

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☐	☒ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	Next Generation Sequencing: Illumina HiSeq 2000 platform; Western blotting: ChemiDoc P system (Bio-Rad), ChemiDoc Touch System (Bio-Rad), and Tanon 4600 (Tanon); Immunofluorescence staining images: Leica TCs SP8 confocal microscope (Leica); RT-PCR: NanoDrop nucleic acid quantitator (Thermo), ProFlex™ PCRsystem (Thermo) and Quantagne q225 Fluorescence quantitative PCR instrument (Beijing Kubo Technology); Cell migration assay and immunohistochemistry staining images: inverted microscope (Leica); ELISA, glycolytic level detection and cell proliferation assay: Multifunctional enzyme-linked immunosorbent assay (ELISA) reader (PerkinElmer).
Data analysis	RNA-seq mapping and quantification were processed by using STAR (v2.5.2b) and RSEM (v1.2.31) software. FACS data were analyzed using FlowJo software (version 10.4). Image J, SPSS 20.0, GraphPad Prism 8 and R language were used for statistical analysis.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The raw RNA-sequencing data of GBM clinical samples reported in CMU cohort (Fig. 1a-c) generated in this study has been deposited in the Genome Sequence Archive in National Genomics Data Center, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences under accession code HRA006353 (<https://bigd.big.ac.cn/gsa-human/browse/HRA006353>). The raw RNA-sequencing data of GSC shHEXB and control samples (Fig. 3a) has been deposited in Gene Expression Omnibus (GEO) database under accession code GSE242231 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE242231>). The raw data of MS to identify the potential interacting proteins (Fig. 4a) has been deposited in the Proteomics IDentifications database via the PRIDE partner repository with the dataset identifier PXD045019 (<http://www.ebi.ac.uk/pride/archive/projects/PXD045019>). Public databases include: the Chinese Glioma Genome Atlas (CGGA) RNA-seq cohorts, including CGGA325 and CGGA693 cohorts (<http://www.cgga.org.cn>), and the Cancer Genome Atlas RNA-seq cohort (TCGA cohort, <https://tcga-data.nci.nih.gov/tcga/>). All data are available in the main text or in the supplementary materials upon request, access can be obtained by contacting the corresponding author via email. The reagent and resource presented in present study was provided in Supplementary Table 9. The related data generated in this study are provided in the Supplementary Information and Source Data file. Source Data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender

Table S1, Fig. S1e-k and Fig. S3 report the sex information of the grade IV glioma patients used in the study. In Supplementary Fig. 1e-k, we report the gender ratio and related prognosis of patients with grade IV glioma, and find that there was no significant difference in prognosis between males and females in glioma. In Supplementary Fig. 3, we investigate the prognostic differences of HEXB based on gender and found that the prognostic value of HEXB in glioma was independent of gender factors. In addition, although gender plays an important role in HEXB and has no significant impact, we still considered gender and selected primary cells extracted from glioma patients of both genders for molecular biology experiments.

Reporting on race, ethnicity, or other socially relevant groupings

We did not report on race, ethnicity or any other socially relevant information on the patients.

Population characteristics

The covariate-relevant population characteristics of the human research participants include: age, sex, IDH1 status, cancer grade classification, overall survival and status were demonstrated in Table S1.

Recruitment

Human glioblastoma specimens were procured from the affiliated hospital of China Medical University. The patients were recruited randomly and underwent tumor removal surgery conducted in the affiliated hospital of China Medical University. The histological diagnoses of these samples were confirmed by two neuropathologists according to the 2021 World Health Organization (WHO) classification guidelines.

Ethics oversight

This study was approved by the Ethics Committee of China Medical University. Informed consent was obtained from each patient.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

The sample size for each experiment indicated in the figure legend. Statistical methods were not employed to predetermine the sample sizes. Sample size was determined based on similar studies previously performed and published by the lab.

Data exclusions

No data were excluded.

Replication	All experiments were reproduced to reliably support conclusions stated in the manuscript. Specifically, in vivo survival analyses were performed at least twice with minimum 6 mice per group included each time. All IHC images presented were imaged at least 3 independent regions for a single data point. For flow cytometry analysis, at least 3 independent biological replicates were used for each genotype. qPCR and in vitro culture experiments were repeated at least three times, with consistent results.
Randomization	Experiments performed in vitro were done using unbiased techniques. Therefore, randomization was not used. After establishment of tumors in vivo, mice were allocated randomly into different treatment groups.
Blinding	In vivo experiments, the investigator was not blinded to groups since the data was acquired and analyzed by the same person.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

HEXB Santa Cruz sc-376781
 HEXB Proteintech 16229-1-AP
 PKM2 Proteintech 15822-1-AP
 IBA1 Abcam ab178846
 GFAP Proteintech 60190-1-AP
 YAP1 CST 14074
 p-YAP1 CST 13008
 LATS1 CST 3477
 p-LATS1 CST 9157
 ITGB1 Proteintech 12594-1-AP
 ILK Proteintech 12955-1-AP
 GST CST 2625
 HIF1 α CST 36169
 CD163 Proteintech 16646-1-AP
 CD4 Proteintech 67786-1-Ig
 CD8 Proteintech 66868-1-Ig
 IDH1-R132H Cayman 32326
 CCR2 Abcam Ab273050
 CX3CR1 Proteintech 13885-1-AP
 CD86 Proteintech 13395-1-AP
 Flag Sigma-Aldrich F1804; RRID: AB_262044
 β -actin Sigma-Aldrich A1978; RRID: AB_476692
 HEXA Santa Cruz sc-376777
 GM2A Proteintech 10864-2-AP
 GLUT1 Proteintech 21829-1-AP
 GLUT3 Proteintech 20403-1-AP
 HK2 Proteintech 22029-1-AP
 LDHA Proteintech 19987-1-AP
 GAPDH Proteintech 60004-1-Ig
 Myc Proteintech 16286-1-AP
 CD11b flow cytometry antibody (Human) BD Pharmingen 340712
 MHCII flow cytometry antibody (Human) BD Pharmingen 340549
 CD206 flow cytometry antibody (Human) BD Pharmingen 564062
 HRP-conjugated Affinipure Goat Anti-Mouse IgG(H+L) Proteintech SA00001-1; RRID: AB_2722565
 HRP-conjugated Affinipure Goat Anti-Rabbit IgG(H+L) Proteintech SA00001-2; RRID: AB_2722564
 Goat Anti-Mouse IgG(H+L), FITC conjugate Proteintech SA00003-1

Goat Anti-Rabbit IgG(H+L), FITC conjugate Proteintech SA00003-2
 Goat Anti-Mouse IgG(H+L), Rhodamine conjugate Proteintech SA00007-1
 Goat Anti-Rabbit IgG(H+L), Rhodamine conjugate Proteintech SA00007-2

Validation

HEXB Santa Cruz 35181782 (MJ Kim et al. Hum Mol Genet (2022)) 32397873 (J Han et al. Autophagy (2021))
 HEXB Proteintech 25976368 (C Sims-Robinson et al. Mol Neurobiol (2016)) 36207292 (S Boland et al. Nat Commun (2022))
 PKM2 Proteintech 18337823 (HR Christofk et al. Nature (2008)) 35081364 (Y Zhu et al. Mol Cell (2022))
 IBA1 Abcam 36410420 (E Saponara et al. Am J Pathol (2023)) 36600259 (M Bellut et al. J Neuroinflammation (2023))
 GFAP Proteintech 29751053 (D Xin et al. Brain Behav Immun (2018)) 30345361 (Y Yang et al. Sci Adv (2018))
 YAP1 CST 38336988 (A Nagel et al. Oncogene (2024)) 38245803 (F Huang et al. Biol Res (2024))
 p-YAP1 CST 37307823 (J Yan et al. Aging Dis (2024)) 38245803 (F Huang et al. Biol Res (2024))
 LATS1 CST 38233853 (JH Yu et al. Cell Commun Signal (2024)) 38163861 (L Li et al. Biol Direct (2024))
 p-LATS1 CST 37924380 (L Lei et al. Breast Cancer Res Treat (2024)) 37957190 (C Inoue et al. Sci Rep (2023))
 ITGB1 Proteintech 33087348 (AL Wishart et al. Sci Adv (2020)) 35618735 (YI Chen et al. Nat Commun (2022))
 ILK Proteintech 37939958 (X Wang et al. Sci Total Environ (2024)) 32485356 (L Lin et al. Int Immunopharmacol (2020))
 GST CST 38102139 (R Berkane et al. Nat Commun (2023)) 37787533 (Y Li et al. J Virol (2023))
 HIF1α CST 37692479 (C Wu et al. Genes Dis (2023)) 37984734 (RS Najjar et al. J Nutr Biochem (2024))
 CD163 Proteintech 37707957 (G Zhang et al. J Clin Invest (2023)) 38342630 (B Liu et al. Adv Sci (Weinh) (2024))
 CD4 Proteintech 38407943 (L Tang et al. Cancer Commun (Lond) (2024)) 37525587 (Q Wang et al. Clin Transl Med (2023))
 CD8 Proteintech 38407943 (L Tang et al. Cancer Commun (Lond) (2024)) 35241665 (X Liu et al. Nat Commun (2022))
 IDH1-R132H Cayman 15173171 (X Xu et al. J Biol Chem (2004)) 20129244 (C Frezza et al. Cancer Cell (2010))
 CCR2 Abcam 35556260 (J Kwon et al. Neurobiol Urodyn (2022)) 35562376 (Y Liu et al. Nat Commun (2022))
 CX3CR1 Proteintech 36709697 (M Takata et al. Tissue Cell (2023)) 33792662 (Y Xia et al. Brain (2021))
 CD86 Proteintech 35985666 (Q Feng et al. Adv Mater (2022)) 38441389 (B Wu et al. Adv Sci (Weinh) (2024))
 Flag Sigma-Aldrich 25697406 (M Srivastava et al. Nat Commun (2015)) 27630089 (Y Liu et al. Virol J (2016))
 β-actin Sigma-Aldrich 24687991 (M Buler et al. FASEB J (2014)) 28129947 (YG Zhang et al. Clin Ther (2017))
 HEXA Santa Cruz 32762772 (OR Brekk et al. Acta Neuropathol Commun (2020)) 31578452 (C Bedia et al. Sci Rep (2019))
 GM2A Proteintech 30404974 (S Ishihara et al. Cell Struct Funct (2018)) 36131294 (YC Hsieh et al. Mol Neurodegener (2022))
 GLUT1 Proteintech 29455928 (L Li et al. Cancer Cell (2018)) 30111835 (Y Wang et al. Int J Oral Sci (2018))
 GLUT3 Proteintech 35773744 (B Yao et al. Mol Cancer (2022)) 35538151 (X Qi et al. Cell Death Differ (2022))
 HK2 Proteintech 31761565 (C Zhang et al. Cell Metab (2020)) 35726058 (X Dong et al. Nat Neurosci (2022))
 LDHA Proteintech 29358703 (Z Yang et al. Nat Cell Biol (2018)) 29455928 (L Li et al. Cancer Cell (2018))
 GAPDH Proteintech 36477534 (R Zhou et al. Nature (2022)) 31666698 (Z Li et al. Nature (2019))
 Myc Proteintech 36823147 (W Zheng et al. Signal Transduct Target Ther (2023)) 37291137 (XH Ran et al. Nat Commun (2023))
 CD11b flow cytometry antibody (Human) BD Pharmingen 37744344 (S Cooray et al. Front Immunol (2023)) 34364880 (D Wang et al. Am J Pathol (2021))
 MHCIi flow cytometry antibody (Human) BD Pharmingen 36369358 (J Schanin et al. Commun Biol (2022)) 34471863 (C Carre et al. iScience (2021))
 CD206 flow cytometry antibody (Human) BD Pharmingen 37042686 (L Gallucci et al. EMBO Rep (2023)) 36325060 (Q Guo et al. iScience (2022))
 HRP-conjugated Affinipure Goat Anti-Mouse IgG(H+L) Proteintech 37286607 (L Chen et al. Nature (2023)) 37098345 (D Cao et al. Cell (2023))
 HRP-conjugated Affinipure Goat Anti-Rabbit IgG(H+L) Proteintech 37286607 (L Chen et al. Nature (2023)) 35788567 (L Si et al. Nat Biotechnol (2022))
 Goat Anti-Mouse IgG(H+L), FITC conjugate Proteintech 29751053 (D Xin et al. Brain Behav Immun (2018)) 28585532 (Y Wang et al. Nat Commun (2017))
 Goat Anti-Rabbit IgG(H+L), FITC conjugate Proteintech 29618817 (P Zhou et al. Nature (2018)) 33420426 (S Wang et al. Cell Res (2021))
 Goat Anti-Mouse IgG(H+L), Rhodamine conjugate Proteintech 33420426 (S Wang et al. Cell Res (2021)) 30462330 (WX Bian et al. Nucleic Acids Res (2019))
 Goat Anti-Rabbit IgG(H+L), Rhodamine conjugate Proteintech 31147887 (J Liang et al. Angiogenesis (2019)) 28528817 (C Wu et al. Mol Ther (2017))

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

Human cell lines including THP-1, SH-SY5Y, NHA and Jurkat were obtained from the Chinese Academy of Sciences Cell Bank (Shanghai, China). The glioma spheres (GSC1, GSC21, GSC24, and GSC63) used in this study was generated from primary GBM tumours. mGSCs were extracted from murine spontaneous glioma established by sleeping beauty (SB) transposon method described before. Briefly, SB is a two-part system consisting of transposon DNA and transposase. SB transposase could cut off the transposon DNA and paste it into the TA dinucleotide of the target genome. We separated the transposase and transposon on different plasmids. The transposon plasmid with oncogenic genes (SV40-LgT and NRAS-G12V) was mixed with the plasmid encoding transposase and injected into the brain of fetal mouse (within 24 h after born) to induce spontaneous glioma.

Authentication

THP-1, SH-SY5Y, NHA and Jurkat cell lines from the Chinese Academy of Sciences Cell Bank were authenticated by the vendor using short tandem repeat (STR) analysis, and were not validated further in our laboratory.

Mycoplasma contamination

All cell lines were tested routinely for Mycoplasma infection. All tests were negative.

Commonly misidentified lines
(See [ICLAC](#) register)

No commonly misidentified cell lines were used.

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals	Six-to-eight-week-old female BALB/c nude mice and male C57BL/6N mice were purchased from Beijing Vital River Laboratory Animal Technology. All mice were resided in specific pathogen-free (SPF) conditions.
Wild animals	No wild animals were used in this study.
Reporting on sex	The findings are not limited to a specific sex. Sex was not taken into account in the study design.
Field-collected samples	No field-collected samples were used in this study.
Ethics oversight	All mouse work was performed in accordance with the institutional animal care use committee and relevant guidelines of China Medical University.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	NA
Study protocol	For the in-house human tumor samples used in our study, the protocol was approved by Shengjing Hospital of China Medical University. All studies were performed in accordance with guide lines and regulations by Shengjing Hospital of China Medical University, and in accordance with the Declaration of Helsinki Principles.
Data collection	Tumor tissue samples were collected at the time of surgery after informed consent. The histological diagnoses of these samples were confirmed by two neuropathologists according to the 2021 World Health Organization (WHO) classification guidelines. The libraries were sequenced on the Illumina HiSeq 2000 platform using the 101-bp pair-end sequencing strategy. The original image data generated by the sequencing machine were converted into sequence data via base calling (Illumina pipeline CASAVA v1.8.2). Hg 19 Ref Seq (RNA sequences, GRCh37) was downloaded from the UCSC Genome Browser. Gene expression was calculated using the FPKM method.
Outcomes	Overall survival (OS) was calculated from the date of diagnosis to death or the end of follow-up. The point of death was defined by death certification, which could be acquired by local hospitals or police stations.

Plants

Seed stocks	<i>Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.</i>
Novel plant genotypes	<i>Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.</i>
Authentication	<i>Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.</i>

Flow Cytometry

Plots

Confirm that:

- ☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☒ All plots are contour plots with outliers or pseudocolor plots.
- ☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation

For M1 and M2 macrophage marker measurement, macrophages were collected and stained with anti-CD11b followed by incubation with the indicated antibodies (MHCII and CD206) for 30min and analyzed by flow cytometry. For cell apoptosis analysis, the cells were collected and suspended in PBS containing Annexin V and PI for 15 minutes and then directly run on a flow cytometry.

Instrument

CytoFLEX flow cytometer (Beckmann Coulter).

Software

FACS data were analyzed using FlowJo software (version 10.4).

Cell population abundance

FACS sort was not performed in this study.

Gating strategy

For flow cytometry data, the relevant gating strategy was provided, as can be seen in Supplementary Figure 10c and 15g.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.