

Reporting Summary

Nature Research 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 Research policies, see [Authors & Referees](#) 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
<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. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P 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 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 data collection softwares came with the equipment utilized for experiments, including FV10-ASW 3.0 (Olympus), EnVision Manager Version 1.13 (PerkinElmer), BIAevaluation 4.1 software (GE Healthcare), QuantStudio 12K Flex software version 1.3 (Applied Biosystems).
Data analysis	The softwares utilized for analysis were all commercially available or could be downloaded from open source, including ImageJ 1.52a, GraphPad Prism 8, Schrödinger (version 2018-1), Bruker Topspin 3.6.1, Microsoft Excel 2016, MaxQuant 1.2.1

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [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 list of figures that have associated raw data
- A description of any restrictions on data availability

The 3D atom coordinates of TRADD and TRAF2 interaction complex were obtained from PDB (<https://www.rcsb.org>) with PDB ID of 1F3V. Source Data for all Figures are provided with the paper. Uncropped western blot scans are shown in Supplementary Fig. 1. The proteomics datasets are provided as supporting material with the paper.

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	Sample sizes were chosen according to the standards of the field and was based on our previous work (DOI: 10.1126/science.aaf6803, DOI: 10.1016/j.cell.2018.07.041). We aimed for a number of at least 3 animals per group to allow basic statistical analysis, which gave sufficient statistics for the effect sizes of interest and supported meaningful conclusions. Based on previous experience from similar studies (DOI: 10.1016/j.cell.2018.07.041), in vitro experiments with cultured cells for cell death assay were performed at least 3 times (biological replicates including 3 technical replicates for each experiment) to confirm reproducibility.
Data exclusions	Data were not excluded from analysis.
Replication	Whenever possible, readouts were performed with at least 3 animals per group. For in vitro studies we independently replicated all experiments at least 3 times (biological replicates) for cell death assay (including 3 technical replicates for all the experiments) and at least three times (biological replicates) for the immunoblotting analysis. All attempts at replication were successful.
Randomization	Animals were assigned randomly to experimental and control groups with same number (e.g. six animals were randomly assigned to two groups, one control group and one experimental group, three animals in each group.). Where possible, animals were age- and sex-matched. However all cells experiments were analyzed equally with no sub-sampling and thus, there was no requirement for randomization.
Blinding	For the in vivo experiment, the experiment and data collection was done by Heng Zhao and the conditions were well controlled. Blinding during analysis in vivo experiments were performed by Daichao between experimental and control groups. For experiments other than in vivo studies, the investigators were blinded during data collection and analysis where possible, included immunofluorescence experiments, drug treatment experiments on brain slices, mass spectrometry data collection and analysis. However, for in vitro study such as cell death assay, blinding is not necessary as the output of cell viability was determined by an automated pipeline using a fluorescent plate reader in an unbiased manner, with pre-established criteria.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used

Anti-Atg14L, CST, 96752, 1:1000
 Anti-HOIP, Abcam, ab46322, 1:1000
 Anti-Vps34, PTG, 12452-1-AP, 1:1000
 Anti-K63 Ub, a generous gift from Vishva Dixit, Genentech, 1:1000 for IP (catalogue number unavailable)
 Anti-M1 Ub, a generous gift from Vishva Dixit, Genentech, 1:1000 for IP (catalogue number unavailable)
 Anti-LC3B, Sigma-Aldrich L7543, 1:1000
 Anti-SQSTM1/p62, CST 5114, 1:1000
 Anti- α -Tubulin, Sigma-Aldrich T5168, 1:10000
 Anti-Becclin-1, CST 3738, 1:1000
 Anti-Phospho-RIPK1 (Ser166), CST 31122, 1:1000
 Anti-Phospho-RIPK1 (Ser166), Biolyinx, BX60008-C3, 1:500 for IF

Anti-RIPK1, D94C12, CST 3493, 1:1000
 Anti-A20/TNFAIP3, CST 4625, 1:1000
 Anti-TRADD, Santa Cruz sc-7868, 1:500
 Anti-TNF-R1, CST 3736, 1:1000
 Anti- β -Actin, Santa Cruz sc-81178, 1:5000
 Anti-Caspase-3, CST 9662, 1:1000
 Anti-Cleaved Caspase-3, CST 9661, 1:1000
 Anti-TAU-5, Invitrogen AHB0042, 1:1000
 Anti-Phospho-Tau AT8, Invitrogen MN1020, 1:1000
 Anti-MC1, a generous gift from Peter Davies, Feinstein Institute for Medical Research, 1:2000 (commercial source unavailable)
 Anti- mouse cIAP1, homemade, 1:1000
 Anti-TRAF2, CST 4724, 1:1000
 Anti-TRAF2, Santa Cruz, sc-7346, 1:1000
 Anti-Phospho-AMPK α , CST 2535, 1:1000
 Anti-AMPK α , CST 2532, 1:1000
 Anti-Phospho-Acetyl-CoA Carboxylase, CST 3661, 1:1000
 Anti-Acetyl-CoA Carboxylase, CST 3662, 1:1000
 Anti-Phospho-S6, CST 2211, 1:1000
 Anti-S6, CST 2217, 1:1000
 Anti-FADD, abcam ab124812, 1:1000
 Anti-phospho MLKL, CST 91689, 1:1000
 Anti-MLKL, CST 14993, 1:1000
 Anti-phospho RIPK3, CST 57220, 1:1000
 Anti-RIPK3, CST 13526, 1:1000
 Anti-Caspase-8, CST 4790, 1:1000
 Anti-PARP, CST 9542, 1:1000
 Anti-GAPDH, CST 2118, 1:1000
 Anti-Phospho-IkB α , CST 9246, 1:1000
 Anti-IkB α , CST 9242, 1:1000
 Anti-Phospho-IKK α / β , CST 2697, 1:1000
 Anti-IKK β , CST 2684, 1:1000
 Anti-Phospho-Erk1/2, CST 9101, 1:1000
 Anti-Erk1/2, CST 9102, 1:1000
 Anti-Phospho-SAPK/JNK, CST 9251, 1:1000
 Anti-SAPK/JNK, CST 9252, 1:1000
 Anti-Phospho-p38 MAPK, CST 9211, 1:1000
 Anti-p38 MAPK, CST 9212, 1:1000
 Anti-iNOS, CST 2982, 1:1000
 Anti-Cox2, CST 4842, 1:1000
 Anti-Alpha-synuclein, abcam ab6162, 1:1000
 Anti-Flag, Sigma-Aldrich F3165, 1:1000
 Anti-HA, Sigma-Aldrich H6908, 1:1000
 Anti-Bec1, Santa Cruz, sc-48341, 1:100 for IP
 Anti-Bec1, CST, 3495, 1:1000
 Anti-Atg5, Abcam, ab108327, 1:1000

Validation

anti-MC1 antibody has been validated on mouse samples by Michiyo Iba (doi.org/10.1523/JNEUROSCI.2642-12.2013).
 anti-K63, M1 antibody have been validated in previous study by Vishva Dixit group on both human and mouse samples (doi.org/10.1016/j.cell.2008.07.039, doi.org/10.1016/j.jmb.2011.12.053).
 Custom-made anti-mcIAP1 antibody has been validated in cIAP1/2-knockout MEFs in this study.
 All other antibodies have been validated for use as stated on the product webpages or literature, including:
 The Anti-Atg14L, CST 96752 antibody has been validated for Western-blots of both human and mouse samples by many previous publications (e.g. PMID: 31123703).
 The Anti-HOIP Abcam, ab46322 antibody has been validated for Western-blots of both human and mouse samples by previous publications (e.g. PMID: 26148235).
 The Anti-Vps34 antibody has been validated for Western-blots of mouse samples by previous publications (e.g. PMID: 25906440).
 The Anti-K63 Ub antibody has been validated for Western-blots of mouse samples by previous publications (e.g. PMID: 22227388).
 The Anti-M1 Ub antibody has been validated for Western-blots of mouse samples by previous publications (e.g. PMID: 26649818).
 The Anti-LC3B Sigma-Aldrich L7543 antibody has been validated for Western-blots of both human and mouse samples by previous publications (e.g. PMID: 20038797).
 The Anti-SQSTM1/p62, CST 5114, antibody has been validated for Western-blots of both human and mouse samples by previous publications (e.g. PMID: 31844040).

The Anti- α -Tubulin, Sigma-Aldrich T5168 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 14718566).

The Anti-Bec1-1, CST 3738 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32071300).

The Anti-Phospho-RIPK1 (Ser166), CST 31122 antibody has been validated for Western-blot of mouse samples by previous publications (e.g. PMID: 32269263).

The Anti-Phospho-RIPK1 (Ser166), Biolyx, BX60008-C3 has been validated for IF of mouse samples by previous publications (e.g. PMID: 31827280).

The Anti-RIPK1, D94C12, CST 3493 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32444644).

The Anti-A20/TNFAIP3, CST 4625 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 29622561).

The Anti-TRADD, Santa Cruz sc-7868 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 24336074).

The Anti-TNF-R1, CST 3736 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32411707).

The Anti- β -Actin, Santa Cruz sc-81178 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 30814309).

The Anti-Caspase-3, CST 9662 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 31971852).

The Anti-Cleaved Caspase-3, CST 9661 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32223461).

The Anti-TAU-5, Invitrogen AHB0042 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 28367114).

The Anti-Phospho-Tau AT8, Invitrogen MN1020 antibody has been validated for Western-blot IF and IHC of both human and mouse samples by previous publications (e.g. PMID: 29379433).

The Anti-MC1, a generous gift from Peter Davies, Feinstein Institute for Medical Research, 1:2000 antibody has been validated for Western-blot and IHC of both human and mouse samples by previous publications (e.g. PMID: 23325240).

The Anti- mouse cIAP1 antibody has been validated for Western-blot of mouse samples by previous publications (e.g. PMID: 30146158).

The Anti-TRAF2, CST 4724 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32065579).

The Anti-TRAF2, Santa Cruz, sc-7346 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 29920217).

The Anti-Phospho-AMPK α , CST 2535 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 31970200).

The Anti-AMPK α , CST 2532 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32439975).

The Anti-Phospho-Acetyl-CoA Carboxylase, CST 3661 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32273511).

The Anti-Acetyl-CoA Carboxylase, CST 3662 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 31680948).

The Anti-Phospho-S6, CST 2211 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32444668).

The Anti-S6, CST 2217 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32444668).

The Anti-FADD, abcam ab124812 antibody has been validated for Western-blot of mouse samples by previous publications (e.g. PMID: 31949127).

The Anti-phospho MLKL, CST 91689 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32433961).

The Anti-MLKL, CST 14993 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32195002).

The Anti-phospho RIPK3, CST 57220 antibody has been validated for Western-blot of mouse samples by previous publications (e.g. PMID: 32269263).

The Anti-RIPK3, CST 13526 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32444644).

The Anti-Caspase-8, CST 4790 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32246052).

The Anti-PARP, CST 9542 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32195376).

The Anti-GAPDH, CST 2118 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32452418).

The Anti-Phospho-IkBa, CST 9246 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32411707).

The Anti-IkBa, CST 9242 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32425739).

The Anti-Phospho-IKK α / β , CST 2697 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32431607).

The Anti-IKK β , CST 2684 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32448393).

The Anti-Phospho-Erk1/2, CST 9101 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32440348).

The Anti-Erk1/2, CST 9102 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32440348).

The Anti-Phospho-SAPK/JNK, CST 9251 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32072069).

The Anti-SAPK/JNK, CST 9252 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 31854220).

The Anti-Phospho-p38 MAPK, CST 9211 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32405532).

The Anti-p38 MAPK, CST 9212 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32348937).

The Anti-iNOS, CST 2982 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32079242).

The Anti-Cox2, CST 4842 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32079242).

The Anti-Alpha-synuclein, abcam ab6162 antibody has been validated for Western-blot and IF of both human and mouse samples by previous publications (e.g. PMID: 30783136).

The Anti-Flag, Sigma-Aldrich F3165 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 20376207).

The Anti-HA, Sigma-Aldrich H6908 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 10966468).

The Anti-Bec1, Santa Cruz, sc-48341, 1:100 for IP antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 29439667).

The Anti-Bec1, CST 3495 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 32377725).

The Anti-Atg5, Abcam, ab108327 antibody has been validated for Western-blot of both human and mouse samples by previous publications (e.g. PMID: 31949142).

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)

HEK293T (ATCC CRL-1573)
MEF (CF-1) (ATCC SCRC-1040)
Jurkat (ATCC TIB-152)
HeLa (ATCC CCL-2)
SH-SY5Y (ATCC CRL-2266)
HT-29 (ATCC HTB-38)
U-937 (ATCC CRL-1593.2)
H4 (ATCC HTB-148)

Authentication

None of the cell lines have been authenticated.

Mycoplasma contamination

The cells were tested every two months by a TransDetect PCR Mycoplasma Detection Kit (Transgen Biotech, cat. no. FM311-01) to ensure that they are mycoplasma free.

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

No commonly misidentified cell lines were used.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals

8 weeks and 4 months old female WT (Catalog No. 004781) and Tg tauP301S (Catalog No. 008169) male mice were from The Jackson Laboratory.

Wild animals

No wild animals were used in this study.

Field-collected samples

No field-collected samples were used in this study.

Ethics oversight

The mouse work was performed under the study protocol IS00001127, as approved by the Harvard Medical School 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.