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Corresponding author(s): Peihua Luo

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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.

Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.
For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

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	SRB - Thermo MULTISKAN SPECTRUM; Hematoxylin-eosin staining - Aperio AT2; qPCR - CFX96TM Real-Time System; Western blot - Amersham Imager 600.
Data analysis	Western blot images were performed using Amersham Imager 600, thickness determination and densitometric values are analyzed by ImageJ (Version 1.51k), SRB colorimetric assay was detected by Thermo MULTISKAN SPECTRUM, qPCR data was processed using Microsoft Excel, statistical analysis using SPSS 21.0.

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 authors declare that all data supporting the findings of this study are available within the paper and the Supplementary Information files.

Human research participants

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

Reporting on sex and gender	n/a
Population characteristics	n/a
Recruitment	n/a
Ethics oversight	n/a

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	Sample size for cellular and animal experiments were determined according to the minimal number of independent biological replicates powered to significantly identify an effect. Mouse experiments were expected to yield significant results based on previous experience using this mouse model.
Data exclusions	No data was excluded.
Replication	Western blot, qPCR and cell survival assay were repeated and our data are based on three independent experiments with similar results. Details are described in the legends of the corresponding figures.
Randomization	The randomized selection was done by picking unlabeled mouse from a large cage and placing in one of the experimental cages to match mean animal weight between groups.
Blinding	(1) For all western blot, qPCR and cell survival assay related experiments, no blinding was used during data collection because data from different groups were generated simultaneously, no personal bias will be involved. (2) For animal related experiments, the technicians who collected the data were blind to the genotypes and treatments. (3) Thickness determination and densitometric values are analyzed by ImageJ (Version 1.51k) and there is no personal bias during data analysis.

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

Western blot: all antibodies were diluted at 1:1000
anti-GAPDH (Diagbio, db106), anti-p53 (Santa Cruz Biotechnology, sc-126), anti-EphA2 (Cell Signaling Technology, #6997), anti-phospho-EphA2 (Ser897) (Cell Signaling Technology, #6347), anti-phospho-EphA2 (Tyr588) (Cell Signaling Technology, #12677), anti-MDM2 (Huabio, RT1382), anti-phospho-MDM2 (Ser166) (Cell Signaling Technology, #3521), anti-c-PARP (Huabio, ET1608-10), anti-HA tag (Diagbio, db2603), anti-FLAG tag (Diagbio, db7002), anti-Lamin B1 (Huabio, R1508-1), anti-ERK (Santa Cruz Biotechnology, sc-81457), anti-phospho-ERK (Tyr204) (Santa Cruz Biotechnology, sc-7383), anti-LC3 (Cell Signaling Technology, #4108), anti-phospho-Akt (Ser473) (Cell Signaling Technology, #4060).

Immunohistochemical staining:
anti-p53 (Origene, TA808657, 1:100), anti-Phospho-MDM2 (Ser166) (Cell Signaling Technology, #3521, 1:150) or anti-p-ERK (Tyr204) (Santa Cruz Biotechnology, sc-7383, 1:100) .

Immunofluorescence:
anti-p53 (Santa Cruz Biotechnology, sc-126, 1:100), anti-EphA2 (Cell Signaling Technology, #6997,1:100), anti-Phospho-EphA2 (Ser897) (Cell Signaling Technology, #6347, 1:100), anti-MDM2 (Affinity Biosciences LTD, AF0208, 1:200), anti-p-ERK (Tyr204) (Santa Cruz Biotechnology, sc-7383, 1:200).

Validation

Western blot: all antibodies were diluted at 1:1000.
anti-GAPDH (Diagbio, db106), http://diagbio.com/prodetail.aspx?caid3=73&pid=40278;
anti-p53 (Santa Cruz Biotechnology, sc-126), https://www.scbt.com/p/p53-antibody-do-1?requestFrom=search;
anti-EphA2 (Cell Signaling Technology, #6997), https://www.cellsignal.cn/products/primary-antibodies/epha2-d4a2-xp-rabbit-mab/6997?site-search-type=Products&N=4294956287&Ntt=%236997&fromPage=plp&_requestid=1736314;
anti-phospho-EphA2 (Ser897) (Cell Signaling Technology, #6347), https://www.cellsignal.cn/products/primary-antibodies/phospho-epha2-ser897-d9a1-rabbit-mab/6347?site-search-type=Products&N=4294956287&Ntt=236347&fromPage=plp&_requestid=1736524;
anti-phospho-EphA2 (Tyr588) (Cell Signaling Technology, #12677), https://www.cellsignal.cn/products/primary-antibodies/phospho-epha2-tyr588-d7x2l-rabbit-mab/12677?site-search-type=Products&N=4294956287&Ntt=%2312677&fromPage=plp&_requestid=1736829; anti-MDM2 (Huabio, RT1382), http://www.huabio.cn/product/MDM2-antibody-RT1382;
anti-phospho-MDM2 (Ser166) (Cell Signaling Technology, #3521), https://www.cellsignal.cn/products/primary-antibodies/phospho-mdm2-ser166-antibody/3521?site-search-type=Products&N=4294956287&Ntt=%233521&fromPage=plp;
anti-c-PARP (Huabio, ET1608-10), http://www.huabio.cn/product/Cleaved-PARP-antibody-ET1608-10;
anti-HA tag (Diagbio, db2603), http://diagbio.com/prodetail.aspx?caid3=73&pid=40299;
anti-FLAG tag (Diagbio, db7002), http://diagbio.com/prodetail.aspx?caid3=73&pid=40317;
anti-Lamin B1 (Huabio, R1508-1), http://www.huabio.cn/product/Lamin-B1-antibody-R1508-1##;
anti-ERK (Santa Cruz Biotechnology, sc-81457), https://www.scbt.com/p/erk-2-antibody-12a4?requestFrom=search;
anti-phospho-ERK (Tyr204) (Santa Cruz Biotechnology, sc-7383), https://www.scbt.com/p/p-erk-antibody-e-4?requestFrom=search;
anti-LC3 (Cell Signaling Technology, #4108), https://www.cellsignal.cn/products/primary-antibodies/lc3a-b-antibody/4108?site-search-type=Products&N=4294956287&Ntt=%234108&fromPage=plp&_requestid=1758413;
anti-phospho-Akt (Ser473) (Cell Signaling Technology, #4060), https://www.cellsignal.cn/products/primary-antibodies/phospho-akt-ser473-d9e-xp-rabbit-mab/4060?site-search-type=Products&N=4294956287&Ntt=%234060&fromPage=plp&_requestid=1758511.

Immunohistochemical staining:
anti-p53 (Origene, TA808657, 1:100), https://www.origene.com.cn/catalog/antibodies/primary-antibodies/ta808657/p53-tp53-mouse-monoclonal-antibody-clone-id-otipab-240;
anti-phospho-MDM2 (Ser166) (Cell Signaling Technology, #3521, 1:150), https://www.cellsignal.cn/products/primary-antibodies/phospho-mdm2-ser166-antibody/3521?site-search-type=Products&N=4294956287&Ntt=%233521&fromPage=plp;
anti-p-ERK (Tyr204) (Santa Cruz Biotechnology, sc-7383, 1:100), https://www.scbt.com/p/p-erk-antibody-e-4?requestFrom=search.

Immunofluorescence:
anti-p53 (Santa Cruz Biotechnology, sc-126, 1:100), https://www.scbt.com/p/p53-antibody-do-1?requestFrom=search;
anti-EphA2 (Cell Signaling Technology, #6997,1:100), https://www.cellsignal.cn/products/primary-antibodies/epha2-d4a2-xp-rabbit-mab/6997?site-search-type=Products&N=4294956287&Ntt=%236997&fromPage=plp&_requestid=1736314;
anti-phospho-EphA2 (Ser897) (Cell Signaling Technology, #6347, 1:100), https://www.cellsignal.cn/products/primary-antibodies/phospho-epha2-ser897-d9a1-rabbit-mab/6347?site-search-type=Products&N=4294956287&Ntt=%236347&fromPage=plp&_requestid=1759815
anti-MDM2 (Affinity Biosciences LTD, AF0208, 1:200), http://www.affbiotech.cn/goods-136-AF0208-MDM2_Antibody.html
anti-p-ERK (Tyr204) (Santa Cruz Biotechnology, sc-7383, 1:200), https://www.scbt.com/p/p-erk-antibody-e-4?requestFrom=search.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	The human primary hepatocytes were provided by BioreclamationIVT (F00995-P and M00995-P, Hicksville, New York, USA), and the clinical characteristics of the donors are shown in Table S1-S3. HL-7702 (JNO-048) was purchased from GuangZhou Jennio Biotech Co.,Ltd. SW-480 (TCHu 86), HCT-116 (TCHu 99), Bel-7402 (TCHu 10), Hep-G2 (TCHu 72), and HEK-293T (GNHu 18) cells were originally obtained from the Cell Bank of China Science Academy.
Authentication	Cells were used without modification once received from the supplier and therefore were not authenticated.
Mycoplasma contamination	Cells lines used in this study tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines 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	Animal experiments involved male mice, of the C57BL/6J, aged 6 weeks.
Wild animals	The study did not involve the use of wild animals.
Reporting on sex	There was no sex bias in the animals used in this study.
Field-collected samples	The study did not involve the use of samples collected from the field.
Ethics oversight	All experiments were conducted in accordance with protocols approved by the Center for Drug Safety Evaluation and Research of Zhejiang University. All mice were bred according to the protocol of the Institutional Animal Care and Use Committee (IACUC).

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	Flow cytometry analysis of Annexin V-PI staining: The apoptotic ratio was measured with an Pharmingen™ FITC Annexin V Apoptosis Detection Kit I (556547, BD Biosciences, New Jersey, USA). Procedures were performed according to the instructions. Briefly, cells were treated for the indicated time, harvested and washed with PBS for binding and Annexin V-PI staining. For each sample, 1 × 1E+04 cells were acquired and analyzed by BD FACSCalibur™ Flow Cytometer (BD Biosciences, New Jersey, USA). Annexin V–PI–, Annexin V–PI+, Annexin V+PI–, Annexin V+PI+ staining represents viable cells, necrotic cells, early apoptotic cells, and late apoptosis cells being stained, respectively.
Instrument	BD FACSCalibur™ Flow Cytometer
Software	BD FACStation™ 6.1 Software
Cell population abundance	By stained with specific fluoresence-labeled antibodies, cells were separated into different parts and cytometry can calculate the normal or apoptosis fractions according to their damaged conditions.
Gating strategy	For cell apoptosis detection, Annexin V–PI–, Annexin V–PI+, Annexin V+PI–, Annexin V+PI+ staining represents viable cells, necrotic cells, early apoptotic cells, and late apoptosis cells being stained, respectively. PBS-treated cells were stained with/ without Annexin-V-FITC or PI to determine gate.

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