

## 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

- |                                     |                                     |  |
|-------------------------------------|-------------------------------------|--|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | A description of all covariates tested   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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 External data were downloaded by sratoolkit fastq-dump (2.9.6.1).

Data analysis Trim Galore (0.6.4), STAR (2.5.4b), featureCounts (2.0.0), Homer (4.11), edgeR (3.28.1), DESeq2 (1.26.0), GATK (4.1.4.0), Bowtie2 (2.3.5.1), MACS2 (2.2.6), BEDTools(2.92.2), deepTools(3.4.3), bedGraphToBigWig (4), corrplot (0.84), pheatmap (1.0.12), VennDiagram (1.6.20), preseq (2.0.3), zUMIs(2.7.1c), Seurat (3.2.1), IGV (2.6.3), ChIPseeker (1.22.1), clusterProfiler (3.14.3), Monocle2 (2.14), STREAM (1.0), cisTopic (0.3.0), WGCNA (1.69), ggalluvial (0.12.3), Custom scripts used in this study are available from <https://github.com/Fanglab-zju/scSET-seq>

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

The reference genome used in this study is available in UCSC (<http://genome.ucsc.edu>) database under mouse reference genome mm9. The raw and processed sequencing data generated in this study have been deposited in the NCBI Gene Expression Omnibus (GEO) database under accession code GSE168637. Encode (<https://www.encodeproject.org/>) datasets were downloaded with the accession numbers: H3K27me3 (ENCSR059MBO), H3K27me3 input (ENCSR326ULS), H3K4me3 (ENCSR000CGO) and H3K4me3 input (ENCSR095IPH). The other external datasets

were downloaded from NCBI Gene Expression Omnibus (GEO) (<http://www.ncbi.nlm.nih.gov/geo/>), with the accession numbers: Aebp2 CHIP-seq (GSE83082), Paired-Tag (GSE152020), scATAC-seq (GSE100033), Smart-seq2(GSE151334). 10x scRNA-seq datasets were downloaded from the 10x Genomics website (<https://www.10xgenomics.com/>).

## 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](https://www.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	Sample size was determined based on prior published data from similar experiments (Rosenberg et.al., Science, 2018; Cao et.al., Science, 2018; Preissl et.al., Nat. Neuroscience, 2018)
Data exclusions	Sequencing reads adaptor and low-quality bases were removed by Trim Galore (0.6.4), reads mapped to mitochondria and random chromosomes were also removed. PCR duplicates in epigenetic data were removed by GATK (4.1.4.0).
Replication	All experiments were done for at least twice. scSET-seq for gene expression was conducted through 3 independent experiments. scSET-seq for H3K4me3 and H3K27me3 in Fig. 1 were performed with 5 biological independent experiments respectively. scSET-seq for H3K4me3 and H3K27me3 in Wnt3a-induced asymmetric cell division were conducted from 10 and 6 independent experiments, respectively.
Randomization	Rndomization of reads was selected by bedtools for bioinformatics. Experiments allocation was random.
Blinding	The experiments were not blinded as the identities of histone modification, and the clustering of scSET-seq data were unsupervised.

## 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
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Human research participants
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

### Methods

n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

## Antibodies

Antibodies used	Rabbit polyclonal anti-Histone H3 (Cat.# ab1791, Abcam), 1:5000 diluted for Western blot; Rabbit polyclonal anti-Histone H3K27me3 (Cat.# 9733, Cell Signaling Technology), 1:1000 diluted for Western blot, 1:50 diluted for SET-seq, 1:200 diluted for scSET-seq; Rabbit polyclonal anti-Histone H3K4me3 (Cat.# ab8580, Abcam), 1:1000 diluted for Western blot, 1:50 diluted for SET-seq, 1:200 diluted for scSET-seq; Rabbit polyclonal anti-Histone H3K9me3 (Cat.# ab8898, Abcam), 1:1000 diluted for Western blot; Rabbit polyclonal anti-Histone H3K27ac (Cat.# ab4729, Abcam), 1:1000 diluted for Western blot; Rabbit monoclonal anti-EZH2 (Cat.# 5246, Clone name D2C9, Cell Signaling Technology), 1:1000 diluted for Western blot; Rabbit monoclonal anti-AEBP2 (Cat.# 14129, Clone name D7C6X, Cell Signaling Technology), 1:1000 diluted for Western blot; Rabbit polyclonal anti-Jarid2 (Cat.# G-2, Novus Biologicals), 1:1000 diluted for Western blot; Peroxidase AffiniPure Goat anti-Rabbit IgG (H + L) (Cat.# 111-035-003, Jackson ImmunoResearch Laboratories), 1:1000 diluted for Western blot.
Validation	H3 were validated in Yuan L et al., Nucleic Acids Res, 2021; H3K27me3 were validated in Chan et al., Genes & Development, 2014; H3K4me3 were validated in Cai Y et al., Nat Commun, 2021;

H3K9me3 were validated in Liang C et al., Cell Res , 2021;  
 H3K27ac were validated in Wei J et al., Cell, 2021;  
 EZH2 were validated in Gabriela Vilema-Enriquez et al., J Biol Chem, 2020;  
 AEBP2 were validated in Siming Chen et al., Mol Cell, 2020;  
 Jarid2 were validated in Perino M et al., Nat. Genet, 2018.

## Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)	Mouse embryonic stem cell ES-E14TG2a from ATCC (CRL-1821)
Authentication	RNA seq
Mycoplasma contamination	All cell lines were negative for mycoplasma contamination.
Commonly misidentified lines (See <a href="#">ICLAC</a> register)	No commonly misidentified cell lines were used in the study.

## 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=GSE168637>

Files in database submission

H3K27me3\_SET-seq\_10\_cells\_Epi\_1\_rep1.bw,H3K27me3\_SET-seq\_10\_cells\_Epi\_1\_rep1\_1.fq.gz,H3K27me3\_SET-seq\_10\_cells\_Epi\_1\_rep1\_2.fq.gz,H3K27me3\_SET-seq\_10\_cells\_Epi\_1\_rep2.bw,H3K27me3\_SET-seq\_10\_cells\_Epi\_1\_rep2\_1.fq.gz,H3K27me3\_SET-seq\_10\_cells\_Epi\_1\_rep2\_2.fq.gz,H3K27me3\_SET-seq\_100\_cells\_Epi\_1\_rep1.bw,H3K27me3\_SET-seq\_100\_cells\_Epi\_1\_rep1\_1.fq.gz,H3K27me3\_SET-seq\_100\_cells\_Epi\_1\_rep1\_2.fq.gz,H3K27me3\_SET-seq\_100\_cells\_Epi\_1\_rep2.bw,H3K27me3\_SET-seq\_100\_cells\_Epi\_1\_rep2\_1.fq.gz,H3K27me3\_SET-seq\_100\_cells\_Epi\_1\_rep2\_2.fq.gz,H3K27me3\_SET-seq\_1000\_cells\_Epi\_1\_rep1.bw,H3K27me3\_SET-seq\_1000\_cells\_Epi\_1\_rep1\_1.fq.gz,H3K27me3\_SET-seq\_1000\_cells\_Epi\_1\_rep1\_2.fq.gz,H3K27me3\_SET-seq\_1000\_cells\_Epi\_1\_rep2.bw,H3K27me3\_SET-seq\_1000\_cells\_Epi\_1\_rep2\_1.fq.gz,H3K27me3\_SET-seq\_1000\_cells\_Epi\_1\_rep2\_2.fq.gz,H3K27me3\_SET-seq\_10000\_cells\_Epi\_1\_rep1.bw,H3K27me3\_SET-seq\_10000\_cells\_Epi\_1\_rep1\_1.fq.gz,H3K27me3\_SET-seq\_10000\_cells\_Epi\_1\_rep1\_2.fq.gz,H3K27me3\_SET-seq\_10000\_cells\_Epi\_1\_rep2.bw,H3K27me3\_SET-seq\_10000\_cells\_Epi\_1\_rep2\_1.fq.gz,H3K27me3\_SET-seq\_10000\_cells\_Epi\_1\_rep2\_2.fq.gz,H3K27me3\_SET-seq\_10\_cells\_Epi\_2\_rep1.bw,H3K27me3\_SET-seq\_10\_cells\_Epi\_2\_rep1\_1.fq.gz,H3K27me3\_SET-seq\_10\_cells\_Epi\_2\_rep1\_2.fq.gz,H3K27me3\_SET-seq\_10\_cells\_Epi\_2\_rep2.bw,H3K27me3\_SET-seq\_10\_cells\_Epi\_2\_rep2\_1.fq.gz,H3K27me3\_SET-seq\_10\_cells\_Epi\_2\_rep2\_2.fq.gz,H3K27me3\_SET-seq\_100\_cells\_Epi\_2\_rep1.bw,H3K27me3\_SET-seq\_100\_cells\_Epi\_2\_rep1\_1.fq.gz,H3K27me3\_SET-seq\_100\_cells\_Epi\_2\_rep1\_2.fq.gz,H3K27me3\_SET-seq\_100\_cells\_Epi\_2\_rep2.bw,H3K27me3\_SET-seq\_100\_cells\_Epi\_2\_rep2\_1.fq.gz,H3K27me3\_SET-seq\_100\_cells\_Epi\_2\_rep2\_2.fq.gz,H3K27me3\_SET-seq\_1000\_cells\_Epi\_2\_rep1.bw,H3K27me3\_SET-seq\_1000\_cells\_Epi\_2\_rep1\_1.fq.gz,H3K27me3\_SET-seq\_1000\_cells\_Epi\_2\_rep1\_2.fq.gz,H3K27me3\_SET-seq\_1000\_cells\_Epi\_2\_rep2.bw,H3K27me3\_SET-seq\_1000\_cells\_Epi\_2\_rep2\_1.fq.gz,H3K27me3\_SET-seq\_10000\_cells\_epi\_rep1.bw,IgG\_SET-seq\_10000\_cells\_epi\_rep1\_1.fq.gz,IgG\_SET-seq\_10000\_cells\_epi\_rep1\_2.fq.gz,IgG\_SET-seq\_10000\_cells\_epi\_rep2.bw,IgG\_SET-seq\_10000\_cells\_epi\_rep2\_1.fq.gz,IgG\_SET-seq\_10000\_cells\_epi\_rep2\_2.fq.gz,vitro-Tn5-25ng/μl\_rep1.txt,vitro-Tn5-25ng/μl\_rep1\_1.fq.gz,vitro-Tn5-25ng/μl\_rep1\_2.fq.gz,vitro-Tn5-25ng/μl\_rep2.txt,vitro-Tn5-25ng/μl\_rep2\_1.fq.gz,vitro-Tn5-25ng/μl\_rep2\_2.fq.gz,vitro-Tn5-50ng/μl\_rep1.txt,vitro-Tn5-50ng/μl\_rep1\_1.fq.gz,vitro-Tn5-50ng/μl\_rep1\_2.fq.gz,vitro-Tn5-50ng/μl\_rep2.txt,vitro-Tn5-50ng/μl\_rep2\_1.fq.gz,vitro-Tn5-50ng/μl\_rep2\_2.fq.gz,vitro-Tn5-100ng/μl\_rep1.txt,vitro-Tn5-100ng/μl\_rep1\_1.fq.gz,vitro-Tn5-100ng/μl\_rep1\_2.fq.gz,vitro-Tn5-100ng/μl\_rep2.txt,vitro-Tn5-100ng/μl\_rep2\_1.fq.gz,vitro-Tn5-100ng/μl\_rep2\_2.fq.gz,vitro-RNA-300ng\_rep1.txt,vitro-RNA-300ng\_rep1\_1.fq.gz,vitro-RNA-300ng\_rep1\_2.fq.gz,vitro-RNA-300ng\_rep2.txt,vitro-RNA-300ng\_rep2\_1.fq.gz,vitro-RNA-300ng\_rep2\_2.fq.gz,vitro-RNA-3ng\_rep1.txt,vitro-RNA-3ng\_rep1\_1.fq.gz,vitro-RNA-3ng\_rep1\_2.fq.gz,vitro-RNA-3ng\_rep2.txt,vitro-RNA-3ng\_rep2\_1.fq.gz,vitro-RNA-3ng\_rep2\_2.fq.gz,vitro-RNA-30pg\_rep1.txt,vitro-RNA-30pg\_rep1\_1.fq.gz,vitro-RNA-30pg\_rep1\_2.fq.gz,vitro-RNA-30pg\_rep2.txt,vitro-RNA-30pg\_rep2\_1.fq.gz,vitro-RNA-30pg\_rep2\_2.fq.gz,vitro-16°C-5mins\_rep1.txt,vitro-16°C-5mins\_rep1\_1.fq.gz,vitro-16°C-5mins\_rep1\_2.fq.gz,vitro-16°C-5mins\_rep2.txt,vitro-16°C-5mins\_rep2\_1.fq.gz,vitro-16°C-5mins\_rep2\_2.fq.gz,vitro-16°C-10mins\_rep1.txt,vitro-16°C-10mins\_rep1\_1.fq.gz,vitro-16°C-10mins\_rep1\_2.fq.gz,vitro-16°C-10mins\_rep2.txt,vitro-16°C-10mins\_rep2\_1.fq.gz,vitro-16°C-10mins\_rep2\_2.fq.gz,vitro-16°C-15mins\_rep1.txt,vitro-16°C-15mins\_rep1\_1.fq.gz,vitro-16°C-15mins\_rep1\_2.fq.gz,vitro-16°C-15mins\_rep2.txt,vitro-16°C-15mins\_rep2\_1.fq.gz,vitro-16°C-15mins\_rep2\_2.fq.gz,vitro-16°C-30mins\_rep1.txt,vitro-16°C-30mins\_rep1\_1.fq.gz,vitro-16°C-30mins\_rep1\_2.fq.gz,vitro-16°C-30mins\_rep2.txt,vitro-16°C-30mins\_rep2\_1.fq.gz,vitro-16°C-30mins\_rep2\_2.fq.gz,vitro-37°C-5mins\_rep1.txt,vitro-37°C-5mins\_rep1\_1.fq.gz,vitro-37°C-5mins\_rep1\_2.fq.gz,vitro-37°C-5mins\_rep2.txt,vitro-37°C-5mins\_rep2\_1.fq.gz,vitro-37°C-5mins\_rep2\_2.fq.gz,vitro-37°C-10mins\_rep1.txt,vitro-37°C-10mins\_rep1\_1.fq.gz,vitro-37°C-10mins\_rep1\_2.fq.gz,vitro-37°C-10mins\_rep2.txt,vitro-37°C-10mins\_rep2\_1.fq.gz,vitro-37°C-10mins\_rep2\_2.fq.gz

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seq_Exp_5_2.fq.gz,Wnt_beads_H3K27me3_scSET-seq_Exp_counts_matrix.txt,Wnt_beads_H3K27me3_scSET-
seq_Exp_6_1.fq.gz,Wnt_beads_H3K27me3_scSET-seq_Exp_6_2.fq.gz,Wnt_beads_H3K27me3_scSET-
seq_Exp_counts_matrix.txt,Wnt_beads_H3K27me3_scSET-seq_Exp_7_1.fq.gz,Wnt_beads_H3K27me3_scSET-
seq_Exp_7_2.fq.gz,Wnt_beads_H3K27me3_scSET-seq_Exp_counts_matrix.txt,Wnt_beads_H3K27me3_scSET-
seq_Exp_8_1.fq.gz,Wnt_beads_H3K27me3_scSET-seq_Exp_8_2.fq.gz,Wnt_beads_H3K27me3_scSET-
seq_Exp_counts_matrix.txt,Wnt_beads_H3K27me3_scSET-seq_Exp_9_1.fq.gz,Wnt_beads_H3K27me3_scSET-
seq_Exp_9_2.fq.gz,Wnt_beads_H3K27me3_scSET-seq_Exp_counts_matrix.txt,Wnt_beads_H3K27me3_scSET-
seq_Exp_10_1.fq.gz,Wnt_beads_H3K27me3_scSET-
seq_Exp_10_2.fq.gz,H3K27me3_Epi_Aebp2_KO1_rep1.bw,H3K27me3_Epi_Aebp2_KO1_rep1_1.fq.gz,H3K27me3_Epi_Aebp2_
_KO1_rep1_2.fq.gz,H3K27me3_Epi_Aebp2_KO1_rep2.bw,H3K27me3_Epi_Aebp2_KO1_rep2_1.fq.gz,H3K27me3_Epi_Aebp2_
_KO1_rep2_2.fq.gz,H3K27me3_Epi_Aebp2_KO2_rep1.bw,H3K27me3_Epi_Aebp2_KO2_rep1_1.fq.gz,H3K27me3_Epi_Aebp2_K
O2_rep1_2.fq.gz,H3K27me3_Epi_Aebp2_KO2_rep2.bw,H3K27me3_Epi_Aebp2_KO2_rep2_1.fq.gz,H3K27me3_Epi_Aebp2_K
O2_rep2_2.fq.gz,H3K27me3_Exp_Aebp2_KO1_rep1.txt,H3K27me3_Exp_Aebp2_KO1_rep1_1.fq.gz,H3K27me3_Exp_Aebp2_K
O1_rep1_2.fq.gz,H3K27me3_Exp_Aebp2_KO1_rep2.txt,H3K27me3_Exp_Aebp2_KO1_rep2_1.fq.gz,H3K27me3_Exp_Aebp2_K
O1_rep2_2.fq.gz,H3K27me3_Exp_Aebp2_KO2_rep1.txt,H3K27me3_Exp_Aebp2_KO2_rep1_1.fq.gz,H3K27me3_Exp_Aebp2_K
O2_rep1_2.fq.gz,H3K27me3_Exp_Aebp2_KO2_rep2.txt,H3K27me3_Exp_Aebp2_KO2_rep2_1.fq.gz,H3K27me3_Exp_Aebp2_K
O2_rep2_2.fq.gz
```

Genome browser session  
(e.g. [UCSC](#))

no longer applicable

## Methodology

Replicates	Each sequencing was repeated at least twice.
Sequencing depth	The numbers of reads and unique mapped reads is summarized in Supplementary Dataset 7. All reads are sequenced as 150bp with paired-end .
Antibodies	Rabbit polyclonal anti-Histone H3K27me3 (Cat# 9733, Cell Singaling Technology); Rabbit polyclonal anti-Histone H3K4me3 (Cat# ab8580, Abcam)
Peak calling parameters	For H3K27me3 macs2 callpeak --broad -g mm --nomodel For H3K4me3 macs2 callpeak -g mm -B --nomodel Index files used for mapping is mm9 genome
Data quality	Peak qualities were provided as Supplementary Dataset 8.
Software	Trim Galore (0.6.4), Homer (4.11),GATK (4.1.4.0), Bowtie2 (2.3.5.1), MACS2 (2.2.6), BEDTools (2.92.2), deepTools( version 3.4.3), bedGraphToBigWig (4), VennDiagram (1.6.20), preseq (2.0.3), IGV (2.6.3), ChIPseeker(1.22.1)