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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

ZEISS ZEN 3.2 (black edition), ZEISS ZEN 3.2 (blue edition), ImageJ 1.8.0, Xcalibur version 2.1.0 SP1/Tune2.6.0 SP3, XCalibur version 4.1.31.9, SearchGUI 3.2.20, PeptideShaker 2.0.6, Proteome Discoverer 2.2.0.388, Percolator V3.0, Cytoscape 3.6.1, Group size dependent testing statistic (available at https://github.com/Edert/R-scripts), FastQC 0.11.4, PRINSEQ-lite 0.20.4, STAR 2.5.0b, SAMtools 1.7, featureCounts 1.6.0, DESeq2 1.22.2

Data analysis

MS data analysis with SearchGUI / PeptideShaker:
We used msconvert from the ProteoWizard toolkit to convert raw data files to mgf format.
Then we applied SearchGUI (version 3.2.20) against the human Swiss-Prot database (01.2017).
Results were then analyzed with PeptideShaker (version 1.16.15).
O/E ratios of binned Pscores:
We used the heatmap.2 function from the R-package gplots (version 3.0.1).
Clustering for Pscore heat-map:
We used the heatmap.2 function from the R-package gplots (version 3.0.1).
RNA-seq data analysis
We applied FastQC (version 0.11.4) for quality checks, PRINSEQ-lite (version 0.20.4) for trimming and filtering and aligned against the mouse reference genome (GRCm38/mm10) with STAR (version 2.5.0b). Processed the alignments with SAMtools (version 1.7) and obtained the counts per gene with featureCounts (version 1.6.0).
Differential gene expression analysis and normalization prior visualization and clustering where then done with DESeq2 (version1.22.2).
Batch-correction for two library preparation and sequencing runs was done with ComBat from the sva package (3.12).
The heatmap of shared regulated genes was generated with the heatmap.2 function from the R-package gplots (version 3.0.1).
Group size dependent testing statistic (GSDTS)
GSDTS tests a list of values x against a larger universe y of values (x < y) by sub-sampling z-times a list of length of x out of the universe. Each sub-sampled list is checked against the already created lists to ensure unique lists to satisfy "sub-sampling without replacement". The lists x and y as well as the number of sub-sampling repeats z need to be provided by the user. As result the sum, mean or median of all sub-sampling

results are plotted as histogram and the respective sum, mean or median of list x is then indicated by a red bar in the histogram. The script is implemented in R and available at: https://github.com/Edert/R-scripts

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

LC-MS/MS data will be deposited into PRIDE under the accession number PXD022518
RNA-seq data has been deposited into GEO under the accession number GSE159037

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	Calculation of sample size was not performed. Chosen sample sizes were similar to earlier experiments, in which sufficient statistical power was achieved (Grebien et al., Nat Chem Biol. 2015; Skucha et al., Nat Comm. 2018, Schmidt et al., Leukemia 2019).
Data exclusions	No data were excluded from this study.
Replication	Experiments were independently performed in at least three biological and technical replicates as stated in the respective figure legend. All attempts at replication were successful.
Randomization	No randomization was performed. This approach was chosen to enable careful ordering and standardization of experimental conditions to improve internal validity of the obtained results.
Blinding	Experiments and experimenters were not blinded. This approach was chosen to enable careful ordering and standardization of experimental conditions to improve internal validity of the obtained results.

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	mouse anti-HA (Santa Cruz, sc-7392, clone F-7) Alexa Fluor 568 f(ab')2-goat anti-mouse antibody (Thermo Fisher Scientific, A-21237) NUP98 antibody (Abcam, ab50610, clone 2H10) anti-HA.11 (BioLegend, 901513, clone 16B12) anti-alpha Tubulin (Abcam, ab7291)

anti-beta Actin (Cell Signaling, 4967S)
anti-HSC70 (Santa Cruz, sc-7298, clone B-6)
anti-NUP98 (Cell Signaling, #2288, clone L205)
anti-RAE1 (Cell Signaling, sc-374261, A12)
anti-mouse HRP (GE Healthcare Austria GmbH & Co OG, NA931V)
goat anti-rabbit HRP (Cell Signaling, 7074)
sheep anti-mouse HRP (GE Healthcare Austria GmbH & Co OG, NA931V)
goat anti-rabbit HRP (Cell Signaling, 7074)
goat anti-mouse 800 (Thermo Fisher Scientific, SA5-35521)
goat anti-mouse 680 (Thermo Fisher Scientific, A32729)
goat anti-rabbit 800 (Thermo Fisher Scientific, SA5-35571)
goat anti-rabbit 680 (Thermo Fisher Scientific, A32734)

Validation

All antibodies were validated by Western Blotting, immunoprecipitation and/or immunofluorescence according to manufacturer's recommendations via standard laboratory protocols.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

HL-60 (DSMZ): human acute myeloid leukemia
HEK-293T (DMSZ): human embryonal kidney
NIH-3T3 (DSMZ): murine embryo fibroblasts
Plat-E (Cell Biolabs): based on 293T cells

Authentication

None of the cell lines used were authenticated.

Mycoplasma contamination

All cell lines were tested negative for mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

No cell lines found in the ICLAC register were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals

C57BL/6N mice, female. 6-8 weeks

Wild animals

The study did not involve wild animals.

Field-collected samples

The study did not involve samples collected from the field.

Ethics oversight

Animal experiments were approved by the institutional ethics and animal welfare committee and the national authority according to §§ 26ff. of Animal Experiments Act, Tierversuchsgesetz 2012 – TVS 2012 (license number BMWF 68.205/188-V/3b/2018).

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