nature research

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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	ZEN 2011 SP7 was used for immunofluorescence data collection. Xcalibur v2.2 was used for mass spectrometry data collection. ABI 7900HT v2.4.1 was used for qPCR data collection. CLARIOstar v5.4 was used for cell viability data collection.
Data analysis	Qual Browser v2.2 was used to analyze mass spectrometery data. IP2 v6.0.2 and CIMAGE were used to analyze isoTOP-ABPP, SILAC and quantitative ABPP data. ABI 7900HT v2.4.1 was used to analyze qPCR data. Synthego ICE analysis was used to analyze indel of CRISPR clones. ImageJ 2.0 was used to analyze western blot and immunofluorescence data. GraphPad Prism v7.03 was used to perform statistical tests and generate all the bar graphs and waterfall plots.

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 upon request. 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

All data associated with this study are avaiable in the published article and its supplementary information.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size: No statistical methods were used to pre-determine sample size. Sample size (n ≥ 3) was chosen according to literature showing similar methods of analysis.

Data exclusions: No data was excluded.

Replication: Concentration-dependent degradation of stably expressed FLAG-FKBP12_NLS in DCAF16+/+ (clone 6) and DCAF16-/- (clone 3) HEK293 cells following treatment with KB02-SLF (2) (Fig. 4a) was replicated on different days using different batches of compounds by a different lab member, yielding similar results. KB02 bifunctionals-mediated ternary complex interaction between FLAG-FKBP12_NLS or BRD4-FLAG and HA-DCAF16 (Fig. 4c and Fig. 6e) were replicated on different days using different batches of compounds, yielding similar results. Anti-FLAG affinity enrichment coupled to mass spectrometry (MS)-based proteomics (Fig. 3d, Supplementary Fig. 4e, Supplementary Fig. 5c) were replicated on different days using different batches of compounds and a different mass spectrometry, yiedling similar results. MS-based proteomic analysis of KB02 bifunctionals-treated HEK293T cells (Fig. 6h) were replicated on different days using different batches of compounds and a different mass spectrometry, yiedling similar results.

Randomization: Mammalian cells used for this study were grown under identical conditions, so randomization was not used.

Blinding: Mammalian cells used for this study were grown under identical conditions, so blinding was not used.

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 Passer domesticus, all Stenocereus thurberi 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

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials

Describe any restrictions on the availability of unique materials OR confirm that all unique materials used are readily available from the authors or from standard commercial sources (and specify these sources).

Antibodies

Antibodies used

Anti-HA-tag monoclonal antibody (C29F4), Cell Signaling, cat# 3724, 1:5000 dilution; Anti-HA-tag monoclonal antibody (6E2), Cell Signaling, cat# 2367, 1:5000 dilution; Anti-FLAG-tag monoclonal antibody (D6W5B), Cell Signaling, cat# 14793, 1:5000 dilution; Anti-FLAG-tag monoclonal antibody (9A3), Cell Signaling, cat# 8146, 1:5000 dilution; Anti-His-tag monoclonal antibody (27E8), Cell Signaling, cat# 9991, 1:1000 dilution; Anti-FLAG-tag-HRP monoclonal antibody (clone M2), Sigma-Aldrich, cat# A8592, 1:10000 dilution; Anti-DDB1 monoclonal antibody (D4C8), Cell Signaling, cat# 6998, 1:1000 dilution; Anti-BRD4 monoclonal antibody (E2A7X), Cell Signaling, cat# 13440, 1:1000 dilution; Anti-Lamin A/C polyclonal antibody, Cell Signaling, cat# 2032, 1:1000 dilution; Anti-K48-linkage polyubiquitin polyclonal antibody, Cell Signaling, cat# 4289, 1:1000 dilution; Anti-β-Actin monoclonal antibody (C4), Santa Cruz Biotechnology, cat# sc-47778, 1:10000 dilution; Anti-rabbit IgG-HRP antibody, Cell Signaling, cat# 7074, 1:3000 dilution; Anti-mouse IgG-HRP antibody, Cell Signaling, cat# 7076, 1:3000 dilution; Alexa Fluor 488-conjugated goat anti-mouse IgG (H+L) secondary antibody, Invitrogen, cat# A-11001, 1:5000 dilution; Alexa Fluor 568-conjugated goat anti-rabbit IgG (H+L) secondary antibody, Invitrogen, cat# A-11011, 1:5000 dilution; Anti-FLAG affinity gel (clone M2), Sigma-Aldrich, cat# A2220, 1:50 (v/v) dilution; Anti-HA agarose (clone HA-7), cat# A2095, 1:50 (v/v) dilution.

Validation

Anti-HA-tag monoclonal antibody (C29F4), Cell Signaling, cat# 3724: validated for western blotting by manufacturer using extracts from HA-FoxO4- or HA-Akt3-transfected HeLa cells;
Anti-HA-tag monoclonal antibody (6E2), Cell Signaling, cat# 2367: validated for western blotting by manufacturer using extracts from HA-ER-transfected COS cells;
Anti-FLAG-tag monoclonal antibody (D6W5B), Cell Signaling, cat# 14793: validated for western blotting by manufacturer using extracts from FLAG-GFP-transfected HEK293T cells;
Anti-FLAG-tag monoclonal antibody (9A3), Cell Signaling, cat# 8146: validated for western blotting by manufacturer using extracts from FLAG-FoxG1-transfected HEK293T cells;
Anti-His-tag monoclonal antibody (27E8), Cell Signaling, cat# 9991: validated for western blotting by manufacturer using extracts from C-terminal His-tagged Tyro3-transfected COS7 cells;
Anti-FLAG-tag-HRP monoclonal antibody (clone M2), Sigma-Aldrich, cat# A8592: validated for western blotting using extracts from mock- or FLAG-FKBP12-transfected HEK293T or MDA-MB-231 cells;
Anti-DDB1 monoclonal antibody (D4C8), Cell Signaling, cat# 6998: validated for western blotting by manufacturer using extracts from HeLa, LOX-IMVI, DLD-1, HCT-116, SH-SY5Y, MDA-MB-231, C2C12, NIH/3T3, KNRK, PC-12, COS-7 or Vero cells;
Anti-BRD4 monoclonal antibody (E2A7X), Cell Signaling, cat# 13440: validated for western blotting by manufacturer using extracts from RL-7, HEK293T or Jurkat cells;
Anti-Lamin A/C polyclonal antibody, Cell Signaling, cat# 2032: validated for western blotting by manufacturer using extracts from untreated or staurosporine-treated (1 μM) HeLa cells;
Anti-K48-linkage polyubiquitin polyclonal antibody, Cell Signaling, cat# 4289: validated for western blotting by manufacturer using recombinant monoubiquitin, K48-linked polyubiquitin and K63-linked polyubiquitin;
Anti-β-Actin monoclonal antibody (C4), Santa Cruz Biotechnology, cat# sc-47778: validated for western blotting by manufacturer using extracts from HeLa, Sol9, C32 or NIH/3T3 cells.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

HEK293T (ATCC), MDA-MB-231 (ATCC), HEK293 (Synthego)

Authentication

HEK293T, MDA-MB-231 and HEK293 cell lines were authenticated by short tandem repeat loci (STRs) profiling.

Mycoplasma contamination

All cell lines used in this study were tested negative for mycoplasma.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell lines were used in this study.

Palaeontology

Specimen provenance | *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).*

Specimen deposition | *Indicate where the specimens have been deposited to permit free access by other researchers.*

Dating methods | *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.*

☐ 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 | *For laboratory animals, report species, strain, sex and age OR state that the study did not involve laboratory animals.*

Wild animals | *Provide details on animals observed in or captured in the field; report species, sex and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*

Field-collected samples | *For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*

Human research participants

Policy information about studies involving human research participants

Population characteristics | *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 & social sciences study design questions and have nothing to add here, write "See above."*

Recruitment | *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.*

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	*Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.*
Instrument	*Identify the instrument used for data collection, specifying make and model number.*
Software	*Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.*
Cell population abundance	*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*
Gating strategy	*Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.*

- [ ] 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	*Indicate task or resting state; event-related or block design.*
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	*Specify: functional, structural, diffusion, perfusion.*
Field strength	*Specify in Tesla*
Sequence & imaging parameters	*Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*
Area of acquisition	*State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI   [ ] Used   [ ] Not used

Preprocessing

Preprocessing software	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*
Normalization	*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*
Normalization template	*Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.*
Noise and artifact removal	*Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).*
Volume censoring	*Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.*

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference
(See Eklund et al. 2016)

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

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

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

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