

## 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

The following software were used for data collection: Olympus FV10-ASW 4.2b. Image Studio Software v5.2.5, BD FACSDiva v6.1.2. LSM 5 Image Browser.

Data analysis

The following software were used for data analysis: -FIJI image processing software (NIH) -FlowJo version (v) 10 (TreeStar) -GraphPad Prism v6 (GraphPad Software Inc) -Excel 16.15 -Image Studio Software v5.2.5, Photoshop.  
-Image Studio Software v5.2.5| analysis of the study. For images analysis, Photoshop and office software was used to fit the data, for flow cytometry using FlowJo.

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 authors declare that all data supporting the findings of this study are available within the article and its Supplementary Information Files or from the corresponding author on reasonable request. The mass spectrometry data have been deposited to the Proteome Xchange Consortium via the PRIDE partner repository with the dataset identifier PXD007253 (BT-549) and HCC38.

## 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	For all experiments, sample size pre-calculation was not performed. In general, experiments were performed greater than or equal to 3 times independently ( $n \geq 3$ ) including technical replicates whenever possible to compensate for experimental variation. These numbers are sufficient to obtain statistical differences or effect sizes.
Data exclusions	No data were excluded from the analyses.
Replication	To compensate for experimental variation, experiments were performed at least three times including technical replicates. There are no findings that were not replicated.
Randomization	NOT relevant
Blinding	NOT relevant

## Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study).
Research sample	State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.
Sampling strategy	Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.
Data collection	Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection.
Timing	Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort.
Data exclusions	If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.
Non-participation	State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation.
Randomization	If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled.

## Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.
Research sample	Describe the research sample (e.g. a group of tagged <i>Passer domesticus</i> , all <i>Stenocereus thurberi</i> within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and

any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source.

**Sampling strategy** *Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.*

**Data collection** *Describe the data collection procedure, including who recorded the data and how.*

**Timing and spatial scale** *Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken*

**Data exclusions** *If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*

**Reproducibility** *Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.*

**Randomization** *Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.*

**Blinding** *Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.*

Did the study involve field work?  Yes  No

## Field work, collection and transport

**Field conditions** *Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).*

**Location** *State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).*

**Access and import/export** *Describe the efforts you have made to access habitats and to collect and import/export your samples in a responsible manner and in compliance with local, national and international laws, noting any permits that were obtained (give the name of the issuing authority, the date of issue, and any identifying information).*

**Disturbance** *Describe any disturbance caused by the study and how it was minimized.*

## 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

### Methods

- n/a  Involved in the study
- Antibodies
- Eukaryotic cell lines
- Palaeontology
- Animals and other organisms
- Human research participants
- Clinical data

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

## Antibodies

**Antibodies used** *The following antibodies were used: mouse anti-ubiquitin (Santa Cruz(P4D1) , sc-8017, 1: 1000); rabbit anti-LC3 (Cell Signaling Technology(D11), #3868, 1: 1000); mouse anti-LAMP1 (Cell Signaling Technology(D4O1S), #15665, 1: 200); mouse anti-USP8 (Sigma-Aldrich(US872), SAB4200527, 1: 1000); rabbit anti-EPG5 (Beijing TDY Biotech CO., Ltd, TDY349F, 1: 1000); mouse anti-Actin (Sigma-Aldrich(AC-15), A5441, 1: 5000); rabbit anti-HA tag (Abcam, ab9110, 1: 1000); mouse anti-FLAG tag (Abmart, M20008, 1: 1000); rabbit anti-Myc tag (Abmart, M20002, 1: 1000); Alexa Fluor® 488 donkey anti-rabbit IgG (H+L) (Invitrogen Thermo Fisher Scientific, A21206, 1: 500); Alexa Fluor® 555 donkey anti-mouse IgG (H+L) (Invitrogen Thermo Fisher Scientific, A21203, 1: 200); Alexa Fluor® 647 donkey anti-mouse IgG (H+L) (Invitrogen Thermo Fisher Scientific, A21235, 1: 500).*

**Validation** *For all antibodies used, validation statements and relevant citations can be found on the manufacturer's website. Further validation of antibodies is supported by western blotting of some experiments in the manuscript (e.g. Figure 1b, Figure 2a,c, Figure 3b,c,d, Figure 4a, Figure 5 a,b,c,d,e,g, Figure 6a,c,f, Figure S1f, Figure S5a,b,c, Figure S6A,b,c, Figure S7a, Figure S10a).*

## Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)	ESC (C57BL/6J), iPSC (C57BL/6J), Hues9, iPSC (Human)
Authentication	Each lines used was authenticated by STR
Mycoplasma contamination	All lines tested for mycoplasma negative
Commonly misidentified lines (See <a href="#">ICLAC</a> register)	N/A

## Palaeontology

Specimen provenance	<i>Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information).</i>
Specimen deposition	<i>Indicate where the specimens have been deposited to permit free access by other researchers.</i>
Dating methods	<i>If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.</i>

Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

## Animals and other organisms

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

Laboratory animals	C57BL/6J mice, both male and female, 2 month old
Wild animals	N/A
Field-collected samples	N/A
Ethics oversight	All animal experiments were approved by the Ethics Committee in the Institute of Zoology, Chinese Academy of Sciences in accordance with the Guidelines for Care and Use of Laboratory Animals established by the Beijing Association for Laboratory Animal Science.

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

## Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	<i>Describe the covariate-relevant population characteristics of the human research participants (e.g. age, gender, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural &amp; social sciences study design questions and have nothing to add here, write "See above."</i>
Recruitment	<i>Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.</i>
Ethics oversight	<i>Identify the organization(s) that approved the study protocol.</i>

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

## Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	<i>Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.</i>
Study protocol	<i>Note where the full trial protocol can be accessed OR if not available, explain why.</i>
Data collection	<i>Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.</i>
Outcomes	<i>Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.</i>

## ChIP-seq

### Data deposition

- Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

#### Data access links

May remain private before publication.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

#### Files in database submission

Provide a list of all files available in the database submission.

#### Genome browser session

(e.g. [UCSC](#))

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

### Methodology

#### Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

#### Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

#### Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

#### Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

#### Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

#### Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

## 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

Cells used for flow cytometry (ESCs) were pre-treated with CQ or EPG5/USP8 KO when indicated. To measure changes in GFP positivity, cells were harvested and measured immediately by flow cytometry. Otherwise, cells were harvested washed and fixed in ice-cold PBS. Cells were permeabilized and blocked with PBS-1%BSA-0.05% Tween20 or with PBS-2%BSA-0.1%Triton for 1 hour and stained with indicated antibodies in the methods section.

#### Instrument

FACS Calibur (Becton Dickinson)

#### Software

All samples were analyzed using FlowJo and Graphpad Prism 7.

#### Cell population abundance

For all experiments, more than 10,000 cells were measured to obtain relevant numbers after gating.

#### Gating strategy

Living cells were initially gated on the FSC/SSC plots. Boundaries between positive and negative populations were determined by samples with isotype-matched control antibody or positive antibody staining to set gates.

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

# Magnetic resonance imaging

## Experimental design

- Design type
- Design specifications
- Behavioral performance measures

## Acquisition

- Imaging type(s)
- Field strength
- Sequence & imaging parameters
- Area of acquisition
- Diffusion MRI  Used  Not used

## Preprocessing

- Preprocessing software
- Normalization
- Normalization template
- Noise and artifact removal
- Volume censoring

## Statistical modeling & inference

- Model type and settings
- Effect(s) tested
- Specify type of analysis:  Whole brain  ROI-based  Both
- Statistic type for inference (See [Eklund et al. 2016](#))
- Correction

## Models & analysis

n/a | Involved in the study

- Functional and/or effective connectivity
- Graph analysis
- Multivariate modeling or predictive analysis

- Functional and/or effective connectivity
- Graph analysis

*Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.*