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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 .

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	Mass spectrometry: Thermo Xcalibur 3.0.63 Flow cytometry: FACSDiva 10.5.3
Data analysis	GraphPad 7.0 was used to perform general statistical analyses. ChIP-seq and RNAseq: FastQC version 0.11.4, Bowtie version 2.2.6, SAMtools version 0.1.19, MACS version 2.2.1, featureCounts version 1.5.0-p1, DAVID Bioinformatics Resources 6.8, HISAT2 version 2.1.0, edgeR version 3.16.5, and Perseus version 1.6.1.1. Mass spectrometry: MaxQuant 1.3.0.5. Flow Cytometry: FlowJo v.10.4.1.

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. 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 ChIP-seq and RNA-seq data have been made available at the Gene Expression Omnibus (GEO) repository under the accession number GSE115354. All other data are available from the authors upon reasonable request.

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	Specific sample sizes are described in figures or figure legends for all experiments. The sample size used for animal experiment is based on previous experience from the Zhao and Becker labs. No statistical test was used to pre-determine sample size.
Data exclusions	No samples or animals were excluded from the analyses.
Replication	The number of repeats for each experiments are described in corresponding figure legends. All repeats support the same conclusion.
Randomization	Cells or mice tissue were randomly assigned to groups (chemical compound/hypoxia/other treatments).
Blinding	For animal related experiments, the investigators were divided into two groups: one group is responsible for collecting samples and the other group is responsible for experiment and outcome assessment.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☐	☒ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

The following antibodies were generated by PTM Bio Inc (Chicago, IL):
pan anti-Kac (PTM-101), 1:2000 (WB)
pan anti-Kla (PTM-1401), 1:2000 (WB)
anti-H3K18la (PTM-1406), 1:5000 (WB), 4ug per per ChIP
anti-H4K8la (PTM-1405), 1:5000 (WB)
anti-H4K5la (PTM-1407), 1:5000 (WB)

The following antibodies were generated by Abcam (Cambridge, MA):
anti-histone H3 (ab12079), 1:10000(WB)
anti-H3K18ac (ab1191), 1:10000 (WB), 4ug per ChIP
anti-H3K27ac (ab4729), 1:5000 (WB)

The following antibodies were generated by Active Motif (Carlsbad, CA):
anti-drosophila spike-in antibody (61686), 2ug per ChIP

The following antibodies were generated by Cell Signaling Technology (Danvers, MA):
anti-LDHA (2012S), 1:2000 (WB)

The following antibodies were generated by Millipore Sigma (Burlington, MA):
anti-a-Tubulin (05-829), 1:5000 (WB)
anti-LDHB (ABC927), 1:2000 (WB)

The following antibodies were generated by Novus Biologicals (Littleton, CO):
anti-HIF-1a (NB100-105), 1:2000 (WB)

The following antibodies were generated by GeneTex (Irvine, CA):
anti-iNOS (GTX130246), 1:2000 (WB)
anti-Arg1 (GTX109242), 1:2000 (WB)

The following antibodies were generated by Santa Cruz Biotechnology, Inc (Dallas, TX):
anti-p300 (sc-584), 1:2000 (WB)

The following antibodies were generated by ThermoFisher Scientific (Waltham, MA):
anti-CD11b Monoclonal Antibody (M1/70), PE-Cyanine7, eBioscience (25-0112-82), 0.125 µg/test (Flow)
anti-F4/80 Monoclonal Antibody (BM8), APC, eBioscience (17-4801-82), 2 µg/test (Flow)

The following antibodies were generated by Jackson ImmunoResearch Laboratories (West Grove, PA):
Peroxidase AffiniPure Goat Anti-Mouse IgG (H+L) (115-035-003), 1:10000 (WB)
Peroxidase AffiniPure Goat Anti-Rabbit IgG (H+L) (111-035-003), 1:10000 (WB)

Validation

Pan anti-Kac (PTM-101):
Species: human, mouse; Application: Western Blot, Immunoprecipitation; Manufacturer's web site: https://www.ptmbiolabs.com/product/ptm-101/
Pan anti-Kla (PTM-1401):
Species: human, mouse; Application: Dot Blot, Western Blot, Immunoprecipitation; Validated in this paper.
Anti-H4K8la (PTM-1405):
Species: human, mouse; Application: Western Blot; Validated in this paper.
Anti-H3K18la (PTM-1406):
Species: human, mouse; Application: Dot Blot, Western Blot, ChIP; Validated in this paper.
Anti-H4K5la (PTM-1407):
Species: human, mouse; Application: Dot Blot, Western Blot; Validated in this paper.

Anti-histone H3 (ab12079):
Species: human, mouse; Application: Western Blot; Manufacturer's web site: https://www.abcam.com/histone-h3-antibody-chip-grade-ab12079.html
Anti-H3K18ac (ab1191):
Species: human, mouse; Application: Western Blot, ChIP; Manufacturer's web site: https://www.abcam.com/histone-h3-acetyl-k18-antibody-chip-grade-ab1191.html
Anti-H3K27ac (ab4729):
Species: human, mouse; Application: Western Blot; Manufacturer's web site: https://www.abcam.com/histone-h3-acetyl-k27-antibody-chip-grade-ab4729.html

Anti-LDHA (2012S):
Species: human, mouse; Application: Western Blot; Manufacturer's web site: https://www.cellsignal.com/products/primary-antibodies/ldha-antibody/2012

Anti-a-Tubulin (05-829):
Species: human, mouse; Application: Western Blot; Manufacturer's web site: https://www.emdmillipore.com/US/en/product/Anti-Tubulin-Antibody-clone-DM1A,MM_NF-05-829
Anti-LDHB (ABC927):
Species: human, mouse; Application: Western Blot; Manufacturer's web site: https://www.emdmillipore.com/US/en/product/Anti-LDHB-Antibody,MM_NF-ABC927

Anti-drosophila spike-in antibody (61686):
Species: drosophila; Application: ChIP; Manufacturer's web site: https://www.activemotif.com/catalog/1091/chip-normalization

Anti-iNOS (GTX130246):
Species: mouse; Application: Western Blot; Manufacturer's web site: https://www.genetex.com/Product/Detail/iNOS-antibody/GTX130246
Anti-Arg1(GTX109242):
Species: mouse; Application: Western Blot; Manufacturer's web site: https://www.genetex.com/Product/Detail/Arginase-1-antibody/GTX109242

anti-p300 (N15) (sc-584):
Species: human; Application: Western Blot; Manufacturer's web site: https://www.scbt.com/scbt/product/p300-antibody-n-15
p300 (N-15) has been discontinued and replaced by p300 (F-4): sc-48343.

Anti-CD11b Monoclonal Antibody (M1/70), PE-Cyanine7, eBioscience (25-0112-82):
Species: mouse; Application: Flow cytometry; Manufacturer's web site: https://www.thermofisher.com/antibody/product/CD11b-Antibody-clone-M1-70-Monoclonal/25-0112-82
Anti-F4/80 Monoclonal Antibody (BM8), APC, eBioscience (17-4801-82),
Species: mouse; Application: Flow cytometry; Manufacturer's web site: https://www.thermofisher.com/antibody/product/F4-80-Antibody-clone-BM8-Monoclonal/17-4801-82

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HeLa, MCF-7, A549, MDA-MB-231, HepG2, MEF, and RAW264.7 cells were obtained from the American Type Culture Collection.
Authentication	HeLa, MCF-7, A549, MDA-MB-231, HepG2, MEF, and RAW264.7 cells were authenticated based on our vast experience working with these cells lines (such as cell morphology, culture conditions, etc.). Furthermore, we believe that the modification we described in the paper is widely existed in various cell lines, not specific to certain cell types.
Mycoplasma contamination	Cells were routinely tested for mycoplasma contamination, and only negative cells were used in experiments
Commonly misidentified lines (See ICLAC register)	None of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC.

Animals and other organisms

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

Laboratory animals	Adult male mice (Mus musculus, C57BL/6, 7-10 weeks old) were purchased from The Jackson Laboratory, and were used to generate bone marrow derived macrophages (BMDMs). Ldhafl/fl mice (Jackson laboratory, 030112) and LysMcre mice (Jackson laboratory, 004781) were used to generate LysMcre+/- Ldhafl/fl and littermate control LysM-cre-/- Ldhafl/fl mice.
Wild animals	The study did not involve samples collected from wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal protocols were approved by Institutional Animal Care and Use Committee (ACUP) at the University of Chicago.

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=GSE115354
Files in database submission	GSM3176446_RH_148_peaks.broadPeak.gz GSM3176447_RH_229_peaks.broadPeak.gz GSM3176449_RH_151_peaks.broadPeak.gz GSM3176450_RH_231_peaks.broadPeak.gz GSE115354_ChIP-seq_normalization.txt.gz
Genome browser session (e.g. UCSC)	N/A

Methodology

Replicates	ChIP-seq samples are prepared as one replicate, pooled from four mice
Sequencing depth	RH_148 (unique reads: 21765076; spike-in reads: 310066) RH_151 (unique reads: 21006731; spike-in reads: 141688) RH_229 (unique reads: 36576826; spike-in reads: 52482) RH_231 (unique reads: 32948615; spike-in reads: 50470)
Antibodies	The anti-H3K18la antibody was generated by PTM biolabs. The process for generating antibodies were described similarly in Cell, 2011. 146: p. 1016-1028. Mol Cell, 2015. 58(2): p. 203-15. Nat Chem Biol, 2014. 10(5): p. 365-70. except for using different immunogens. The anti-H3K18ac antibody was purchased from Abcam(ab1191, lot GR 300534-1)

	The evaluation of the antibody for specificity and ChIP grade is provided in the manuscript. Spike-in information: spike-in chromatin (Active motif, Catalog No. 53083), spike-in antibody (Active motif, Catalog No. 61686)
Peak calling parameters	Peaks were called using MACS version 2.2.1 under q value = 0.01.
Data quality	Sequencing quality was evaluated by FastQC version 0.11.4. All reads were mapped to reference genome of illumina iGenomes UCSC mm10 using Bowtie version 2.2.6, and only uniquely mapped reads were retained. SAMtools version 0.1.1926 was used to convert files to bam format, sort, and remove PCR duplicates. Peaks were called using MACS version 2.2.1 under q value = 0.01. The number of peaks at the cutoff threshold in each sample: 21885 peaks in GSM3176446_RH_148_peaks.broadPeak.gz 41493 peaks in GSM3176447_RH_229_peaks.broadPeak.gz 16139 peaks in GSM3176449_RH_151_peaks.broadPeak.gz 42237 peaks in GSM3176450_RH_231_peaks.broadPeak.gz
Software	Base called by Real-Time Analysis (RTA) Reads were mapped to reference genome of illumina iGenomes UCSC mm10 using Bowtie version 2.2.6, and only uniquely mapped reads were retained. SAMtools version 0.1.19 was used to convert files to bam format, sort, and remove PCR duplicates. Peaks were called using MACS version 2.2.1 under q value = 0.01. Uniquely mapped reads of each gene were counted by featureCounts version 1.5.0-p1, and normalized by corresponding uniquely mapped spiked-in ChIP read counts.

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	0.2 million cells were labeling with different fluorophore conjugated antibody at room temperature for 15mins, followed by two washes.
Instrument	Samples were analyzed using a FACSCanto™ II flow cytometer.
Software	Data were quantified by FlowJo v.10.4.1.
Cell population abundance	Purity for both TAM and Pmac are above 95% based on F4/80 and CD11b cell surface marker. positive gating were determined by negative control.
Gating strategy	Cells were gated by FSC/SSC for total population --> SSC-A/SSC-H for single cells --> cblue labeling for live cells population --> F4/80 and CD11b double positive (compared to negative population) for purity check.

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