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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 *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	Code for standard open-source DESeq differential gene expression RNAseq analysis used in R statistical software is available from the corresponding author upon reasonable request.
Data analysis	All data analysis was performed as described in the Materials and Methods.

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

DATA AVAILABILITY

The raw data that support the findings of this study are available within the paper and its Extended Data files (pertaining to Figures 1, 3, 4, and Extended Data Figures 1, 3, 4, and 5), and/or are available from the corresponding author upon reasonable request. The RNA-seq data have been deposited to the public National Center for Biotechnology Information GEO repository under the data identifier GSE148802.

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	Experiments were performed with the number of experimental points clearly indicated in the legend. Statistics were calculated as described and highlighted in multiple other forms and places during this submission.
Data exclusions	No data were excluded from these experimetns.
Replication	Replicates were included as described in the figure legends.
Randomization	We did not randomize experiments.
Blinding	We did not blind any experiments.

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	Antibodies: APP (6E10, Fisher Scientific Cat #501029533), APP (HRP-4G8, Fisher Scientific Cat #501029498), SEC24D (mouse) antibody was provided as a generous gift from the Balch Lab at TSRI, XBP1s (Cell Signaling Cat #12782S), KDEL (Enzo Cat # ADI-SPA-827-F), eif2a-P (Cell Signaling Cat #9721S), eif2a-total (Abcam Cat # ab5369), PERK (Cell Signaling Cat #3192S), PARP (Cell Signaling Cat #9542S), tubulin (Sigma Cat # T6074-200UL)
Validation	All antibodies have been previously validated in the Wiseman lab using knockout lines and/or overexpression.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	SHSY5Y, HEK293T, and Huh7 cells were purchased from ATCC. HEK293DAX cells, XBP1.Rluc stable HeK293T cells, and ERSE.Fluc HEK293T cells were established in the Wiseman lab (see Shoulders et al (2013) Cell Reports; Plate et al (2016) ELIFE). CHO7PA2 and CHO7WD10 cells were obtained from Edward Koo's lab at UCSD.
Authentication	Cells were routinely tested for mycoplasma every 6 months. No further authentication of cell lines was performed by the authors.
Mycoplasma contamination	Cells were routinely tested for mycoplasma every 6 months. No further authentication of cell lines was performed by the authors.
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

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	TMRE Staining and Flow Cytometry Cells were treated as indicated then incubated with TMRE dye (200 nM) for 30 mins at 37°C. Samples were collected by trypsinization. Trypsin was neutralized by washing into cell culture media and then samples were washed twice in DPBS. Cell pellets were suspended into DPBS supplemented with 0.1% BSA. Fluorescence intensity of TMRE was recorded on the PE channel of a Novocyte Flow Cytometer (ACEA Biosciences, Inc). Data are presented as mean of the fluorescence intensity from 3 experiments. For each experiment, 10,000 cells per condition in triplicates were recorded.
Instrument	Novocyte Flow Cytometer (ACEA Biosciences, Inc).
Software	Flowjo
Cell population abundance	Experiments were performed by scanning >10,000 cells per sample.
Gating strategy	No gating strategies were employed apart from FSC/SSC scattering for viable cells. The presented data show only the histogram of fluorescence or the normalized geometric mean.

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