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 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: No software was used for data collection.

Data analysis: Python 3.7, cutadapt 1.12, STAR 2.5.2b, samtools 1.3.1, featuresCount 1.5.1, RSeqC, Homer 4.11, Meme suite, R 3.5.1 and R packages edgeR: 3.22.5, deSeq2: 1.21, shiny 1.1.0, ggplot2: 3.0.0, caret: 6.0-8.0, RSeqC: 2.6.4, IGV: 2.5.2, Meme suite: 5.0.3

For manuscripts utilizing custom algorithms or software that are 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

RNASeq Fractioned (fastq and bam files): https://www.encodeproject.org/awards/U01HG007912/
ChiPseq (fastq files): https://www.encodeproject.org/awards/U01HG007912/
ActinomycinD RNAseq (reviewer link): https://dataview.ncbi.nlm.nih.gov/object/PRJNA641336?reviewer=2gl9sjgsar9a5z2h4i2upki7ps
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 | The experimental design is a fine timecourse with over a dozen timepoints following a perturbation. Timepoint spacing was chosen such that several timepoints would describe the baseline, rise, peak, and decline of the molecular species. Thereby adjacent timepoints function to confirm measurements. |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data exclusions | No data was excluded. |
| Replication | Timecourses were undertaken in triplicate. |
| Randomization | N/A |
| Blinding | N/A |

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

Antibodies used for ChIP-seq studies of histone modification: H3K4me3 (05-745R, Millipore), H3K36me3 (ab9050, Abcam), H3K27ac (39133, Active-Motif), and H3K79me2 (ab3594, Abcam) antibodies.

Validation

Antibodies used in this study were recommended reagents by ENCODE. The recommended protocol was used. No other validation was undertaken.

Animals and other organisms

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

Laboratory animals

Mus Musculus C57 Bl/6 were used to produce bone-marrow-derived macrophages.

Wild animals

N/A

Field-collected samples

N/A

Ethics oversight

University of California, Los Angeles Division of Laboratory Animal Medicine, accredited by Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC)

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.

Files in database submission

- H3K27ac: https://www.encodeproject.org/experiments/ENCSR933GNW/
  - Replicate 1: ENCCFF937IMG.fastq.gz and ENCCFF412ZXF.fastq.gz
  - Replicate 2: ENCCFF065DFV.fastq.gz and ENCCFF554XRW.fastq.gz
- H3K4me3: https://www.encodeproject.org/experiments/ENCSR916IRY/
  - Replicate 1: ENCCFF916ATM.fastq.gz and ENCCFF588NZB.fastq.gz
  - Replicate 2: ENCCFF871YMY.fastq.gz and ENCCFF934EMT.fastq.gz
- Controls for H3K27ac and H3K4me3: https://www.encodeproject.org/experiments/ENCSR601NNP/
  - Replicate 1: ENCCFF542ROM.fastq.gz and ENCCFF451SQE.fastq.gz
  - Replicate 2: ENCCFF495GLD.fastq.gz and ENCCFF666XOZ.fastq.gz
- H3K79me2: https://www.encodeproject.org/experiments/ENCSR570YMM/
  - Replicate 1: ENCCFF501QHM.fastq.gz
  - Replicate 2: ENCCFF850KGO.fastq.gz and ENCCFF284JUF.fastq.gz
- H3K36me3: https://www.encodeproject.org/experiments/ENCSR280NNQ/
  - Replicate 1: ENCCFF902OXY.fastq.gz
  - Replicate 2: ENCCFF530USD.fastq.gz and ENCCFF413ZVL.fastq.gz
- Controls for H3K79me2 and H3K36me3: https://www.encodeproject.org/experiments/ENCSR698GIN/
  - Replicate 1: ENCCFF016MGA.fastq.gz
  - Replicate 2: ENCCFF972NOO.fastq.gz and ENCCFF503OGW.fastq.gz

Genome browser session

(e.g. UCSC)

no longer applicable

Methodology

Replicates

Two

Sequencing depth

Target File File Total number of reads Number of uniquely mapped read (deduplicated) Sequencing type

| Antibodies used for ChIP-seq studies of histone modification: H3K4me3 (05-745R, Millipore), H3K36me3 (ab9050, Abcam), H3K27ac (39133, Active-Motif), and H3K79me2 (ab3594, Abcam) antibodies. |
| Peak calling parameters | ChIP-seq was analysed using Encode chip-seq pipeline (https://github.com/ENCODE-DCC/chip-seq-pipeline2) v1.5.1: conda activate encode-chip-seq-pipeline caper run chip-seq-pipeline2 -i options.json |
the options.json file lists the options to use for the pipeline:

- Path of files (replicates and inputs)
- "chip.pipeline_type": "histone"
- "chip.aligner": "bwa"
- "chip.align.only": false
- "chip.true_rep_only": false
- "chip.genome.tsv": mm10.tsv
- "chip.paired_end": false
- "chip.cti_paired_end": false
- "chip.always_use_pooled_cit": false

Options not listed here were kept to their default values.

The mm10.tsv index file was downloaded from Encode: https://storage.googleapis.com/encode-pipeline-genome-data/genome_tsv/v3/mm10.tsv and uses Encode ENCF018NEO file as the bwa index (https://www.encodeproject.org/files/ENCF018NEO/)

The peak calling is done by the pipeline using macs2 software with these default options:

- chip.cap.num_peak: 300000
- chip.pval.thresh: 0.01 (corresponds to macs2 callpeaks -p option)
- chip.idr.thresh: 0.05

**Data quality**

Quality was checked by ensuring library complexity as measured by a non-redundant fraction (NRF) $\geq 0.8$, a PCR bottlenecking coefficient 1 (PBC1) $\geq 0.8$, a PCR bottlenecking coefficient 2 (PBC2) $\geq 3$ as well as a irreproducible discovery rate (IDR) rescue ratio and self-consistency ratio $\leq 2$.

Target Nb of peaks at $p$-value $< 0.01$ and fold enrichment $\geq 1.2$. Nb of peaks at fdr $< 0.05$ and fold enrichment $\geq 5$

- H3K27ac 34792 20338
- H3K4me3 1955215975
- H3K79me2 27168 11404
- H3K36me3 396240 1499

**Software**

Chip-seq was analyzed using Encode chip-seq pipeline (https://github.com/ENCODC/chip-seq-pipeline2) v1.5.1