

## 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

The Flow cytometric data: Beckman Gallios  
 The RNA Sequencing data: Illumina Hiseq 4000  
 The CHIP Sequencing data: Hiseq 2500  
 The ATAC Sequencing data: NovaSeq 6000  
 The qRT-PCR data: QuantStudio 7 Flex Real Real-Time PCR System  
 The Phase Separation data: LSM880NLO FLIM

Data analysis

Statistical analysis: GraphPad Prism(ver.8)  
 Flow cytometric analysis: Flowjo(Version 10)  
 Heatmap analyses of RNA Sequencing data: RStudio.  
 Confocal data analysis: Image J (2.1.0)  
 Rank Ordering of Super-Enhancers (ROSE) algorithm: [https://bitbucket.org/young\\_computati on/](https://bitbucket.org/young_computati on/)

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 RNA-Sequencing data and ChIP-sequencing data have been deposited into the Gene Expression Omnibus (accession code GSE169470). The source data underlying for the main figures and supplementary figures are provided as a Source Data file, which is included in the submission.

## 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
- Data exclusions
- Replication
- Randomization
- Blinding

## 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 type="checkbox"/>            | <input checked="" 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 type="checkbox"/>            | <input checked="" type="checkbox"/> Flow cytometry |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging    |

## Antibodies

Antibodies used

Western blot, Confocal and ChIP  
 ZMYND8 antibody ChIP : Bethyl A302-090A, CHIP: 2ug/sample  
 ZMYND8 antibody WB : Sigma HPA020949, 1:1000  
 LSD1 antibody : Abcam ab129195, 2ug/sample, WB 1:1000  
 H3K4me1 antibody : Cell signaling technology 5326s, 2ug.sample  
 H3K4me2 antibody : Abcam ab32356, 2ug/sample  
 p65 antibody : Santa Cruz sc-8008, 2ug/sample, WB 1:1000  
 MYC tag antibody : Santa Cruz sc-40 HRP, 1:2000  
 His-Tag antibody : Santa Cruz sc-8036 1:1000  
 HA-Tag antibody : Santa Cruz sc-7392 1:1000

FLAG tag antibody : Sigma B3111 1:1000  
 actin antibody : Santa Cruz sc-8432 1:2000  
 Lamin B1 antibody : Santa Cruz sc-374015 1:1000  
 Acetylated-Lysine antibody : Cell signaling technology 9441s 1:1000  
 GFP antibody: Cell signaling technology 2555s 1:1000  
 HDAC1 antibody : Santa Cruz sc-81598 1:1000  
 PU.1 antibody : Santa Cruz sc-390405 1:1000  
 KDM5C antibody : Santa Cruz sc-376255 1:1000  
 p38 MAPK (D13E1) antibody : Cell signaling technology 8690s 1:1000  
 Phospho-p38 MAPK (Thr180/Tyr182) (D3F9) : Cell signaling technology 4511s 1:1000  
 p44/42 MAPK (Erk1/2) (137F5) : Cell signaling technology 4695s 1:1000  
 Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (D13.14.4E) : Cell signaling technology 1:1000  
 SAPK/JNK antibody : Cell signaling technology 9252s 1:1000  
 Phospho-SAPK/JNK (Thr183/Tyr185) (G9) : Cell signaling technology 9255s 1:1000  
 Phospho-NF-κB p65 (Ser536) (93H1) : Cell signaling technology 3033s 1:1000

#### Secondary antibody

Peroxidase AffiniPure Goat Anti-Rabbit IgG (H+L) : Jackson ImmunoResearch 111-035-003 1:5000  
 Peroxidase AffiniPure Goat Anti-Mouse IgG (H+L) : Jackson ImmunoResearch 115-035-003 1:5000  
 Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488 : Invitrogen A-11008 1:400  
 Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 594 : Invitrogen A-11005 1:400

#### Flow cytometry

CD11b-BV421 : Biolegend 101251 (clone:M1/70) 1:300  
 F4/80-APC : eBioscience 17-4801-80 (clone:BM8) 1:300  
 Gr-1-PE-CY7 : eBioscience 25-5931-81 (clone:RB6-8C5) 1:300  
 CD11c-FITC : Invitrogen 11-0114-85 (clone:N418) 1:300  
 Fc receptor antibody : Biolegend 101302 (clone:93) 1:300

#### Validation

ZMYND8 Antibody (A302-090A) in IP Detection of human ZMYND8 by western blot of immunoprecipitates. Samples: Whole cell lysate (1 mg for IP, 20% of IP loaded) from HeLa cells. Antibodies: Affinity purified rabbit anti-ZMYND8 antibody A302-090A used for IP at 3 μg/mg lysate. ZMYND8 was also immunoprecipitated by rabbit anti-ZMYND8 antibody A302-089A, which recognizes an upstream epitope. For blotting immunoprecipitated ZMYND8, A302-089A was used at 1 μg/ml. Detection: Chemiluminescence with an exposure time of 10 seconds.

#### Western blot , Confocal and ChIP

ZMYND8 antibody ChIP : Bethyl A302-090A <https://www.thermofisher.cn/cn/zh/antibody/product/PRKCBP1-Antibody-Polyclonal/A302-090A>  
 ZMYND8 antibody WB : Sigma <https://www.sigmaaldrich.cn/CN/en/product/sigma/hpa020949?context=product>  
 LSD1 antibody : Abcam ab129195 <https://www.abcam.com/kdm1lstd1-antibody-epr6825-nuclear-marker-and-chip-grade-ab129195.html>  
 H3K4me1 antibody : Cell signaling technology 5326s <https://www.cellsignal.com/products/primary-antibodies/mono-methyl-histone-h3-lys4-d1a9-xp-rabbit-mab/5326>  
 H3K4me2 antibody : Abcam ab32356 <https://www.abcam.com/Histone-H3-di-methyl-K4-antibody-Y47-ChIP-Grade-ab32356.html>  
 p65 antibody : Santa Cruz sc-8008 <https://www.scbt.com/zh/p/nfkappab-p65-antibody-f-6>  
 MYC tag antibody : Santa Cruz sc-40 HRP <https://www.scbt.com/p/c-myc-antibody-9e10?requestFrom=search>  
 His-Tag antibody : Santa Cruz sc-8036 <https://www.scbt.com/zh/p/his-probe-antibody-h-3?requestFrom=search>  
 HA-Tag antibody : Santa Cruz sc-7392 <https://www.scbt.com/zh/p/ha-probe-antibody-f-7?requestFrom=search>  
 FLAG tag antibody : Sigma B3111 <https://www.sigmaaldrich.cn/CN/en/product/sigma/b3111?context=product>  
 actin antibody : Santa Cruz sc-8432 <https://www.scbt.com/p/actin-antibody-c-2?requestFrom=search>  
 Lamin B1 antibody : Santa Cruz sc-374015 <https://www.scbt.com/zh/p/lamin-b1-antibody-b-10?requestFrom=search>  
 Acetylated-Lysine antibody : Cell signaling technology 9441s <https://www.cellsignal.com/products/primary-antibodies/acetylated-lysine-antibody/9441>  
 GFP antibody: Cell signaling technology 2555s <https://www.cellsignal.com/products/primary-antibodies/gfp-antibody/2555>  
 HDAC1 antibody : Santa Cruz sc-81598 <https://www.scbt.com/zh/p/hdac1-antibody-10e2?requestFrom=search>  
 PU.1 antibody : Santa Cruz sc-390405 <https://www.scbt.com/p/pu-1-antibody-c-3?requestFrom=search>  
 KDM5C antibody : Santa Cruz sc-376255 <https://www.scbt.com/zh/p/smcx-antibody-g-10?requestFrom=search>  
 p38 MAPK (D13E1) antibody : Cell signaling technology 8690s <https://www.cellsignal.com/products/primary-antibodies/p38-mapk-d13e1-xp-rabbit-mab/8690?site-search-type=Products&N=4294956287&Ntt=p38&fromPage=plp>  
 Phospho-p38 MAPK (Thr180/Tyr182) (D3F9) : Cell signaling technology 4511s <https://www.cellsignal.com/products/primary-antibodies/phospho-p38-mapk-thr180-tyr182-d3f9-xp-rabbit-mab/4511?site-search-type=Products&N=4294956287&Ntt=phospho-p38&fromPage=plp>  
 p44/42 MAPK (Erk1/2) (137F5) : Cell signaling technology 4695s <https://www.cellsignal.com/products/primary-antibodies/p44-42-mapk-erk1-2-137f5-rabbit-mab/4695?site-search-type=Products&N=4294956287&Ntt=erk&fromPage=plp>  
 Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (D13.14.4E) : Cell signaling technology 4370 <https://www.cellsignal.com/products/primary-antibodies/phospho-p44-42-mapk-erk1-2-thr202-tyr204-d13-14-4e-xp-rabbit-mab/4370?site-search-type=Products&N=4294956287&Ntt=erk&fromPage=plp>  
 SAPK/JNK antibody : Cell signaling technology 9252 <https://www.cellsignal.com/products/primary-antibodies/sapk-jnk-antibody/9252>  
 Phospho-SAPK/JNK (Thr183/Tyr185) (G9) : Cell signaling technology 9255 <https://www.cellsignal.com/products/primary-antibodies/phospho-sapk-jnk-thr183-tyr185-g9-mouse-mab/9255?site-search-type=Products&N=4294956287&Ntt=jnk&fromPage=plp>

Phospho-NF- $\kappa$ B p65 (Ser536) (93H1) : Cell signaling technology 3033s <https://www.cellsignal.com/products/primary-antibodies/phospho-nf-kb-p65-ser536-93h1-rabbit-mab/3033>

Flow cytometry

CD11b-BV421 : Biolegend 101251 (clone:M1/70) <https://www.biolegend.com/en-us/products/brilliant-violet-421-anti-mouse-human-cd11b-antibody-7163?GroupID=BLG10427>

F4/80-APC : eBioscience 17-4801-80 (clone:BM8) [https://www.thermofisher.cn/cn/zh/antibody/product/F4-80-Antibody-clone-BM8-Monoclonal/17-4801-82?adobe\\_mc=MC MID%7C26088330770613422071955603836484247741%7CMCAID%3D301A4E087FE22D69-4000030F90CBD596%7CMCORGID%3D5B135A0C5370E6B40A490D44%40AdobeOrg%7CTS=1614293705](https://www.thermofisher.cn/cn/zh/antibody/product/F4-80-Antibody-clone-BM8-Monoclonal/17-4801-82?adobe_mc=MC MID%7C26088330770613422071955603836484247741%7CMCAID%3D301A4E087FE22D69-4000030F90CBD596%7CMCORGID%3D5B135A0C5370E6B40A490D44%40AdobeOrg%7CTS=1614293705)

Gr-1-PE-CY7 : eBioscience 25-5931-81 (clone:RB6-8C5) [https://www.thermofisher.cn/cn/zh/antibody/product/Ly-6G-Ly-6C-Antibody-clone-RB6-8C5-Monoclonal/25-5931-82?adobe\\_mc=MC MID%7C26088330770613422071955603836484247741%7CMCAID%3D301A4E087FE22D69-4000030F90CBD596%7CMCORGID%3D5B135A0C5370E6B40A490D44%40AdobeOrg%7CTS=1614293705](https://www.thermofisher.cn/cn/zh/antibody/product/Ly-6G-Ly-6C-Antibody-clone-RB6-8C5-Monoclonal/25-5931-82?adobe_mc=MC MID%7C26088330770613422071955603836484247741%7CMCAID%3D301A4E087FE22D69-4000030F90CBD596%7CMCORGID%3D5B135A0C5370E6B40A490D44%40AdobeOrg%7CTS=1614293705)

CD11c-FITC : Invitrogen <https://www.thermofisher.cn/cn/zh/antibody/product/CD11c-Antibody-clone-N418-Monoclonal/11-0114-85>

## Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s) Raw264.7 cells, HEK293T cells and HeLa cells were purchased from Cell bank of Chinese Academic of Sciences.

Authentication All cell lines were authenticated by observing the morphology.

Mycoplasma contamination There is no mycoplasma contamination in all cell lines.

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 The Zmynd8flox/flox mouse model was established by gene targeting via homologous recombination in C57BL/6 embryonic stem cells (Cygene, Guangzhou, China). LoxP sequences were introduced to flank exons 6 and 7 of the Zmynd8 gene. Zmynd8flox/flox mice were crossed with specific Cre transgenic mice to achieve lineage-specific gene deletion. Lyz2-Cre (also known as LysM-Cre) mice on a C57BL/6 background were purchased from the Jackson Laboratory. Mice were housed under specific-pathogen-free conditions with standard food and water ad libitum in a 12h light / 12h dark cycle. Humidity and ambient temperature were maintained between 45-65% and 20-24°C, respectively. 6-week-old female C57BL/6 mice were used.

Wild animals The study did not involve wild animals.

Field-collected samples The study did not involve sample collected from the field.

Ethics oversight Mouse experimental protocols were approved by the Institutional biomedical research ethics committee of Shanghai Institute of Nutrition and Health Sciences, Chinese Academy of Sciences.

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.* To review GEO accession GSE169470:  
Go to <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE169470>

Files in database submission  
GSE169470 including the below files:  
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M1\_ZMYND8  
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Input-0% 1,6-hex\_BMRC200002491-1A\_2.clean.fq  
Input-6% 1-6-Hex\_BMRC200002492-1A\_1.clean.fq  
Input-6% 1-6-Hex\_BMRC200002492-1A\_2.clean.fq  
0% 1,6-hex\_BMRC200002500-1A\_1.clean.fq  
0% 1,6-hex\_BMRC200002500-1A\_2.clean.fq  
6% 1-6-Hex\_BMRC200002493-1A\_1.clean.fq

6% 1-6-Hex\_BMRC200002493-1A\_2.clean.fq  
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H3K27ac\_NT\_BMRC210000387-1A\_2.clean.fq  
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 WT\_H3K4me1\_NT\_BMRC210002333-1A\_2.clean.fq  
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 WT\_H3K4me2\_NT\_BMRC210002331-1A\_2.clean.fq  
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 KO\_H3K4me1\_NT\_BMRC210002334-1A\_2.clean.fq  
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 KO\_H3K4me2\_NT\_BMRC210002332-1A\_2.clean.fq  
 Input\_KO\_BMRC210000389-1A\_1.clean.fq  
 Input\_KO\_BMRC210000389-1A\_2.clean.fq  
 Input\_WT\_BMRC210000378-1A\_1.clean.fq  
 Input\_WT\_BMRC210000378-1A\_2.clean.fq  
 Input\_LPS\_BMRC210000377-1A\_1.clean.fq  
 Input\_LPS\_BMRC210000377-1A\_2.clean.fq  
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 Input\_WT\_NT\_BMRC210002329-1A\_1.clean.fq  
 Input\_WT\_NT\_BMRC210002329-1A\_2.clean.fq

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

No longer applicable

## Methodology

Replicates	ChIP-seq for each group of the cells, which were pooled from three mice, was performed once.
Sequencing depth	The amount of data for each sample is 6G, Reads were aligned to the mouse genome (mm10), and after removal of duplicate and non-uniquely mapped reads, ~8 million alignments were obtained. They are paired-end.
Antibodies	ZMYND8 antibody ChIP-seq Bethyl A302-090A, LSD1 antibody ChIP-seq Abcam ab129195, H3K4me1 antibody ChIP-seq Cell signaling technology 5326s, H3K4me2 antibody ChIP-seq Abcam ab32356, p65 antibody ChIP-seq Santa Cruz sc-8008.
Peak calling parameters	MACS peak finding was performed to identify the most significant peaks. Using our default cutoff of p-value 1e-7 (control file is input file)
Data quality	The ZMYND8 (A302-090A, Bethyl) antibody for ChIP-seq was validated by Active Motif. The LSD1 (ab129195, Abcam) and H3K4me1 (5326s, Cell signaling technology) antibody for ChIP-seq were validated by Novogene. The correct size of chromatin and libraries was checked in a gel. Only raw reads passing the QC were used for alignment.
Software	We used Galaxy online analysis website to analyse ChIP-seq data. Visualization was performed in IGV.

## Flow Cytometry

### Plots

Confirm that:

- The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- All plots are contour plots with outliers or pseudocolor plots.
- A numerical value for number of cells or percentage (with statistics) is provided.

### Methodology

Sample preparation	The tissues were ground into a single cell suspension, then stained with flow antibody. For surface staining, cells were stained in PBS containing 2% FBS for 30 minutes at 4 degree, followed by washing by PBS for 2 times prior to Flow Cytometry analysis.
Instrument	Beckman Gallios flow cytometer
Software	Flowjo
Cell population abundance	There is no abundance of the relevant cell populations.

Gating strategy

For all experiments, cells were first gated by FSC/SSC to exclude debris, followed by gating FSC-A and FSC-H to eliminate nonsinglets. Then, target cell population for further analysis were gated by cell surface marker.

Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.