Cor = 0.320, $p = 2.04E-11$) (Fig. 7C). CXCL6 expression was negatively associated with the infiltration of B cells (Cor = -0.149, $p = 0.002$) and CD8 + T Cell (Cor = -0.099, $p = 0.042$), and positively associated with the infiltration of dendritic cell (Cor = 0.332, $p = 2.82E-12$) (Fig. 7D). CXCL9 expression was negatively associated with the infiltration of CD8 + T Cell (Cor = -0.220, $p = 5.50E-06$) and CD4 + T Cell (Cor = -0.151, $p = 0.0018$), and positively associated with the infiltration of B cells (Cor = 0.302, $p = 2.84E-10$) dendritic cell (Cor = 0.175, $p = 3.15E-4$) (Fig. 7E). CXCL10 expression was negatively associated with the infiltration of CD8 + T Cell (Cor = -0.172, $p = 4.05E-04$) and CD4 + T Cell (Cor = -0.131, $p = 0.007$), and positively associated with the infiltration of B cells (Cor = 0.309, $p = 1.03E-10$), neutrophil (Cor = 0.123, $p = 0.011$), and dendritic cell (Cor = 0.216, $p = 7.60E-06$) (Fig. 7F). CXCL11 expression was negatively associated with the infiltration of CD4 + T Cell (Cor = -0.120, $p = 0.013$), and positively associated with the infiltration of B cells (Cor = 0.302, $p = 2.86E-10$) and dendritic cell (Cor = 0.109, $p = 0.025$) (Fig. 7G). CXCL12 expression was negatively associated with the infiltration of CD8 + T Cell (Cor = -0.185, $p = 1.38E-4$), and positively associated with the infiltration of neutrophil (Cor = 0.111, $p = 0.023$) and dendritic cell (Cor = 0.287, $p = 2.18E-09$) (Fig. 7H). CXCL13 expression was negatively associated with the infiltration of CD8 + T Cell (Cor = -0.236, $p = 1.01E-06$) and CD4 + T Cell (Cor = -0.127, $p = 0.009$), and positively associated with dendritic cell (Cor = 0.101, $p = 0.037$) (Fig. 7I). CXCL16 expression was negatively associated with the infiltration of CD8 + T Cell (Cor = -0.281, $p = 0.001$), and positively associated with CD4 + T Cell (Cor = 0.349, $p = 3.92E-05$), macrophage (Cor = 0.186, $p = 0.032$), and dendritic cell (Cor = 0.340, $p = 6.43E-05$) (Fig. 7J). Our data revealed all the differentially expressed CXC chemokines are positively with infiltration of dendritic cell. In addition, we evaluated correlation of prognosis and immune cell infiltration in GBM using the Cox proportional hazard model. We found lower dendritic cell ($p = 0.025$) were significantly associated with longer cumulative survival of GMB (Fig. 7K). Previous study reported the autologous dendritic cell vaccine may extend survival in GBM patients¹⁵, suggesting CXC chemokines might be the potential therapeutic targets with modulating infiltration of dendritic cell.

4. Discussion

Chemokines involved in leucocyte trafficking, angiogenesis, tumor growth, invasion, metastasis, and survival⁵. Previous studies^{3, 16} have reported a correlation among CXC chemokines, the tumor microenvironment, and cancer immunotherapy, suggesting that CXC chemokines may modulate tumor progression and immunotherapeutic effect. However, integrative bioinformatics analysis of CXC chemokines to evaluate the progress in GMB has not been well reported.

The eleven differentially expressed genes (CXCL2, CXCL3, CXCL5, CXCL6, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, and CXCL16) were gained in GBM compared to normal tissue using website of UALCAN and GEPIA, all of which are upregulation. In addition, we found that GBM patients with high transcriptional levels of CXCL5 and CXCL6 were significantly associated with worse disease-free survival. Moreover, GBM patients with high transcriptional levels of CXCL3, CXCL5, and CXCL8 were significantly

associated with worse overall survival. The data suggested crucial relevance may exist between differentially expressed CXC chemokines and GBM, especially the outcome of GBM. Many studies reported that CXCL16 mRNA was particularly high in GBM.¹⁷ Expression of CXCL10 have an important role in the proliferation of glioma cells, which associated with increased malignancy grade¹⁸. Moreover, CXCL12 showed tumour-promoting properties on cultured glioma cells.¹⁹ Nevertheless, prognostic value as biomarker of CXC chemokines in GBM is absent.

To overall understanding molecular characteristics of CXC chemokines, we gained genetic alteration and coexpression. High mRNA expression was the most common mutation alteration of CXC chemokines in GBM, which was consistent with the upregulation of differential expressed CXC chemokines⁷, demonstrated CXC chemokines might correlate with the genesis and development of GBM. The result of CXC chemokines coexpression suggested CXC chemokines acted as an orchestra in GBM.

We then explored the function of differentially expressed CXC chemokines and their similar genes using GO and KEGG pathway enrichment analysis. We found that the functions of the related genes are mainly correlated to the cytokine and cytokine receptor, Cytokine-cytokine receptor interaction, IL-17 signaling pathway, TNF signaling pathway, and NF-kappa B signaling. Previous studies have demonstrated that chemokine signaling pathways and cytokine-cytokine receptor interactions play critical roles in cancer cell proliferation, angiogenesis, metastasis, and survival of various cancers^{7, 18, 20}. IL-17 signaling is associated with immunopathology and cancer progression²¹. TNF signaling pathway and NF-kappa B signaling pathway play a significant role in cell proliferation and oncogenesis²². The data suggested that the CXC chemokines might be the new therapeutic targets responding to the pathway for GBM.

We found that two transcription factors (RELA and NFkB1) were associated with the regulation of CXC chemokines. RELA is the downstream transcriptional activators of the canonical NF-κB pathway, and regulate the activity and function of NF-κB including cell differentiation, apoptosis, and tumorigenesis, with various post-translational modifications, especially phosphorylation. A study demonstrated that RELA is a mediator of oncogene of pancreatic ductal adenocarcinoma, and the beneficial effects of RELA were mediated by increased expression of CXCL1 and CXCR2²³. NFkB1 as a suppressor of the NF-κB response contributed to tumorigenesis in many types of cancer, including GBM²⁴. The cumulative data demonstrated CXC chemokine and NF-κB pathway may become potentially molecular targets in the clinical treatment of GBM. The probable targets of the differentially expressed CXC chemokines suggested CDK1, CDK2, PRKCD, MAPK14, ATM, LCK, MTOR, and GRK3. CDK1 is a critical modulator in the initiation and transition process from the G2 phase into mitosis of the cell cycle and has been proposed as a tumor specific anti-cancer target²⁵. CDK2 is mainly associated with tumor growth in multiple cancer types, and CDK2 inhibition may provide a therapeutic benefit against certain tumors²⁶. PRKCD is known to be an important regulator of apoptosis²⁷. ATM was related to DNA damage response, and utilization of ATM inhibitors may provide a novel anti-cancer treatment strategy. LCK is expressed in the brain and in tumor cells, where it regulates cellular functions like proliferation, survival, and memory²⁸. mTOR is frequently activated in cancer, which is associated with controls cell growth and

metabolism²⁹. GRK3 dysregulation may play an important part in the metastasis of tumor. Summary, the kinases are involved in cell cycle modulation, DNA damage, apoptosis, metastasis, and survival. Therefore, we inferred differentially expressed CXC chemokines may modulate tumor cell migration, invasion, and apoptosis in GBM by regulating these kinases.

Tumour microenvironment consisted of chemokines, chemokine receptors, and different immune cell subsets, which had distinct effects on tumour progression and therapeutic outcomes³. Chemokines can recruit specific immune cells into the tumour microenvironment to form tumour immunity and therapeutic responses. In our study, the differently expressed CXC-chemokines were accompanied by various immune cell infiltration, especially all of which were positively associated with dendritic cell. Moreover, we found lower dendritic cell were significantly associated with longer cumulative survival of GMB. Previous evidences^{15,30} revealed the dendritic cell were associated with progress and acted as immunity therapeutic targets in GBM in phase III clinical trial. Collectedly, CXC-chemokines might be a potentially effective approach for predicting clinical outcome and target treating in GBM.

5. Conclusion

In a word, the significant chemokines and pathways may open up brand-new possibilities for prognostic biomarkers and immunotherapeutic treatment of GMB; however, further researches are still required for untangling the mechanism of occurrence and development of GBM.

Abbreviations

GBM: Glioblastoma multiforme; PPI: Protein -protein interaction; GO: Gene ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; TCGA: The Cancer Genome Atlas; TFs: transcription factors; BP: biological processes; MF: molecular function; CC: category cellular components.

Declarations

Ethics approval and consent to participate

The study was not a clinical trial. All data generated or analysed during this study are included in the public database.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Authors' contributions: WGW designed the study, LHL contributed to drafting the manuscript, ZJG read and approved the final manuscript.

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Figures

Figure 1

Aberrant expression of CXC chemokines in GBM from UALCAN database. The transcriptional levels of CXCL3/5/6/9/10 /11/12/13/16 in GBM tissues were significantly elevated compared to normal tissue.

Figure 2

The transcriptional of CXC chemokines in GBM from GEPIA database. The transcriptional levels of CXCL2/3/8/9/10/11/16 were significantly increased in GBM vs normal tissue.

Figure 3

Prognostic values of differentially expressed CXCL chemokines for disease free survival in GBM patients using GEPIA.

Figure 4

Prognostic values of differentially expressed CXC chemokines for overall survival in GBM patients using GEPIA.

Figure 5

The molecular characteristics and PPI network analysis of CXC Chemokines in Patients with GBM. A. Genetic alteration of differentially expression CXC chemokine in GBM. B. Gene coexpression of differentially expression CXC chemokine in GBM with STRING. C. Protein-protein interaction network of differentially expressed CXC chemokines with STRING.

Figure 6

Functional enrichment analysis of the differentially expressed CXC Chemokines and their similar genes in patients with GBM using R software. A. Bar-plot of GO enrichment in biological process terms and molecular function terms. B. Bar-plot of KEGG enriched terms.

Figure 7

Immune cell infiltration correlated with expression of CXC chemokines and prognosis in GBM. A-J: Immune cell infiltration (B cells, CD4+ T cells, CD8+ T cells, Neutrophils, Macrophages, and Dendritic cells) of CXC chemokines in GBM. K: correlation of cumulative survival and immune cell infiltration in GBM using the Cox proportional hazard model.