nature portfolio

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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

OLYMPUS (FV3000) for images collection;
OLYMPUS (BX53) for frozen section images collection;
Biorad (CFX96) for performing real-time PCR assay;
Biorad (ChemiDoc XRS +) for the detection Western Blotting bands;
Hitachi (H-9500) for the observation of virus particle morphology;
Immunohistochemical analysis are obtained through the PANNORAMIC MIDI II automatic digital slide scanner (3DHISTECH, Budapest, Hungary).
BD LSRFortessa flow cytometer for flow cytometry raw data collection.

Data analysis

GraphPad Prism 9 was used to perform statistical analysis and to draw line, column and survival plots;
FCS Express 7 was performed to analyze flow cytometry data;
Adobe Illustrator CS5 was used to organize figures;
Adobe PhotoShop CS5 was used to display photo items;
ImageJ was used to quantify the intensity of bands from Western Blotting;
Proteome, phosphoproteome and acetylproteome data acquisition: timsTOF Pro mass pectrometry system. Peptide identification and quantification: Maxquant (v1.6.15.0, https://maxquant.net/maxquant/)
Bioinformatic and downstream analysis was done with R(4.0.4, https://www.r-project.org/).
The R packages ggplot2 (v3.4.2, https://CRAN.R-project.org/package=ggplot2), dplyr (v1.1.2, https://CRAN.R-project.org/package=dplyr), tidyr (v1.3.0, https://CRAN.R-project.org/package=tidyr), KSEA (v 0.99.0, https://github.com/casecpb/KSEAapp), clusterProfiler (v4.8.1, https://bioconductor.org/packages/release/bioc/html/clusterProfiler.html), Biostrings (v 2.52, https://

bioconductor.org/packages/release/bioc/html/Biostrings.html),
were employed to perform downstream analysis.
Multiple sequence alignment was conducted using the CLUSTALW tool (https://www.genome.jp/tools-bin/clustalw.).
Protein structure was analyzed using the AlphaFold3 online platform (https://deepmind.google/technologies/alphafold/).
Protein visualization were visually inspected and mapped using the PyMOL software (https://pymol.org).
Database include Gene Ontology (GO) database (version 3.14.0), Kyoto Encyclopedia of Genes and Genomes (KEGG) database (version 3.14.0), String database (version 12.0), and DAVID database (version December, 2021), Chlorocebus proteome (Blast_Chlorocebus_sabaeus_60711_PR_20210928) and Mycoplasma proteome (UniProt-reviewed_yes+AND+organism_mycoplasma)

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

All original mass spectrometry data of this paper are publicly accessible and have been deposited in the ProteomeXchange partner repository (http://www.proteomexchange.org/) under accession number PXD048439. All other study data are included in the main text and/or supporting information. 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	We took peripheral blood samples for the induction of pluripotent stem cells to construct brain organoids, the sex or gender has no significant impact on our study. So the participants were recruited randomly without no sex or gender consideration.
Reporting on race, ethnicity, or other socially relevant groupings	We have no groupings on any socially relevant factors.
Population characteristics	Please see above.
Recruitment	Informed consent was obtained from participants who provided peripheral blood samples for the purpose of inducing pluripotent stem cells
Ethics oversight	The generation of brain organoids and the related experiments was approved by the Medical Ethics Committee of the First Affiliated Hospital of Jilin University (2023-661).

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	For animal experiments, the sample size is 5 in each group. For cell experiments, at least biological triplicates were used in repeated experiments.
Data exclusions	No data exclusions.
Replication	The results of the in vivo studies were repeated for two or three times; the results of cell or tumor tissue-based studies were repeated for three or more times.
Randomization	6-8 weeks old mice with similar weight and healthy status were randomly grouped.

Blinding	The investigatiors were blinded to group allocations during data collection.

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	Flag tag (Proteintech, 66008-4-Ig, 8H6A10, 00099894), MYC tag (Proteintech, 60003-2-Ig, 1A5A2, 00118338), Tick-borne Encephalitis Virus NS1 (R&D Systems, MAB101061, 1004120, CMED012211) , HA tag (Proteintech, 51064-2-AP, Polyclona, 001229118), Alpha Synuclein (SNCA, Proteintech, 10842-1-AP, Polyclona, 00118118), phosphor-KAP1 (Ser824) (Abcam, ab133440, EPR5248, 1076951-6), KAP1 (Zen-Bioscience, R24790, R07-5E6, N20MY9P), Phospho-DNA PKcs (Ser2056) (Zen-Bioscience, 380800, Polyclona, M09JA09) ,DNA PKcs (Zen-Bioscience, 200618-6D1, 6D1-C11-F10, EE0903), phospho-ATM (Ser1981) (Zen-Bioscience, 380751, 380751, Polyclona, M11MY12), ATM (Zen-Bioscience, R23317, R05-8D4, M09MY01), phosphor-ATR (T1989) (Abcam, ab223258, EPR21991, GR3236057-4), ATR (Zen-Bioscience, 161471, Polyclona, M11MY03), RRM2 (Zen-Bioscience, R25626, R09-4G8, 00101166) , Phospho-Chk1 (Ser317) (Proteintech,28807-1-AP, Polyclonal, 0122786), Chk1 (Proteintech,25887-1-AP,Polyclonal,00136096), Phospho-Chk2 (Thr68) (Zen-Bioscience, 340766, Polyclona, M20NO01) , Chk2 (Zen-Bioscience, R23921,R04-8E5,N22JA20), gamma H2A.X (Ser139) (Abcam, ab11174 , Polyclona, 1028395-9), Histone H3 (Proteintech,17168-1-AP, Polyclona, 00106223), 53BP1 (Abcam, ab175933, EPR2172(2), 1015299-36), Pan Acetylation (Proteintech,66289-1-Ig,1D5F2,10004258) , SIRT1 (Proteintech, 13161-1-AP, Polyclonal, 00102771) , Vinculin (Proteintech, 66305-1-Ig, 2B5A7, 10020241), Ku70 (Zen-Bioscience, 200995, 7B1-E12-G4, EE0903), Ku80 (Zen-Bioscience, 201004, 8H1-C3-G10, DD0729), LC3 (Proteintech, 14600-1-AP, Polyclona, 00125366), phospho-AKT1 (Ser473)(Zen-Bioscience, 381555, Polyclona,M29MA03), phospho-AKT1 (Thr308) (Zen-Bioscience, 341790, Polyclona, L22OC01), AKT1 (Proteintech, 80457-1-RR, 4I5, 23000647), phospho-mTOR (Ser2448) (Zen-Bioscience, 381557, Polyclona, M27MA0P), mTOR (Zen-Bioscience, 380411, Polyclona, M29MA08), VPS11 (Zen-Bioscience, R389076, R02-5O5, M20JL11), VPS41 (Zen-Bioscience, R26098, R08-1J7, M11SE01), LAMP1 (Beyotime, AF7353, Polyclona, B292397) and VPS18 (Zen-Bioscience, R389082, R09-3D6, M01SE05) , STX17 (Proteintech, 17815-1-AP, Polyclona, 00097435) , Phospho-eIF2α (Ser51)(Cell Signaling Technology,3398S,D9G8,05), EIF2α(Proteintech,11170-1-AP, Polyclona, 00116393) , Phospho-PERK (Thr980) (Cell Signaling Technology, 3179,16F8, 08), PERK (Zen-Bioscience, R25331,R09-1F9,N23MY5P) , Mouse IgG1 , (Proteintech, 66360-1-Ig, 1F8D3, 10028151)
Validation	SIRT1 (Proteintech, 13161-1-AP, Polyclonal, 00102771, KD/KO VALIDATED) , KAP1 (phospho S824) (Abcam, ab133440, EPR5248, 1076951-6, KD/KO VALIDATED) 53BP1(Abcam, ab175933, EPR2172(2), 1015299-36, KD/KO VALIDATED) Chk1 (Proteintech,25887-1-AP, Polyclonal, 00136096, KD/KO VALIDATED) Histone H3 (Proteintech, 17168-1-AP, Polyclona, 00106223, KD/KO VALIDATED) STX17 (Proteintech, 17815-1-AP, Polyclona, 00097435, KD/KO VALIDATED) EIF2α(Proteintech,11170-1-AP, Polyclona, 00116393, KD/KO VALIDATED) LC3 (Proteintech, 14600-1-AP, Polyclona, 00125366,KD/KO VALIDATED)

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	All the cell lines used in this study, including Vero cells (CL-0242), HEK-293T cells (CL-0242), A549 cells (CL-0242) and T98G cells (CL-0242) were purchased from Procella, Wuhan, China
Authentication	All cell lines have been identified for authenticity by the supplier, details can be found on their official website.
Mycoplasma contamination	All cells were verified to be mycoplasma-free.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified 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-week-old female BALB/c mice
Wild animals	No wild animals were used.
Reporting on sex	female mice
Field-collected samples	No field-collected samples were used.
Ethics oversight	All infectious experiments involving mice were conducted in the BSL-3 facility at the Changchun Veterinary Research Institute, Chinese Academy of Agricultural Sciences. The protocol was reviewed and approved by the Animal Welfare and Ethics Committee of Jilin University (2023-0166).

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

Plants

Seed stocks	*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.*
Novel plant genotypes	*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.*
Authentication	*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, mosiacism, off-target gene editing) were examined.*

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	A549 cells for analysis of cell cycle and Brdu staining using flow cytometry. Cells were plated in the 12-well plate, after overnight adherance, cells were infected with TBEV at the MOI of 1.0, cells were collected after 48 hours and fixed in pre-cooled in 70% ethanol overnight at 4°C. The cells were then proccessed and stained with PI and/or Brdu for flow cytometry analysis.
Instrument	BD LSRFortessa flow cytometer
Software	The results were analyzed by ModFit LT 5.0 and flowJo 7.6.1
Cell population abundance	We collected a total of 20,000 cells for analysis. Initially, a group of cells was gated based on FSA-A and SSC-A parameters, followed by gating of mononuclear cells using FSC-A and FSC-H. Subsequently, the cells were analyzed for the indicated antibodies or stainings.
Gating strategy	we have provided the gating strategy in Figure S15

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