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Corresponding author(s): Mohamed-ali HAKIMI / Alexandre BOUGDOUR
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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<br>*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<br>*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<br>*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 | Agilent Feature Extraction software (version 11.0.1.1) was used to analyze the acquired array images. Quantile normalization and subsequent data processing were performed with using the GeneSpring GX v12.1 software (Agilent Technologies). After quantile normalization of the raw data, genes that at least 3 out of 27 samples have flags in Detected ("All Targets Value") were chosen for further data analysis. |
| Data analysis | Hierarchical Clustering was performed using the R software (version 2.15). KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis were performed using the DAVID Bioinformatics Resources. Gene set enrichment analysis (GSEA, http://software.broadinstitute.org/gsea/index.jsp) was used to find candidate transcription factors and canonical pathways. Distant Regulatory Elements of co-regulated genes (DiRE, https://dire.dcode.org/) was also used. |

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

Microarray data has been uploaded to GEO Datasets under accession number (GSE113618).

# 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 estimation was not performed. |
| Data exclusions | no data exclusions |
| Replication | All the experiments were performed at least in triplicate independent experiments in accordance with well-established reporting procedures for all the assays. |
| Randomization | We used randomization to reduces bias in mice selection and outcome assessment. |
| Blinding | Blinding was used during data collection by assigning numbers in place of genotype and infection status to mice in the studies. |

# 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 | Primary antibodies mouse anti-HA (Roche, RRID:AB_2314622), MIC2 (provided by D. Sibley, Washington University School of Medicine, St Louis, MO), Toxofilin (provided by I. Tardieux, IAB, Grenoble, France), GRA7, E2F3 (Sigma-Aldrich, RRID:AB_1841394), E2F4 (Sigma-Aldrich, RRID:AB_1841395), E2F3 (Santa Cruz Biotechnology, RRID:AB_2096807), E2F4 (Santa Cruz Biotechnology, RRID:AB_2097106 and AB_2097104), TFDP-1 (Sigma-Aldrich, RRID:AB_259233), EZH2 (Cell Signaling Technology, RRID:AB_10694683 and AB_10694383), EZH2 (BD, RRID:AB_2102429), H3K27me3 (Diagenode, RRID:AB_2616049) and TBP1 (Abcam, RRID:AB_306337) |
| Validation | Validation data ara available at manufacters website. |

## Eukaryotic cell lines

Policy information about cell lines

| | |
|---|---|
| Cell line source(s) | Human primary fibroblasts (ATCC® CCL-171™), Human primary Astrocytes (Science Cell Laboratories, cat #1800), T-Rex-293 cell line (RRID:CVCL_D585), L929 cell line (Sigma-Aldrich Cat# 85011425), J774 cell line (J774A.1, Sigma-Aldrich Cat# 91051511), RAW264.7 cell line (ATCC Cat# TIB-71, RRID:CVCL_0493) and THP1-Blue™ NF-κB Cells cell line (InvivoGen Cat # thp-nfkb) |
| Authentication | none of them were authenticated |
| Mycoplasma contamination | The cultures were free of mycoplasma, as determined by qualitative PCR. |
| Commonly misidentified lines (See ICLAC register) | *Name any commonly misidentified cell lines used in the study and provide a rationale for their use.* |

## Animals and other organisms

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

| | |
|---|---|
| Laboratory animals | BALB/cJRj and BL6 mice were obtained from Charles River Laboratories. |
| Wild animals | This study did not involve wild animals. |
| Field-collected samples | This study did not involve samples collected from the field. |