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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

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 (*n*) 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 *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ 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. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ 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 *d*, Pearson's *r*), 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	All the sequencing data used in this manuscript are public available in Chinese Glioma Genome Atlas (CGGA): http://www.cgga.org.cn/.
Data analysis	For RNA-seq data analysis, differential genes expression analysis was performed by using glmFit function in edgeR package (v3.28.1). Significant differentially expressed genes (DEGs) were defined as genes with expression fold change ≥2 and a false discovery rate (FDR)<0.05. With reference to KEGG database, over-represented pathways were measured for genes with positive correlation to LOC expression using clusterProfiler package (v3.14.3, RRID:SCR_016884). For the whole-exome sequencing and data analysis, the initial alignment BAM files were subjected to sorting (SAMtools, RRID:SCR_002105), removal of duplicated read (Picard), local realignment of reads around potential small insertions/deletions, and recalibration of the base quality score (Genome Analysis Toolkit). MuTect (RRID:SCR_000559) was used to generate high-confidence mutation calls. Variant Effector Predictor was used to annotate the called mutations. For the methylation microarray analysis, positional information of the array (Illumina Infinium HumanMethylation27 Bead-Chips, Illumina Inc.) was downloaded from Illumina's official website of product support document. Genomic regions of the array were first lifted over from human genome version hg18 to version hg38 using UCSC utility LiftOver tool. Differential methylation signal analysis was then performed between wildtype and mutant IDH samples by using Student's t-test. Finally, CpG islands upstream (+/-1.5kb gene start) of differentially expressed genes (in RNA-Seq of the same comparison) were extracted and CpG island with significant (p<0.05) methylation signal difference were selected. For calculating glioma infiltrating microglia/macrophage (GIM) score: to estimate the extent of glioma infiltration of microglia/macrophages in each patient, we obtained GIM gene sets from previous study and performed single sample gene set enrichment analysis (ssGSEA) for bulk RNA-seq profiles using R GSVA packets with the parameter "method= 'gsa'". Bulk RNA-seq data of 198 primary GBM patients from CGGA cohort was used. For single-cell sequencing and data analysis, with reference to expression data of the same patients from bulk RNA-seq, we grouped the

scRNA-seq samples into three groups based on the expression levels of LOC. Downstream data analysis below were done using functions in Seurat R package (v3.2.3). Expression normalization and scaling were first implemented before performing dimensional reduction analysis using RunPCA and RunTSNE functions. All cells were then clustered based on the expression profile. Gene markers representing each cluster were identified and by comparing to database of known cell type markers (CellMarker database), the cell type of each cluster is classified. Proportions of each cell type were then calculated using R software (v4.0.4) and Student's t-test was used to test the significance of proportion shift between patients with high and low LOC expression. For the scRNA-seq data from 10X genomics, raw scRNA sequencing data (FASTQ) were downloaded from 10X Genomics public repository (Parent_SC3v3_Human_Glioblastoma_fastqs.tar) and processed with CellRanger software (v6.0.2). Downstream data analysis was done using functions in Seurat R package. Gene module score analysis was performed by using AddModuleScore function.
For tumor cell copy number inference analysis, the copy number alteration prediction was performed using inferCNV, limiting the inferred copy number values to (-1,0,1) by replacing all values above 1.05 by one and below 0.95 by -1. The values ranging from 0.95 to 1.05 were normalized to 0. Finally, we defined CNV levels as the average normalized copy number values of all cells in each sample. t-SNE plot of 5232 cells showing the major cell clusters in gliomas, including astrocytes (tumor cells), GAMs, oligodendrocytes, T cells, pericytes.
For cell annotation based on cellular states in glioma, we first obtained the gene sets for six cellular states in gliomas as defined in previous study. This dataset is downloaded from 10X genomics website (https://www.10xgenomics.com/resources/datasets/human-glioblastoma-multiforme-3-v-3-whole-transcriptome-analysis-3-standard-4-0-0). For each cell, we calculated six cellular states score value by using the R Seurat AddModuleScore function. For a cell, the cell state with the highest score is defined as the cell's final cell state.
For Ligand-receptor interaction analysis, all significant ligand-receptor interaction pairs were identified using CellPhoneDB v2.0 (RRID:SCR_017054). Basically, putative interactions between different cell types were identified based on the expression of a receptor by one cell type and the expression of an interacting ligand by another cell type. A ligand or receptor transcript was defined as "expressed" by a given cell type if its average expression in that cell type was above the threshold of 0.5 in log2 scale, and it was expressed in at least 10% of cells of that type.
For mass spectrometry data analysis, Data was searched using X! Tandem Vengeance (2015.12.15.2) or Mascot with the following: fixed modification on cysteine carbamidomethyl, variable modifications on oxidized methionine and N-acetylation and, maximum missed cleavages of 2, parent ion tolerance of 10ppm using X! Tandem Vengeance or 6ppm using Mascot and fragment ion tolerance of 0.5Da – searched against the human and human decoy database. Spectrum counts of peptides and proteins were derived using Scaffold Proteomics Software (version 3, Matrix Science) with 95% confidence interval and minimum of 2 peptides as criteria.

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

Single-cell RNA-seq (part 1, for Fig.3A-C), bulk RNA-seq and whole-exome sequencing data, and corresponding clinical traits information were downloaded from the Chinese Glioma Genome Atlas database (CGGA, 325 samples for mRNAseq_325 dataset; 693 samples for mRNAseq_693 dataset; 286 samples for WEseq_286; 286 samples for WEseq_286 dataset; 6148 cells for scRNA-seq, http://www.cgga.org.cn). For mRNAseq_325 dataset, data source: Raw Fastq Data (BIGD accession number: PRJCA001747), https://bigd.big.ac.cn/bioproject/browse/PRJCA001746; For mRNAseq_693 dataset, data source: Raw Fastq Data (BIGD accession number: PRJCA001747), https://bigd.big.ac.cn/bioproject/browse/PRJCA001747; for WEseq_286 dataset, data source: Raw Fastq Data (BIGD accession number: PRJCA001636), https://bigd.big.ac.cn/bioproject/browse/PRJCA001636; For single-cell RNA-seq (part 1, for Fig.3A-C), data source: Raw Fastq Data (BIGD accession number: HRA000179), https://ngdc.cncb.ac.cn/gsa-human/browse/HRA000179; for For single-cell RNA-seq (part 2, for Fig.3E and 3F), data source: https://www.10xgenomics.com/datasets/human-glioblastoma-multiforme-3-v-3-whole-transcriptome-analysis-3-standard-4-0-0.Code to reproduce the main results included in the paper is available on Zenodo at https://doi.org/10.5281/zenodo.10836321.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	We did not recruit any patients for this study as we just analyzed the sequencing data from the well-established bio-repositories including Chinese Glioma Genome Atlas and Samsung Medical Center. Please see detailed information from CGGA website: http://www.cgga.org.cn/ (CGGA cohort) and Supplementary Table S2 (SMC cohort).This study does not focus on sex and gender difference.
Population characteristics	We did not recruit any patients for this study as we just analyzed the sequencing data from Chinese Glioma Genome Atlas and Samsung Medical Center. Please see detailed information from CGGA website: http://www.cgga.org.cn/ (CGGA cohort) and Supplementary Table S2 (SMC cohort).
Recruitment	No patients were recruited for this study. The sequencing data used in this study were obtained from Chinese Glioma Genome Atlas and Samsung Medical Center.
Ethics oversight	The biospecimens for this study were provided by CGGA including patients treated at Beijing Tiantan Hospital, Sanbo Hospital in Beijing, Tianjin Medical University General Hospital, The First Affiliated Hospital of Nanjing Medical University, Harbin

Medical University, China Medical University) under IRB KY2013-017-01 and Samsung Medical Center BioBank under the IRB number 2010-04-004. Patient samples used in this study were collected with the consent from each cohort before the surgical operation.

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

Life sciences study design

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

Sample size	No specific method was applied to pre-define the sample size.
Data exclusions	No data were excluded from the analysis.
Replication	Each experiment is performed with with proper replications. All attempts of replication were successful.
Randomization	Mice for tumor xenograft model were randomly grouped. No randomization was performed for other experiments as control group and treated group (such as knockdwon/knockout, overexression,with or without drug treatment) were already defined.
Blinding	The investigators were blinded to group allocation during data collection and analysis including IF analysis of the protein staining intensity.

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

Methods

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

Antibodies

Antibodies used	anti-p-p38 (Thr180/Tyr182) (Cell signalling; #9215S, 1:1000 dilution, RRID:AB_331762), anti-p38 (Santa Cruz; #sc-728,1:1000 dilution RRID:AB_632141), anti-p-p65 (Ser536) (Cell signalling; #3031L, 1:500 dilution, RRID:AB_330559), anti-p65 (Santa Cruz; #sc-8008, 1:1000 dilution, RRID:AB_628017), anti-actin (Sigma; #A2066, 1:2000 dilution, RRID:AB_476693), anti-HSP90α/β (F-8) (Santa Cruz; #sc-13119, 1:2000 dilution, RRID:AB_675659), anti-Wip1 (Santa Cruz; #sc-376257, :1000 dilution, RRID:AB_10986000) and anti-mutant IDH1 (Origene, #TA190113, :1000 dilution, RRID:AB_3076158). (CD45-FITC, Biolegend, cat:103108, 1:100 dilution,RRID: AB_312973; CD11b-PE, Biolegend, 1:100 dilution,cat:101208, RRID: AB_312791). Anti-Ki67 (1:100 dilution, Abcam, cat: ab245113, RRID:AB_2923193), anti-IBA1 (1:500 dilution, Abcam, cat: ab178846, RRID:AB_2636859). MIF1, abcam, cat:ab187064,1:200 dilution, RRID:AB_2934299; SOX2, Santa cruz, cat:sc-365823, 1:100 dilution, RRID:AB_10842165; anti-GFP antibody (1:1000 dilution, Invitrogen; #A-11122), anti-DHX15 antibody (1:1000 dilution, Santa Cruz; #sc-271686).
Validation	Antibody validation was performed as described by the manufacturer. For example: For the anti-p-p38 (Thr180/Tyr182) (Cell signalling; #9215S), the validation was provided by the manufacturer's website and also performed by using Jurkat, C6, NIH/3T3 COS and Hela cells for WB,IF and FACS analysis. For the anti-p38 (Santa Cruz; #sc-728, RRID:AB_632141), the validation was provided by the manufacturer's website and also performed by using Jurkat A-431, MCF7,KNRK and HeLa cells for WB analysis and Immunoperoxidase staining of formalin fixed, paraffin-embedded human skeletal muscle tissue. For the anti-p-p65 (Ser536) (Cell signalling; #3031L, RRID:AB_330559), the validation was provided by the manufacturer's website

and also performed by using HeLa cells with or without TNFa treatment for western blot anlaysis.
For the anti-p65 (Santa Cruz; #sc-8008), the validation was provided by the manufacturer's website and also performed by using THP-1, K-562, MOLT-4, Jurkat, T24 and HUV-EC-C for fluorescent western blot anlaysis.
For the anti-HSP90α/β (F-8) (Santa Cruz; #sc-13119), the validation was provided by the manufacturer's website and also performed by using A-431, HepG2, Jurkat, SK-BR-3 and K-562 for fluorescent western blot anlaysis.
For the anti-Wip1 (Santa Cruz; #sc-376257), the validation was provided by the manufacturer's website and also performed by using Jurkat, Y79, U266 and SH-SY5Y for western blot anlaysis.
For anti-mutant IDH1 (Origene, #TA190113), the validation was provided by the manufacturer's website and also performed by using HEK293T cells transfected with the pCMV6-ENTRY control or pCMV6-wildtype IDH1 or pCMV6-ENTRY IDH1 mutated (R132H) cDNA for western blot anlaysis.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	GL261 cells (RRID:CVCL_X986) were obtained from the Tumour Bank Repository at the National Cancer Institute (Frederick, Maryland). Human microglia cells (cat: ABC-TC3704) were purchased from AcceGen Biotech. Patient-derived cell lines were established by Samsung Medical Center. 293T and LN18 were purchased from ATCC.
Authentication	293T and LN18 were purchased from ATCC with vendor's authentication. GL261 cells purchased from Tumour Bank Repository at the National Cancer Institute with vendor's authentication.
Mycoplasma contamination	All cell lines used in this study were tested to be negative for Mycoplasma contamination using abm's Mycoplasma PCR Detection Kit (Cat. No. G238).
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines from the ICLAC register were used in this study.

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	6-8 weeks old female NSG mice were purchased from Invivos. Gm16685 knockout mice were generated by Dr. Masahito Ikawa's group (Research Institute for Microbial Diseases, Osaka University). Gm16685 knockout C57BL/6 mice were bred and maintained at Biological Resource Centre (A*STAR,Singapore) at pathogen-free conditions. All animal studies were conducted in accordance with the Institutional Animal Care and Use Committee at A*STAR (Singapore) or Samsung Medical Center. All procedures were approved under the IACUC protocol ID #221680 and ID #201572.
Wild animals	This study did not involve wild animals.
Reporting on sex	This study does not focus on sex difference. Female NSG mice were mostly used for tumor xenograft experiments. Both female and male wildtype and Gm16685 knockout C57BL/6 mice were used for the syngeneic glioma mouse model.
Field-collected samples	The study did not involve samples collect from the field.
Ethics oversight	All animal studies were conducted in accordance with the Institutional Animal Care and Use Committee at A*STAR (Singapore) or Samsung Medical Center.

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

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	Brain tumors were collected and dissociated using the Brain Tumor Dissociation Kit (cat:130-095-942, Miltenyi Biotec) in

Sample preparation	combination with the gentleMACS™ Dissociator according to the manufacturer's protocol.
Instrument	BD LSRFortessa
Software	BD FACSDiva
Cell population abundance	Cell type abundance was determined based on their surface markers. Such as CD45+CD11b+ which are known to use for label GAMs.
Gating strategy	Briefly, we excluded cell debris and subsequently selected single cells by FSC-A and FSC-H gating. By using single stain controls, we adjusted the laser power and compensations when required. Single stains were used to apply positive and negative gating.

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