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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 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	MaxQuant v.1.6.4.0 (free, https://maxquant.net/maxquant/), PEAKS v.8.0 (licensed, http://www.bioinfor.com/peaks-studio/).
Data analysis	Perseus v.1.6.2.3 (free, https://maxquant.net/perseus/), PEAKS v.8.0 (licensed, http://www.bioinfor.com/peaks-studio/).

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 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 gel lanes depicted in Figures 5 and 6 are shown uncropped Supplemental Figures 1 and 2. The mass spectrometry proteomics data used for Figure 7 have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD022490.

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 sample size-calculations were performed. For in-gel visualisation and/or optimalisation of metabolic labelling, single replicates were utilised. For chemical proteomics analysis, all biological conditions were tested in triplicates, allowing robust data filtering for valid values (cut-off set at a minimum of two out of three valid values for each biological condition)
Data exclusions	No data were excluded.
Replication	For in-gel visualization we performed each experiment separately at least once. For chemical proteomics analysis, all biological conditions were tested in triplicates, allowing robust data filtering for valid values (cut-off set at a minimum of two out of three valid values for each biological condition)
Randomization	Randomization was not relevant for this study. Experimental groups were linked to treatment (e.g. lipid probe, with/without inhibitor, in DMSO) and always matched with a mock-treated control (e.g. DMSO).
Blinding	Blinding was not relevant to this study due to the nature of the material.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	ARL1 antibody (rabbit anti-human, 16012-1-AP, Proteintech, https://scicrunch.org/resolver/RRID:AB_2243131) PRKACA antibody (rabbit anti-human, 4782S, Cell Signaling, https://scicrunch.org/resolver/RRID:AB_2170170) IFITM3 antibody (rabbit anti-human, 59212S, Cell Signaling, https://scicrunch.org/resolver/RRID:AB_2799561) CANX antibody (rabbit anti-human, 2679S, Cell Signaling, https://scicrunch.org/resolver/RRID:AB_2228381) HRAS antibody (mouse anti-human, MAB3291, Millipore, https://scicrunch.org/resolver/RRID:AB_94790) ULK3 antibody (rabbit anti-human, ab124947, Abcam, https://scicrunch.org/resolver/RRID:AB_10972508) RHOA antibody (mouse anti-human, sc-418, Santa Cruz Biotechnology, https://scicrunch.org/resolver/RRID:AB_628218) RAB8A antibody (rabbit anti-human, ab188574, Abcam, https://scicrunch.org/resolver/RRID:AB_2814989) Hedgehog antibody. The shown results were with rabbit anti-human, sc-9024 (https://scicrunch.org/resolver/RRID:AB_2239216), Santa Cruz Biotechnology, but this has been discontinued; this product has been replaced by sc-365112 (https://scicrunch.org/resolver/RRID:AB_10709580), but we have not tested this antibody. TUBA antibody (mouse anti-human, ab7291, Abcam, https://scicrunch.org/resolver/RRID:AB_2241126) HSP90 antibody (mouse anti-human, sc-69703, Santa Cruz Biotechnology, https://scicrunch.org/resolver/RRID:AB_2121191)
Validation	Please see the relevant RRID information for the specific antibody.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	EA.hy926 (https://scicrunch.org/resolver/RRID:CVCL_3901), HeLa (https://scicrunch.org/resolver/RRID:CVCL_0030), HEK293A (https://scicrunch.org/resolver/RRID:CVCL_6910), HEK239T (https://scicrunch.org/resolver/RRID:CVCL_0063), MCF-7 (https://scicrunch.org/resolver/RRID:CVCL_0031), MDA-MB-231 (https://scicrunch.org/resolver/RRID:CVCL_0062), RPE-1 (https://scicrunch.org/resolver/RRID:CVCL_4388)
Authentication	Cell lines were validated by STR analysis by Cell Services (The Francis Crick Institute, London, UK)
Mycoplasma contamination	All cell lines used were free of Mycoplasma.
Commonly misidentified lines (See ICLAC register)	Not applicable.