nature portfolio

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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	Fluorescent and Histological images were acquired with Leica SP8 microscope with LAS X software (v3.5.7.23225). Illumina HiSeq 2500 was used to generate RNA-seq, MBD-seq and ChIP-seq data.
Data analysis	All statistical analyses were performed using the GraphPad Prism software 9.0 (GraphPad Software, Inc. USA). RNA-seq data was analyzed using edgeR package (v3.36.0). ChIP-seq was analyzed using the encode chipseq pipeline (https://github.com/ENCODE-DCC/chip-seq-pipeline2). DiffBind (v3.0.15) was used to identify differential methylation region. ChIPSeqSpike (v1.9.0) was used to normalize spike in control. Image J (v1.0) software from NIH was used for image analysis. TCGA data analysis was performed with GEPIA2 webtool (http://gepia2.cancer-pku.cn). Genomic distribution was analyzed with ChIPseeker (v1.26.2). Motif analysis was carried out with RSAT webtool (http://rsat.sb-roscoff.fr). Chip-seq peak overlap analysis was done with Deeptools (v 3.5.0).

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

RNA-seq, MBD-seq and ChIP-seq data that support the findings of this study have been deposited in the Gene Expression Omnibus (GEO) under accession numbers

GSE178227.
All other data supporting the findings of this study are available from the corresponding author on reasonable request. Source data are provided with this paper.

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 statistical method was used to predetermine sample size. Sample sizes were determined based on what is standard practice in the field (sample size >= 3 per group).
Data exclusions	No data was excluded
Replication	All experiment results were successfully reproduced at least three times using biological replicates.
Randomization	Mice were decided based on littermates, when possible. Mice were randomly allocated to ensure equal sex/ age cross genotype. All other sample allocation was random in all experiments
Blinding	No blinding was performed because none of the analyses reported involved procedures that could be influenced by investigator bias

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	For western blot, anti-TET1 (1:1000, GeneTex, GTX124207), anti-TEAD1 (1:500, BD Transduction Laboratories, 610923), anti-TEAD4 (1:1000, abcam, ab58310), anti-GAPDH (clone 6C5) (1:3000, Millipore Sigma, MAB374), HRP-linked ECL anti-mouse IgG (1:5000, GE Healthcare, NA931) and HRP-linked ECL anti-rabbit IgG (1:5000, GE Healthcare, NA9340). For ChIP, anti-TEAD4 (4 µg, abcam, ab58310), anti-RNA polymerase II (2 µg, Millipore Sigma, 05-623), anti-trimethyl-Histone H3 (Lys4) (2 µl, Millipore Sigma, CS200580), anti-acetyl-Histone H3 (Lys 27) (2 µl, Millipore Sigma, 07-360) and anti-normal rabbit IgG (2 µl, Millipore Sigma, CS200581). For DNA dot blot, anti-5mC (1:500, Epigentek, A-1014), anti-5hmC (1:2000, Epigentek, A-1018). For immunostaining, anti-Ki-67 (1:500, DAKO GA62661-2), anti-wide spectrum screening cytokeratin (pan-CK) (1:500, DAKO, Z0622), anti-AFP (alpha fetal protein, 1:20, R & D Systems, MAB1368), anti-CK19 (cytokeratin 19, 1:500, AbboMax, 602-670), anti-PH3 (phosphorylated histone H3, 1:500, Millipore Sigma, MABE939), anti-ALB (albumin, 1:1000, Millipore Sigma, SAB3500217), anti-HNF4A (hepatocyte nuclear factor 4 alpha, 1:500, ThermoFisher, MA1-199), and anti-cleaved caspase-3 (1:500, Cell Signaling, 9661). For immunofluorescent staining, Alexa488-conjugated goat anti-mouse secondary antibodies (ThermoFisher, A-11001), Alexa488-conjugated goat anti-chicken secondary antibodies (ThermoFisher, A-11039), Alexa546-conjugated goat anti-rabbit secondary antibodies (ThermoFisher, A-11010) , Alexa546-conjugated goat anti-rat secondary antibodies (ThermoFisher, A-11081) and Alexa647-conjugated goat anti-rat secondary antibodies (ThermoFisher, A-21247).
Validation	The validation of commercially available antibodies was available on the manufacturer's website. TET1: https://www.genetex.com/Product/Detail/TET1-antibody-N3C1/GTX124207 TEAD1: https://www.bdbiosciences.com/en-us/products/reagents/microscopy-imaging-reagents/immunofluorescence-reagents/purified-mouse-anti-tef-1.610923 TEAD4: https://www.abcam.com/tead4-antibody-5h3-ab58310.html

GAPDH: https://www.emdmillipore.com/US/en/product/Anti-Glyceraldehyde-3-Phosphate-Dehydrogenase-Antibody-clone-6C5,MM_NF-MAB374
RNA PolII: https://www.emdmillipore.com/US/en/product/Anti-RNA-polymerase-II-Antibody-clone-CTD4H8,MM_NF-05-623
H3K4me3: https://www.emdmillipore.com/US/en/product/ChIPAb-Trimethyl-Histone-H3-Lys4-ChIP-Validated-Antibody-and-Primer-Set-rabbit-monoclonal,MM_NF-17-614?ReferrerURL=https%3A%2F%2Fwww.google.com%2F
H3K27Ac: https://www.emdmillipore.com/US/en/product/Anti-acetyl-Histone-H3-Lys27-Antibody,MM_NF-07-360
5mC:https://www.epigentek.com/catalog/methylcytosine-mc-monoclonal-antibody-33d3-p-186.html
5hmC:https://www.epigentek.com/catalog/hydroxymethylcytosine-hmc-monoclonal-antibody-hmc4d9-p-3660.html
Ki67 https://www.agilent.com/en/product/immunohistochemistry/antibodies-controls/primary-antibodies/ki-67-antigen-(dako-omnis)-76239#:~:text=Ki%2D67%20Antigen%20(Dako%20Omnis),-Clone%20MIB%2D1&text=The%20Ki%2D67%20antigen%20is,of%20a%20variety%20of%20tumors.
AFP: https://www.rndsystems.com/products/human-mouse-alpha-fetoprotein-afp-antibody-189502_mab1368
CK-19 https://www.thermofisher.com/antibody/product/Cytokeratin-19-CK-19-Antibody-Polyclonal/602-670
PH3: https://www.rndsystems.com/products/human-mouse-alpha-fetoprotein-afp-antibody-189502_mab1368
ALB https://www.sigmaaldrich.com/US/en/product/sigma/sab3500217
HNF4A https://www.thermofisher.com/antibody/product/HNF4A-Antibody-clone-K9218-Monoclonal/MA1-199
Cleaved Caspase-3: https://www.cellsignal.com/products/primary-antibodies/cleaved-caspase-3-asp175-antibody/9661

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	293T (Cat#CRL-3216,ATCC)
Authentication	Authentication was not performed for this study. Cell line was brought directly from ATCC. Morphological shape of cell line was monitored during the whole experimental process.
Mycoplasma contamination	All cell lines were tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	All experiments were performed in both male and female mice unless otherwise stated. Albumin-cre (Alb-cre)(003574) and Tet1 knockout (Tet1-/-)(017358) mice were obtained from the Jackson Laboratory.To generate liver-specific gene overexpression mice, ApoE-rtTA mice were bred with TRE-TAZ4SA mice. To generate liver-specific gene deletion mice, Alb-cre mice were bred with Mst1-/-; Mst2flox/flox, Nf2flox/flox, Sav1flox/flox or YAPflox/flox mice. To generate Tet1-deficient mice, Tet1-/- mice were bred with ApoE-rtTA-Yap, Alb-cre; Nf2flox/flox or Alb-cre; Sav1flox/flox mice. Both males and females were used for genetic experiments, and treatments started at about 1 month old. All mice in this study were housed at the Animal Resource Center at the UT Southwestern Medical Center and bred inside an facility with 12h dark/12h light cycles and a climate control system monitoring the ambient temperature and humidity. Mice were provided standard laboratory chow and allowed free access to water.
Wild animals	The study did not involve wild animal.
Field-collected samples	The study did not involve field-collected samples.
Ethics oversight	All animal experiments were performed with protocols approved by the Institutional Animal Care and Use Committee of the University of Texas Southwestern Medical Center.

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

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.*	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE178227 Reviewer token: yzkbwcoshtwdjcj
Files in database submission	WT1_R1_001.fastq.gz WT2_R1_001.fastq.gz WT3_R1_001.fastq.gz YAP1_R1_001.fastq.gz YAP2_R1_001.fastq.gz YAP3_R1_001.fastq.gz AH1_R1_001.fastq.gz AH2_R1_001.fastq.gz

AH3_R1_001.fastq.gz
DAC1_S6_R1_001.fastq.gz
DAC2_S7_R1_001.fastq.gz
DAC3_S8_R1_001.fastq.gz
WT_methylation1_S1_R1_001.fastq.gz
WT_methylation2_S2_R1_001.fastq.gz
YAP_methylation1_S3_R1_001.fastq.gz
YAP_methylation2_S4_R1_001.fastq.gz
AH_methylation1_S7_R1_001.fastq.gz
AH_methylation2_S8_R1_001.fastq.gz
DAC_methylation1_S5_R1_001.fastq.gz
DAC_methylation2_S6_R1_001.fastq.gz
WT_input1_S1_R1_001.fastq.gz
WT_input2_S2_R1_001.fastq.gz
YAP_input1_S3_R1_001.fastq.gz
YAP_input2_S4_R1_001.fastq.gz
AH_input1_S7_R1_001.fastq.gz
AH_input2_S8_R1_001.fastq.gz
TEAD_1_MERGED_R1_001.fastq.gz
TEAD_2_MERGED_R1_001.fastq.gz
TEAD_3_MERGED_R1_001.fastq.gz
TEAD_4_MERGED_R1_001.fastq.gz
TEAD_5_MERGED_R1_001.fastq.gz
TEAD_6_MERGED_R1_001.fastq.gz
TET_1_MERGED_R1_001.fastq.gz
TET_2_MERGED_R1_001.fastq.gz
TET_3_MERGED_R1_001.fastq.gz
TET_4_MERGED_R1_001.fastq.gz
WT1 raw.bigWig
WT2 raw.bigWig
YAP1 raw.bigWig
YAP2 raw.bigWig
AH1 raw.bigWig
AH2 raw.bigWig
DAC1 raw.bigWig
DAC2 raw.bigWig
TEAD4_WT1.bigwig
TEAD4_WT2.bigwig
TEAD4_YAP1.bigwig
TEAD4_YAP2.bigwig
TEAD4_AH1.bigwig
TEAD4_AH2.bigwig
TET1_WT1.bigwig
TET1_WT2.bigwig
TET1_YAP1.bigwig
TET1_YAP2.bigwig

Genome browser session
(e.g. UCSC)

No public available genome browser section

Methodology

Replicates

Two replicates for each antibdoy per group

Sequencing depth

35-45M raw sequencing reads for each sample, 75bp length of read, single-end.

Antibodies

TET1 antibody GeneTex Cat#: GTX124207
TEAD4 antibody Abcam Cat#: ab58310

Peak calling parameters

TET1 and TEAD4 peaks were called against mm10 background using MACS2 default parameters.

Data quality

Raw sequence data was quality checked with FastQC v.0.11.5. Mapped data in BAM and bigWig format was quality assessed with SAMTools v.1.3.1, PICARD v.2.6.0, deepTools v.2.4.3 and by visual inspection on the UCSC genome browser.

Software

Reads were aligned with Bowtie2 to the mm10 mouse genome and duplicates were removed from the mapped data using PICARD. Peaks were called against input samples of each condition using MACS2 default parameters. Aligned results were normalized with ChipSeqSpike R package and visualized by uploading normalized Bigwig files into mm10 assembly of USCS genome browser. TET1 and TEAD4 peaks were called against mm10 background using MACS2 default parameters. Correlation between TEAD4 and TET1 ChIP-seq signal was visualized by plotting the average of normalized read count data at each overlapped peak with ggplot2 R package. TEAD4 ChIP-seq signals summit to TET1 peaks, TET1 ChIP-seq signals summit to TEAD4 peaks and TET1/TEAD4/H3K27ac ChIP-seq signals summit to TET1/TEAD4 overlapped peaks were performed with Deeptools 3.5.0 and visualized with plotHeatmap function in Deeptools. Distribution of TEAD motif at TET1 peaks was performed with TFmotifView website.