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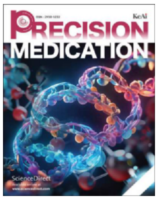

Predictive potential of five genes of cuproptosis for survival in LGG

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ABSTRACT

Low-grade glioma (LGG) is a common primary tumor in the central nervous system. The function of several types of cell death has been proved in tumorigenesis of low-grade glioma (LGG). **Cuproptosis**, a new form of cell death, has been defined in recent years. We put forward the function between cuproptosis and LGG for the first time. According to TCGA datasets, we performed a univariate Cox regression analysis and got 5 hub risk genes related to the survival of LGG. Then, we constructed a prognostic risk mode by using LASSO method and demonstrated that risk score is independent prognostic risk factor by using univariate and multivariate Cox regression analyses**.** The above results were verified in CGGA datasets. Next, we compared the immune characteristics by using CIBERSORT, ssGSEA and demonstrated that 5 hub genes play an important role in tumor immunotherapy. Finally, we performed GO term and KEGG pathway analyses and found 5 hub genes are likely to change the biological functions of LGG by regulating the metabolism related components. We believe that our results will provide a new strategy for tumor treatment.

Introduction

Glioma can be classified into four grades, according to the WHO grading system.[1, 2] Low-grade gliomas (LGG), WHO grade II and III gliomas, are less aggressive than grade IV glioma.[3] The median overall survival (OS) times were 78.1 months for LGG.[4] LGG has unclear pathogenesis and unsatisfied therapeutic effects, and some patients will progress to GBM within a few months,[5] leading to decreased treatment responses and a poor prognosis.

Bob Weinberg and Douglas Hanahan have proposed 14 hallmarks of cancer,[6, 7] which are the cornerstone of cancer research. Cuproptosis is a newly discovered mode of regulated cell death in recent months.[8] The function of cell death such as apoptosis, necrosis, ferroptosis, autophagy has been reported,[9–12] but the function of cuproptosis has not been reported.

It is well known that immunotherapy improves the prognosis of cancer patients.[13, 14] Therefore, it is still important to find and validate new targets to predict the clinical outcome and immunotherapy of LGG patients. In this research, we found five cuproptosis-related genes associated with prognosis, suggesting a potential new therapy for LGG.

For a long time, metabolism is directly related to oncogenes, so tumor metabolism has always been a potential target of cancer therapeutic drugs.[15] In this research, we performed GO term and KEGG pathway analyses and indicated that five cuproptosis-related genes are likely to change the biological functions of LGG by regulating the metabolism related components. Our results demonstrated that a new field may has a significant impact on the survival and immunotherapy response and tumor metabolism in patients with LGG.

Materials and methods

Data collection

There were 447 LGG patients of TCGA datasets and 413 LGG patients of CGGA datasets were used in this study, including RNA expression and clinical information were downloaded from GLIOVIS platform.[16]

Using UCSCXENASHINY,[17] the 1152 normal samples and 523 LGG samples were analyzed in TCGA and GTEX, respectively. Ten

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cuproptosis-related genes identified from the literature[8] were preserved with complete expression values for further analysis.

LGG subclasses identification

To decrease the dimensions of non-negative matrix factorization (NMF) clustering,[18] univariate Cox regression analysis was applied to determine the genes that had prognostic values. The "Consensus Cluster Plus" and "survival" package in R was applied to cluster the LGG samples. Finally, five cuproptosis-related genes with significant prognostic value ($P < 0.05$) were selected for sample clustering.

Survival analysis

Survival analysis was performed to compare the overall survival (OS) time between two groups using "survminer" and "survival" packages in the R software. Kaplan–Meier method was used to plot the survival curve, and log rank as the statistical significance test.

Cox regression analysis

R language loaded with package "survival" was used for Cox regression.

Risk scoring model

The prognostic risk features were evaluated using "survival" and "glmnet" R package according to the least absolute shrinkage and selection operator (LASSO) method.[19] Risk scores were calculated using the following formula: Risk score = (0.751*FDX1) + (-0.903*LIAS) + (0.449*DLD) + (0.034*DLAT) + (-0.170*CDKN2A).

Heatmap of clinical features

The relation between mRNA expression of genes and clinical features of LGG was investigated and visualized using "pheatmap" and "limma" package in R statistical software.

Analysis of immune response level

Evaluating the tumor microenvironment (TME) of LGG, along with stromalScore, immuneScor, ESTIMATEScore, and tumor purity by R package "estimate", we based on ESTIMATE, which is a method that decides the fractions of immune and stromal cells according to gene expression features in tumor patients.[20] CIBERSORT is used to predict the level of immune cell infiltration in a mixed cell population.[21] This method was used to figure out the proportion of 22 immune cells in each patient with LGG. A statistically significant difference was indicated when $p < 0.05$. R language loaded with package "GSVA"[22] was used for single-sample gene set enrichment analysis (ssGSEA) method. Then we figured out the infiltration of for immune cells based on the expression levels in 28 published gene sets.

Enrichment analysis

GO and KEGG enrichment analyses were executed in R language with the aid of packages "clusterProfiler".

Results

Classification of LGG according to cuproptosis-related genes

According to TCGA datasets and a total of 10 cuproptosis-related genes,[8] we divided LGG samples into 2 different clusters (cluster 1 and cluster 2) as shown in the heatmap (Fig. 1A). We showed that LGG in cluster 1 have a significant survival advantage (log-rank, $P < 0.001$) compared with those in cluster 2 (Fig. 1B). We performed a univariate Cox regression analysis and got a forest plot of associations between 5 risk genes and the survival of LGG (Fig. 1C). Five hub cuproptosis-related genes (FDX1, LIAS, DLD, DLAT, CDKN2A) were used for later research.

Construction of the prognostic risk model

We observed the expression of five hub genes. The data showed that the expression of the 5 genes was significantly different ($P < 0.001$) in tumor group and normal group, with upregulated expression in the LGG (Fig. 2A). Next, we used LASSO to establish a prognostic risk model and used the ROC curves to verify the diagnostic values. We observed the Kaplan–Meier analyses for high-risk patients and low-risk patients and found that high-risk patients have a poor prognosis ($P < 0.05$) (Fig. 2B). We then looked at AUC values of 0.679, 0.694, and 0.711 for the ROC curves at 1, 3, 5 years, respectively (Fig. 2C). Subsequently, the survival status and risk scores distributions of LGG were divided into low-risk and high-risk groups according to the median risk score (Fig. 2D). The above results are verified in CGGA datasets (Fig. 3).

Univariate, multiple cox regression analysis and clinical features

In order to determine that five cuproptosis-related genes were an independent prognostic indicator, univariate and multivariate Cox regression analyses were performed on LGG. Univariate Cox regression analysis showed that the risk score of LGG was related to the OS rate ($P < 0.001$). Low-risk scores correlated with rich survival (Fig. 4A). Multivariate Cox regression analysis showed that risk score is independent prognostic risk factor ($P < 0.05$) (Fig. 4B). We then discussed the relationship between five genes and clinical features. Our results showed that the five genes were differentially expressed in different IDH status, MGMTp methylation status and 1p/19q codeletion status (Fig. 4C).

Relationship between the five genes in LGG and immunotherapy

CIBERSORT was used to estimate differences in the infiltration of 22 immune cell types in the LGG patients (Fig. 3C). Immune checkpoint genes had an important role in therapy response.[23] We found that 18 immune checkpoint genes have significant difference ($P < 0.05$) in two risk groups of patients (Fig. 5A). Besides, TME components were estimated in high-risk groups and low-risk groups. We observed that StromalScore, ImmuneScore, and EstimateScore are higher in high-risk group (Fig. 5B), which demonstrated that five cuproptosis-related genes play an important role in TME of LGG.

Furthermore, we divided LGG into two groups according to the expression of five cuproptosis-related genes and 22 immune cells. CIBERSORT analysis indicated that group 2 have a higher proportion of monocytes and M2 cells than group 1 (Fig. 5C). ssGSEA also showed that group 2 have a higher expressing of 16 immune cell subtypes (Fig. 5D), which indicated that group 2 preferred to have a stronger immune infiltration, especially regarding CD8 T cells.

Relationship between the five genes in LGG and tumor metabolism

Various metabolic and immune mechanisms regulated the response of tumor cells to metabolites. Recently, it has been reported that tumor metabolism has an important relationship with patient survival.[15] In order to better understand the biological function of 5 genes in LGG, GO term and KEGG pathway analyses were performed. GO term analyses indicated that the biological processes and molecular functions strongly associated with LGG were metabolism related components, such as acetyl – CoA biosynthetic process from pyruvate of biological process (BP), mitochondrial matrix of cell component (CC), acting on the aldehyde or oxo group of donors of molecular function (MF) (Fig. 6A).

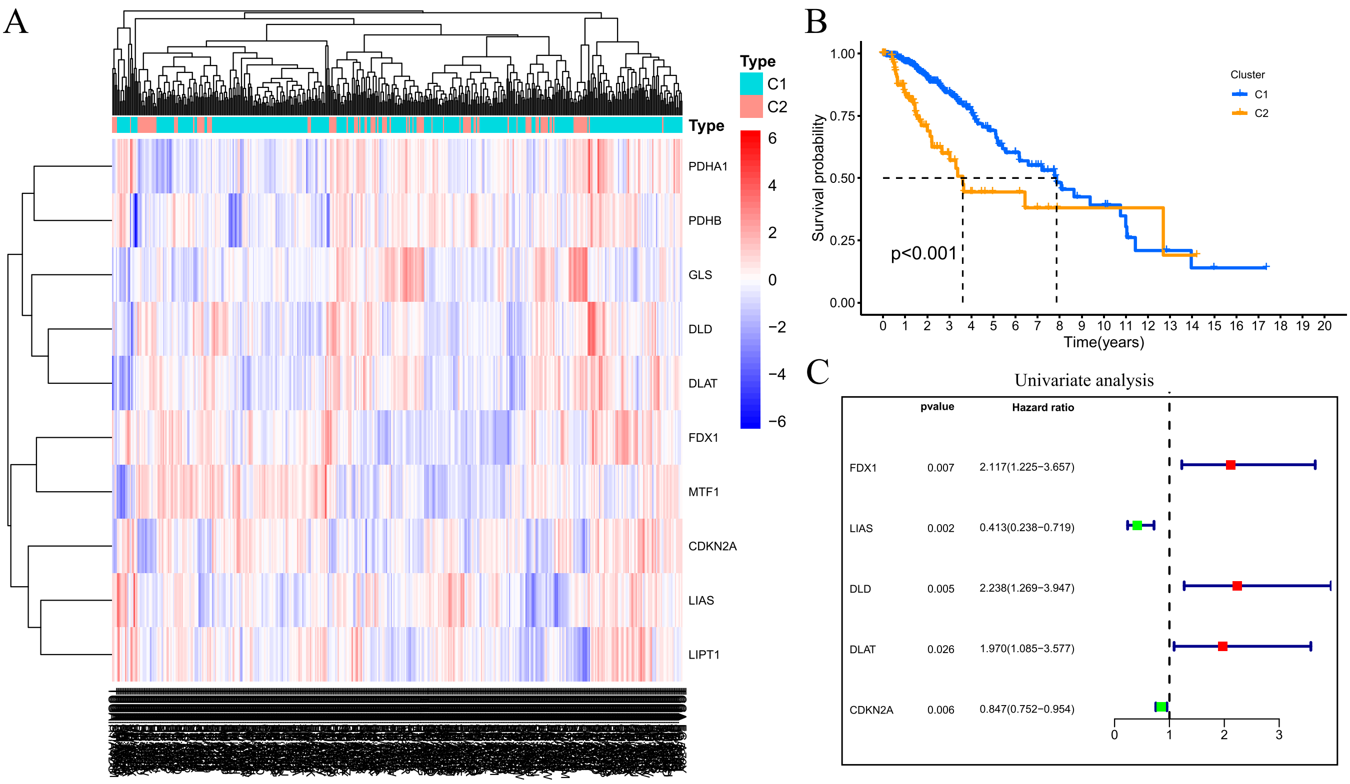

Fig. 1. Identification 5 genes with different prognosis in the LGG related to the cuproptosis set. (A) Heat map of two clusters defined by the 10 cuproptosis -related genes expression in the LGG patients of TCGA dataset. (B) Survival analysis of LGG patients in Clusters 1 and 2. (C) Univariate Cox regression analysis. Forest plot of associations between 5 risk genes and the survival of LGG.

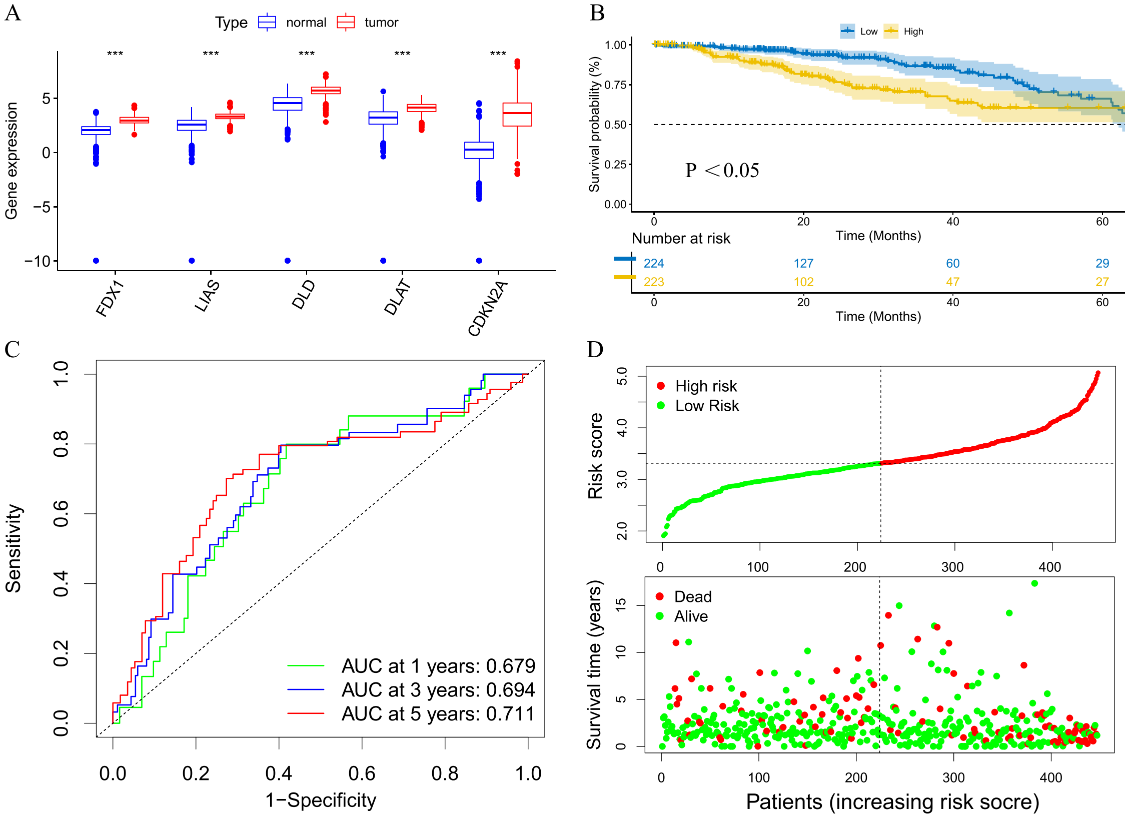

Fig. 2. Construction of the prognostic risk model. (A) Expression of the 5 genes in normal and LGG tumor patients. (B) Kaplan–Meier analyses for high-risk patients and low-risk patients. (C) 1-year, 3-year, 5-year ROC curves showed the predictive efficiency of the risk features. (D) Distribution model of risk score, status of patients and survival time. The P values are labeled using asterisks (NS, no significance, *P < 0.05, **P < 0.01, ***P < 0.001).

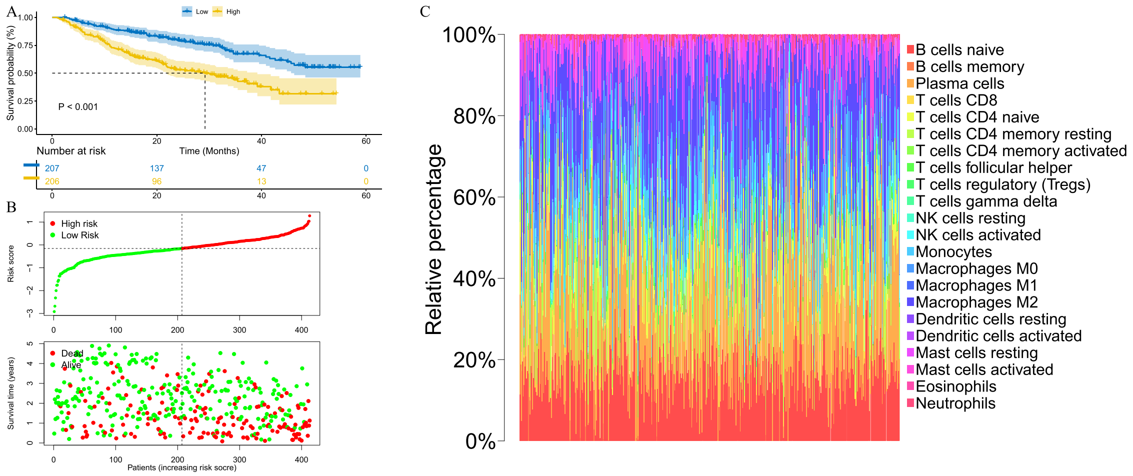

Fig. 3. The prognostic risk model of CGGA datasets and immune cell subtypes in LGG. (A) Kaplan–Meier analyses for high-risk patients and low-risk patients in CGGA datasets. (B) Time ROC curves showed the predictive efficiency of the risk features. Distribution model of risk score, status of patients and survival time. (C) The relative proportion of 22 immune cell subtypes in LGG patients. The P values are labeled using asterisks (NS, no significance, *P < 0.05, **P < 0.01, ***P < 0.001).

KEGG pathway analysis indicated five metabolic related pathways that had a significant correlation with LGG expression (Fig. 6B). These findings indicated that five cuproptosis-related genes are likely to change the biological functions of LGG by regulating the metabolism related components.

Discussion

LGG has unclear pathogenesis and unsatisfied therapeutic effects, and some patients will progress to GBM within a few months.[5] Interestingly, cuproptosis is a new form of cell death.[8] We believe that it may provide a new strategy for tumor treatment. We put forward the correlation between cuproptosis and LGG for the first time. Hence, we constructed a prognostic risk model aiming to identify and verify new genes to predict the prognosis and immunotherapy response of LGG patients.

First, according to TCGA datasets and a total of 10 cuproptosis-related genes, we divided 447 LGG samples into 2 different clusters, which with significantly different prognoses. Then, we performed a univariate Cox regression analysis and got 5 hub risk genes related to the survival of LGG. Futhermore, we constructed a prognostic risk mode and demonstrated that risk score is an independent prognostic risk factor by using univariate and multivariate Cox regression analyses. We also demonstrated that IDH status of clinical features is an independent prognostic risk factor, which consistent with the results of recent articles.[24, 25] Five hub cuproptosis-related genes (FDX1, LIAS, DLD, DLAT, CDKN2A) were used for our research.

FDX1 plays an important role in the synthesis of various steroid hormones.[26] FDX1 promotes a unique copper dependent cell death by rescuing elesclomol-induced cell death.[27] The prognosis and metabolism of FDX1 in lung adenocarcinoma have been reported,[28] but its role in LGG is not known. LIAS is an iron–sulfur cluster protein and with possible connections to human disease states.[29] It has been reported that LIAS mutation leads to glycine encephalopathy.[30] DLAT coordinates liver cancer metabolism and autophagy through HGF-MET axis.[31] Cyclin-dependent kinase inhibitor 2 A (CDKN2A*)* is a gene located at chromosome 9 and its homozygous deletion is a sign of poor prognosis.[32–34]

Considering that IDH mutation is a key driver in LGG and our study observed differential expression of the 5 cuproptosis-related hub genes

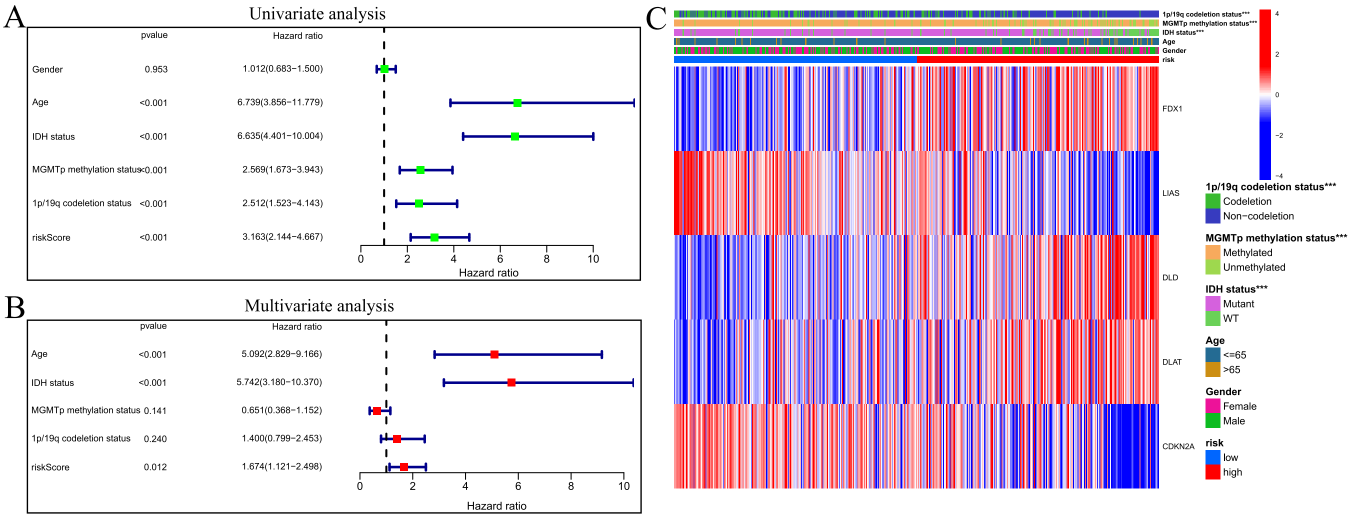

Fig. 4. Univariate, multiple Cox regression analysis and group heatmap. (A) Univariate Cox regression analysis of associations between clinical factors and the survival of LGG. (B) Multiple Cox regression analysis indicating that clinical features and 5 cuproptosis -related genes signature are an independent predictor of LGG. (C) Heat map of two groups defined by the 5 cuproptosis -related genes expression and clinical features. The P values are labeled using asterisks (NS, no significance, *P < 0.05, **P < 0.01, ***P < 0.001).

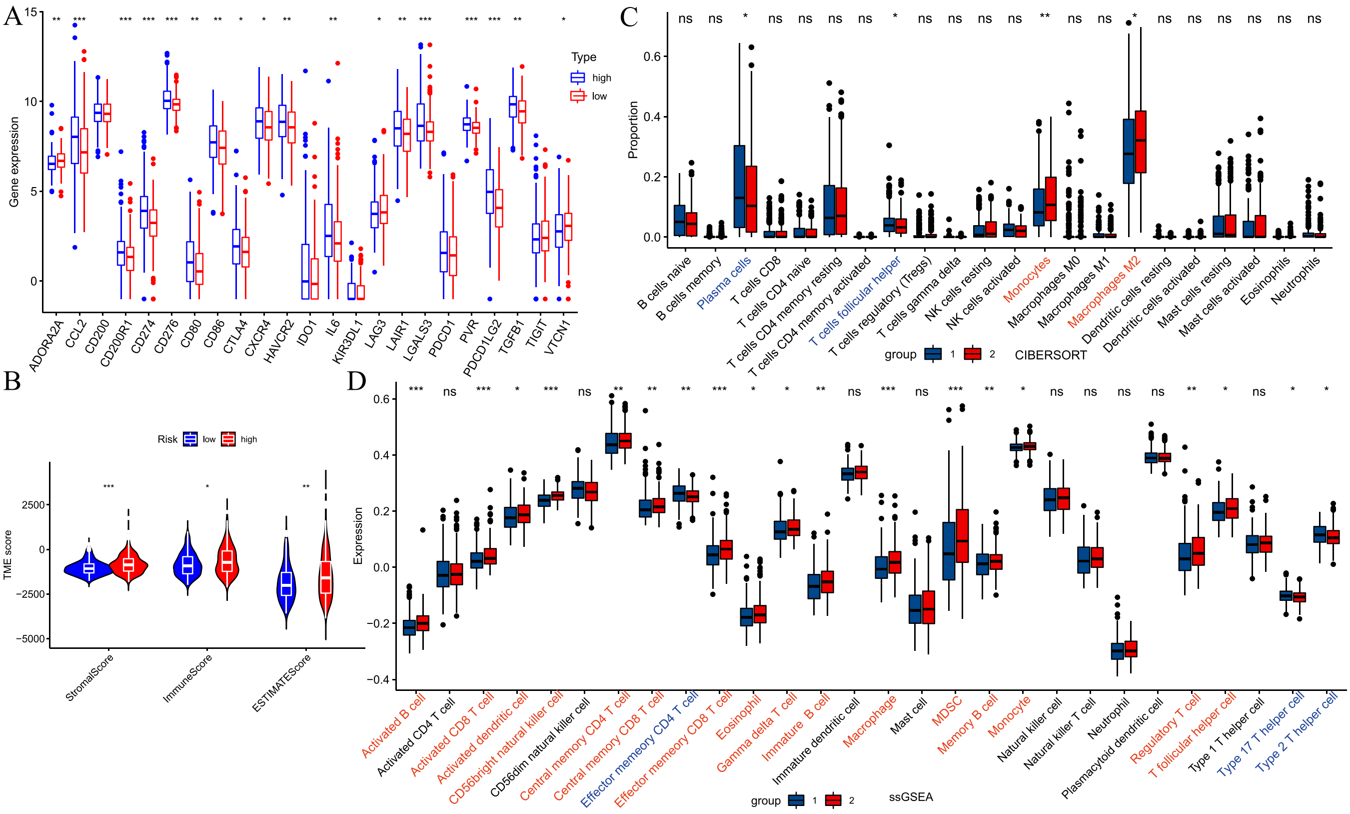

Fig. 5. Analysis of immune characteristics between two groups. (A) Expression of 23 immune checkpoint genes in two clusters. (B) TME of high-risk patients and low-risk patients. (C) Proportion of immune cells between two groups. (D) Expression of immune cells between two groups in ssGSEA. The P values are labeled using asterisks (NS, no significance, *P < 0.05, **P < 0.01, ***P < 0.001).

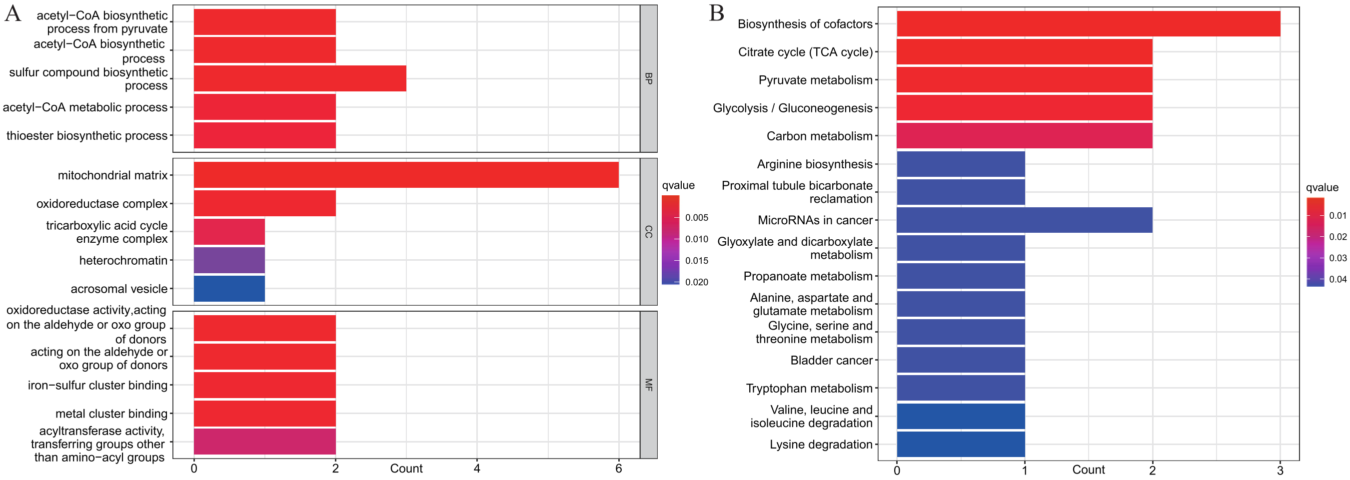

Fig. 6. GO, and KEGG analysis. Functional annotation of genes using GO terms(A) and KEGG pathway(B). “BP” stands for “biological process”, “CC” stands for “cellular component”, and “MF” stands for “molecular function”.

across different IDH statuses (Fig. 4C), we hypothesize that IDH mutation-induced 2-hydroxyglutarate accumulation may perturb intracellular redox homeostasis or copper ion availability, thereby modulating the activity of cuproptosis-related genes (e.g., FDX1, LIAS) and their downstream metabolic pathways, which in turn affects LGG progression and therapeutic response. This potential interaction could provide a rationale for combining IDH inhibitors with copper ion modulators to enhance therapeutic efficacy in LGG, strengthening the translational relevance of our findings.

To found the reasons for the poor prognosis of patients of LGG, we checked the immune checkpoint in the high and low risk group, because immunotherapies based on immune checkpoint genes have gradually become a promising treatment for cancers.[35] Our results indicated that the expression of most immune checkpoint genes was elevated in high-risk group. TME is closely related to immune cells, and its immunophenotype is closely related to occurrence and progression of tumor. We observed that StromalScore, ImmuneScore, and EstimateScore are higher in high-risk group, which indicated that high-risk group has a vibrant tumor immune microenvironment.

Besides, CD8 T cells played a key role on patient prognosis in most tumor infiltrating immune cell subtypes.[36] We compared the immune characteristics of the two groups. ssGSEA showed that group 2 have a higher expressing of 16 immune cell subtypes. Therefore, group 2 may has more immunological competence and be easier to benefit from immunotherapy.

The metabolism of tumor is closely related to the prognosis of patients.[15] In recent articles, a large number of new insights on the molecular mechanism of glioma metabolism have emerged.[37] In order to better understand the biological function of LGG, we performed GO term and KEGG pathway analyses. In the GO term analyses, the 5 hub genes are significantly enriched in "acetyl-CoA biosynthetic process from pyruvate" (biological process), a critical step linking glycolysis to the tricarboxylic acid (TCA) cycle. FDX1, DLD, and DLAT, as components of the pyruvate dehydrogenase complex, directly regulate this process. In cellular components, enrichment in "mitochondrial matrix" highlights their roles in mitochondrial function (e.g., LIAS in iron-sulfur cluster synthesis). For molecular function, "acting on aldehyde/oxo groups" relates to lipid metabolism, potentially involving cuproptosis-mediated lipoylated protein oxidation.In the KEGG pathway analyses, key pathways include "pyruvate metabolism" and "TCA cycle," where DLD and DLAT govern pyruvate-to-acetyl-CoA conversion, while FDX1 modulates mitochondrial metabolism via copper-dependent lipoylated protein degradation, collectively regulating energy supply and redox homeostasis in LGG.These findings indicated that five cuproptosis-related genes are likely to change the biological functions of LGG by regulating the metabolism related components.

Although the above analysis improved our understanding of the relationship between five cuproptosis-related genes and immunity, mechanism, there are still certain limitations in our study. First, our study was a retrospective study. Therefore, a prospective investigation should be conducted for the sake of avoid analysis bias related to retrospective studies. In addition, we could not demonstrate the direct mechanisms of five genes in tumor immunity and metabolism. Our future research will focus on unravelling the direct mechanism in glioma, including in vivo and in vitro experiments.

Declarations

Not applicable.

Authors' contributions

Xiaopeng Li: Writing – original draft, Validation, Software, Formal analysis, Data curation. **Yanpeng Xia:** Formal analysis. **Chunyan Zhu:** Investigation. **Qian Zhang:** Methodology. **Rongliang Guo:** Writing – review & editing. **Shuanli Xin:** Visualization, Validation, Supervision, Funding acquisition. **Zhou Tao:** Formal analysis.

Ethics approval and consent to participate

As the study utilized publicly accessible databases, there was no requirement for ethics committee approval or informed consent from participants. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of Material and Data

The datasets of TCGA and CGGA analyzed in our study can be found in the GLIOVIS platform (https://gliovis.bioinfo.cnio.es/). TCGA and GTEX datasets can be found in UCSCXENASHINY (https://shiny.hiplot.com.cn/ucsc-xena-shiny/).

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Declarations of Competing Interests

The authors declare no competing interests.

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Authors' other information

Not applicable.

References

1. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 2016;131(6):803–820.
2. Yang Liao ZW, Xu Hangwei, Zhang Zhichao, Zhu Feng. Unlocking precision medicine: Innovative strategies for druggable target identification and therapeutic enhancement. *Precis Medicat Precis Medicat.* 2024;1(1):100002.
3. Brat DJ, Verhaak RG, Aldape KD, et al. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. *N Engl J Med.* 2015;372(26):2481–2498.
4. Jiang T, Nam DH, Ram Z, et al. Clinical practice guidelines for the management of adult diffuse gliomas. *Cancer Lett.* 2021;499:60–72.
5. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol J Am Soc Clin Oncol.* 2013;31(3):344–350.
6. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144(5):646–674.
7. Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov.* 2022;12(1):31–46.
8. Tsvetkov P, Coy S, Petrova B, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science.* 2022;375(6586):1254–1261.
9. Strasser A, Vaux DL. Cell death in the origin and treatment of cancer. *Mol Cell.* 2020;78(6):1045–1054.
10. Wan RJ, Peng W, Xia QX, Zhou HH, Mao XY. Ferroptosis-related gene signature predicts prognosis and immunotherapy in glioma. *CNS Neurosci Ther.* 2021;27(8):973–986.
11. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci.* 2017;42(4):245–254.
12. Zheng Y, Ji Q, Xie L, et al. Ferroptosis-related gene signature as a prognostic marker for lower-grade gliomas. *J Cell Mol Med.* 2021;25(6):3080–3090.
13. Wang J, Ren J, Liu J, Zhang L, Yuan Q, Dong B. Identification and verification of the ferroptosis- and pyroptosis-associated prognostic signature for low-grade glioma. *Bosn J Basic Med Sci.* 2022.
14. Zhao Z, Wang Z, Wu Y, Liao D, Zhao B. Comprehensive analysis of TAMs marker genes in glioma for predicting prognosis and immunotherapy response. *Mol Immunol.* 2022;144:78–95.
15. Holbert CE, Cullen MT, Casero Jr RA, Stewart TM. Polyamines in cancer: integrating organismal metabolism and antitumour immunity. *Nat Rev Cancer.* 2022.
16. Bowman RL, Wang Q, Carro A, Verhaak RG, Squatrito M. GlioVis data portal for visualization and analysis of brain tumor expression datasets. *Neuro Oncol.* 2017;19(1):139–141.
17. Zhao Z, Wang Z, Song Z, Wu Y, Jin Q, Zhao Z. Predictive potential of STEAP family for survival, immune microenvironment and therapy response in glioma. *Int Immunopharmacol.* 2021;101(Pt A):108183.
18. Gaujoux R, Seoighe C. A flexible R package for nonnegative matrix factorization. *BMC Bioinforma.* 2010;11:367.
19. Simon N, Friedman J, Hastie T, Tibshirani R. Regularization paths for Cox's proportional hazards model via coordinate descent. *J Stat Softw.* 2011;39(5):1–13.
20. Yoshihara K, Shahmoradgoli M, Martínez E, et al. Inferring tumour purity and stromal and immune cell admixture from expression data. *Nat Commun.* 2013;4:2612.
21. Newman AM, Liu CL, Green MR, et al. Robust enumeration of cell subsets from tissue expression profiles. *Nat Methods.* 2015;12(5):453–457.
22. Hänzelmann S, Castelo R, Guinney J. GSVA: gene set variation analysis for microarray and RNA-seq data. *BMC Bioinforma.* 2013;14:7.
23. Allison JP. Immune Checkpoint Blockade in Cancer Therapy: The 2015 Lasker-DeBakey Clinical Medical Research Award. *JAMA.* 2015;314(11):1113–1114.
24. Zhang J, Liu M, Fang Y, Li J, Chen Y, Jiao S. TP53 R273C mutation is associated with poor prognosis in LGG patients. *Front Genet.* 2022;13:720651.
25. Yixin Cao YL, Wei Lingxi, Zhou Yan, Gao Fei, Qi Yu. Application status of traditional computational methods and machine learning in cancer drug repositioning. *Precis Medicat.* 2024;1(2):100014.
26. Sheftel AD, Stehling O, Pierik AJ, et al. Humans possess two mitochondrial ferredoxins, Fdx1 and Fdx2, with distinct roles in steroidogenesis, heme, and Fe/S cluster biosynthesis. *Proc Natl Acad Sci USA.* 2010;107(26):11775–11780.
27. Tsvetkov P, Detappe A, Cai K, et al. Mitochondrial metabolism promotes adaptation to proteotoxic stress. *Nat Chem Biol.* 2019;15(7):681–689.
28. Zhang Z, Ma Y, Guo X, et al. FDX1 can impact the prognosis and mediate the metabolism of lung adenocarcinoma. *Front Pharm.* 2021;12:749134.

29. Hendricks AL, Wachnowsky C, Fries B, Fidai I, Cowan JA. Characterization and Reconstitution of Human Lipoyl Synthase (LIAS) Supports ISCA2 and ISCU as Primary Cluster Donors and an Ordered Mechanism of Cluster Assembly. *Int J Mol Sci.* 2021;22(4).
30. Tsurusaki Y, Tanaka R, Shimada S, et al. Novel compound heterozygous LIAS mutations cause glycine encephalopathy. *J Hum Genet.* 2015;60(10):631–635.
31. Huang X, Gan G, Wang X, Xu T, Xie W. The HGF-MET axis coordinates liver cancer metabolism and autophagy for chemotherapeutic resistance. *Autophagy.* 2019;15(7):1258–1279.
32. Appay R, Dehais C, Maurage CA, et al. CDKN2A homozygous deletion is a strong adverse prognosis factor in diffuse malignant IDH-mutant gliomas. *Neuro Oncol.* 2019;21(12):1519–1528.
33. Reis GF, Pekmezci M, Hansen HM, et al. CDKN2A loss is associated with shortened overall survival in lower-grade (World Health Organization Grades II-III) astrocytomas. *J Neuropathol Exp Neurol.* 2015;74(5):442–452.
34. Roy DM, Walsh LA, Desrichard A, et al. Integrated genomics for pinpointing survival loci within arm-level somatic copy number alterations. *Cancer Cell.* 2016;29(5):737–750.
35. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol J Am Soc Clin Oncol.* 2015;33(17):1974–1982.
36. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. *Nat Rev Cancer.* 2020;20(11):662–680.
37. Bi J, Chowdhry S, Wu S, Zhang W, Masui K, Mischel PS. Altered cellular metabolism in gliomas - an emerging landscape of actionable co-dependency targets. *Nat Rev Cancer.* 2020;20(1):57–70.