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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	LAS AF software for Leica TCS SP5 II was used to acquire confocal images. LASV4.4 software was used to acquire pictures of cell cultures with a Leica DM IRB microscope. NDPscan3.1 was used to acquire IHC images. ImageQuant LAS 4000 1.2 was used to acquire western blot images. QuantStudio Design & Analysis Software v1.4.3 was used to acquire qPCR data
Data analysis	TopHat (version 2.0.5), HTSeq (version 0.6.0), edgeR package and R (version 3.0.0) were used to analyze RNA-seq data. Software used for the analysis of ChIP-seq data are described in the dedicated section of this Reporting Summary. GraphPad Prism 7.0d for Mac was used for statistical analysis.

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 from this study have been deposited in the GEO database under accession number GSE102409 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE102409).

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	Sample size was not predetermined. Generally accepted samples sizes were used, with reproducible differences between conditions indicating that the sample size is sufficient.
Data exclusions	All data were included.
Replication	All experiments were reproducible. Every figure states how many times each experiment was performed with similar results.
Randomization	For animal experiments, littermates were randomly allocated to treatment groups.
Blinding	Investigators were blinded for the evaluation of histological sections. Investigators were not blinded for analyses relying on unbiased measurements of quantitative parameters.

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

Antibodies

Antibodies used

Antibodies used in ChIP-seq experiments were:
anti-BRD4: A301-985A, Bethyl-Lab (lot A301-985A100-5)
anti-PolII: ab817, Abcam (lot GR271062-1)
anti-Histone H3 (acetyl K122): ab33309, Abcam (GR284790-3)
normal rabbit IgG: I5006, Sigma
Antibodies used for all other experiments were:
anti-BRD4: E2A7X, CST
anti-YAP1: 13584-1-AP, Proteintech
anti-WWTR1: HPA007415, Sigma
normal rabbit IgG: I5006, Sigma
anti-YAP/TAZ: sc-101199, Santa Cruz

anti-HA: Y-11, sc-805, Santa Cruz
anti-BRD2: D-2, sc-514102, Santa Cruz
anti-GAPDH: MAB347, Millipore
anti-TEF1: clone 31, 610923, BD Biosciences
horseradish-peroxidase-conjugated anti-FLAG: clone M2, A8592, Sigma
anti-BRD4: HPA015055, Sigma
anti-H3: ab1791, Abcam
anti-RNA polymerase II CTD repeat YSPTSPS antibody: ab817, Abcam
anti-HA: F-7, sc-7392, SantaCruz
anti-FLAG: F-7425, Sigma
anti-YAP1: EP1674Y, Abcam
anti-Ki67: clone SP6, M3062, Spring Bioscience
anti-cytokeratin wide spectrum screening: ZO622, Dako
anti-HNF4α: sc-6556, Santa Cruz
anti-SOX9: AB5535, Millipore
anti-GFP: ab13970, Abcam
anti-YAP1: ab52771, Abcam

Validation

All antibodies were validated by the producer. Moreover, the validation of BRD4 antibody for ChIP is reported in Supplementary figure 2a.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

MDA-MB-231 cells were from ICLC. HEK293T and MCF10A cells were from ATCC. SUM149PT and SUM-159PT were kindly provided by Dr. S. Ethier. Hs578T cells were obtained from ICLC. M229 and M229-R5 cells were a gift from Dr. JC Marine. WM3248 and WM3248-R6 cells, and SKMEL28 and SKMEL28-R2 were a gift from Dr. J.Kim.

Authentication

MDA-MB-231, MCF10A and HEK293T were authenticated by DSMZ service.

Mycoplasma contamination

All cell lines were routinely tested for mycoplasma contamination and were negative.

Commonly misidentified lines
(See ICLAC register)

None of the cell lines used in this study is present in the database of commonly misidentified cell lines.

Animals and other organisms

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

Laboratory animals

All experimental mice used in this study were mixed strains and more than 6-8 weeks old at the beginning of experiments. For mammary gland experiments we used exclusively female mice; for other experiments, both male and female mice were used.

Wild animals

No wild animals were used in this study.

Field-collected samples

The study did not involve samples collected on the field.

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=GSE102409

Files in database submission

raw files:
1-piccolo-160901_ep_TCAGCCTT_L003_R1_001.fastq.gz
2-piccolo-160901_ep_AAGGCTCT_L003_R1_001.fastq.gz
3-piccolo-160901_ep_TGTTCCGT_L003_R1_001.fastq.gz
4-piccolo-160901_ep_GGAATGTC_L003_R1_001.fastq.gz
9-piccolo-160901_ep_TCGGATTC_L004_R1_001.fastq.gz
10-piccolo-160901_ep_CGGAGTAT_L004_R1_001.fastq.gz
11-piccolo-160901_ep_GAACCTTC_L004_R1_001.fastq.gz
12-piccolo-160901_ep_AGAGGATG_L004_R1_001.fastq.gz
17-piccolo-160901_ep_ATGGCGAT_L005_R1_001.fastq.gz
18-piccolo-160901_ep_AACGCCTT_L006_R1_001.fastq.gz
19-piccolo-160901_ep_GTAAGGTG_L005_R1_001.fastq.gz
20-piccolo-160901_ep_TGTCGACT_L006_R1_001.fastq.gz
5-piccolo-160901_ep_CATCCAAG_L003_R1_001.fastq.gz
6-piccolo-160901_ep_GTCAACAG_L003_R1_001.fastq.gz

7-piccolo-160901_with_additional_reads.fastq.gz
8-piccolo-160901_ep_AGCCTATC_L004_R1_001.fastq.gz
13-piccolo-160901_ep_ACGCTTCT_L005_R1_001.fastq.gz
14-piccolo-160901_ep_CACAGGAA_L005_R1_001.fastq.gz
15-piccolo-160901_ep_ACGAATCC_L005_R1_001.fastq.gz
16-piccolo-160901_ep_CCTTCCAT_L005_R1_001.fastq.gz
21-piccolo-160901_ep_ACTCTGAG_L006_R1_001.fastq.gz
22-piccolo-160901_ep_GATGGAGT_L006_R1_001.fastq.gz
23-piccolo-160901_ep_CTAGCTCA_L006_R1_001.fastq.gz
24-piccolo-160901_ep_CTGTACCA_L006_R1_001.fastq.gz
DMSO_Input_rep3.fastq.gz
DMSO_Input_rep4.fastq.gz
DMSO_H3K122ac_rep1.fastq.gz
DMSO_H3K122ac_rep2.fastq.gz
JQ1_Input_rep3.fastq.gz
JQ1_Input_rep4.fastq.gz
JQ1_H3K122ac_rep1.fastq.gz
JQ1_H3K122ac_rep2.fastq.gz
siYT_Input_rep3.fastq.gz
siYT_Input_rep4.fastq.gz
siYT_H3K122ac_rep1.fastq.gz
siYT_H3K122ac_rep2.fastq.gz
Processed files:
MACS_SPMR_DMSO_BRD4.bw
MACS_SPMR_DMSO_H3K122ac.bw
MACS_SPMR_DMSO_Pol2.bw
MACS_SPMR_JQ1_BRD4.bw
MACS_SPMR_JQ1_H3K122ac.bw
MACS_SPMR_JQ1_Pol2.bw
MACS_SPMR_siYT_BRD4.bw
MACS_SPMR_siYT_H3K122ac.bw
MACS_SPMR_siYT_Pol2.bw

Genome browser session
(e.g. UCSC)

n.a.

Methodology

Replicates

For every experimental condition 2 biological replicates were produced. Sample processing (from cell seeding to chromatin immunoprecipitation) was performed independently for the 2 replicates.

Sequencing depth

BRD and RNA Pol II: 40 millions of single-end reads per sample
H3K122ac: 60 millions of single-end reads per sample

Antibodies

BRD4: Bethyl laboratories, cat. A301-985A, lot A301-985A100-5; see validation of specificity by ChIP-qPCR with BRD4 siRNA in MDA-MB-231 cells in Supplementary Figure 2a.
RNA polymerase II, clone 8WG16: Abcam, ab817 (ChIP grade), lot GR271062-1 (validation by supplier: http://www.abcam.com/rna-polymerase-ii-ctd-repeat-ysptsps-antibody-8wg16-chip-grade-ab817.html)
Histone H3 (acetyl K122): Abcam, ab33309, lot GR284790-3 (used for ChIP-seq in human cells in PUBMED 23415232)

Peak calling parameters

Raw reads were aligned using Bowtie to build version hg19 of the human genome retaining only uniquely mapped reads. Indexes were retrieved from Illumina's iGenomes collection for UCSC hg19 genome. Redundant reads were removed using SAMtools.
MACS callpeak function was used to generate bedGraph files for pooled replicates using the -B --SPMR parameters and appropriate control samples (IgG for BRD4, Input DNA for Pol2 and H3K122ac).
BedGraph files were converted to bigWig format with UCSC bedGraphToBigWig utility.
Peak calling was not performed in this study.

Data quality

FastQC was used to assess raw sequence data quality. ngs.plot was used to check ChIP average profile around TSS and gene bodies.

Software

CASAVA (version 1.8.4)
FastQC (version 0.11.5, https://www.bioinformatics.babraham.ac.uk/projects/fastqc/)
Bowtie (version 0.12.7, Langmead et al., 2009)
SAMtools (version 0.1.18, Li et al., 2009)
ngs.plot (version 2.00, Shen et al., 2014)
MACS2 (version 2.0.10, Zhang et al., 2008)
UCSC bedGraphToBigWig (http://hgdownload.soe.ucsc.edu/admin/exe/linux.x86_64/)