nature portfolio

Corresponding author(s): Jun Yang

Last updated by author(s): May 15, 2024

Reporting Summary

Nature Portfolio 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 Portfolio 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	Bulk RNA-seq and ATAC-seq data were collected by pair-end sequencing on HiSeq4000 (Illumina) in the Hartwell Center at St Jude Children's Research Hospital
Data analysis	For bulk RNA-seq data analysis, Trim-Galore version v0.60, STAR v2.7, RSEM v1.31, gsea2.2.3 and MSigDB 6.2 were used. For ATAC-seq analysis, Picard (version 1.65), samtools (version 1.3.1, parameter ''-q 1 -F 1024''), MACS2, BEDtools, HOMER61 and the Integrated Genomic Viewer (IGV 2.3.82) were used.

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The bulk RNA-seq, ATAC-seq data have been deposited to the Gene Expression Omnibus-GEO (NCBI). The bulk RNA-seq is under accession number GSE240980. The ATAC-seq is under accession number GSE262074. DepMap data (https://depmap.org/portal/).

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	A minimum of two biological replicates were used for each experiment to ensure the reproducibility and to perform statistical analysis.
Data exclusions	No data exclusion
Replication	Data was obtained from three technical replicates and in at least two biological replicates. Independent biological replicates are shown in all figures.
Randomization	Randomization was not relevant. All cell lines or biological samples were analyzed or treated in the same manner.
Blinding	Experiments were not blinded in order to allow the investigators to have correct identification of samples and to ensure the correct data collection. In other hand, blinding strategy was applied to computational biologists who performed bioinformatic analyses.

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

Hif1α Cayman 10006421, RRID: AB_409037
Hif2α Novus NB100-122, RRID: AB_10002593
VHL Cell Signaling Technology 68547S, RRID: AB_2716279
PRMT5 ABclonal A1520, RRID: AB_2762092
MTAP Cell Signaling Technology 4158S, RRID: AB_1904054
HSP90 Santa Cruz sc13119, RRID: AB_675659
ACTIN Sigma A2066, RRID: AB_476693
MAC2 Accurate/CEDARLANE CL-8942AP, RRID: AB_10060357

Validation	All antibodies were purchased from commercial vendors and were validated by manufactures, other studies and/or in this study.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Murine: NEJF6(this manuscript) Murine: NEJF10 (this manuscript) HepG2 ATCC HB-8065 HepG2-LeveV2 (this manuscript) HepG2-VHL-KO-1 (this manuscript) HepG2-VHL-KO-2 Yang lab N/A NEJF10-shCtrl (this manuscript) NEJF10-shPRMT5-1 (this manuscript) NEJF10-shPRMT5-2 (this manuscript) NEJF10-shPRMT5-3 (this manuscript) U2OS ATCC HTB96 HCT116 ATCC CCL-247
Authentication	Cell lines were authenticated by short tandem repeat (STR) using Promega PowerPlex 16 HS System once per month.
Mycoplasma contamination	PCR-based method was used for detection of Mycoplasma with LookOut Mycoplasma PCR Detection Kit (Sigma) and JumpStart Taq DNA Polymerase (Sigma) once per month to ensure cells were mycoplasma negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

Animals and other organisms

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

Laboratory animals	Albumin-Cre (Alb-Cre) (Strain #003574), R26StopFLMYC (CAG-MYC) (Strain #020458), and Prmt5 floxed mouse (Strain #034414) mice were obtained from the Jackson Laboratory.
Wild animals	No wild animals were used in this study
Field-collected samples	No Field-collected samples were used in this study
Ethics oversight	All experiments that involved the use of mice were performed in accordance with the guidelines outlined by the St Jude Children's Research Hospital Institutional Animal Care and Use Committee (IACUC).

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