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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	FACS BD Aria II, Influx, FACS Canto II were used to collect flow cytometry sorting and analysis data. Halo software (v3.0.311.201) was used to quantify data from immunohistochemistry. Skyline software (v4.1) was used for raw mass spectometry files. Asylum Research sotware packager version IX was used for height profiles on atomic force microscopy. ELISPOT plates were evaluated using an automated Zeiss ELISPOT reader system (ZellNet Consulting, Inc.). Biolayer interferometry measurements were taken on an Octen Red96e system (v11).
Data analysis	FlowJo software v10.5.3, R version 3.4.4 (2017-11-30), R package Slingshot version 1.2.0, R package Seurat 3.0.2, R package EdgeR v3.16.5 and v3.20.9, R package EDAseq 2.22.0, R package DeSeq2 1.27.1, Sarek pipeline version 2.5.1 ChIP-seq reads were aligned using bwa-mem function of the BWA suite. Peaks were called using the SICER algorithm. RNA-seq reads were aligned to mm10 using STAR and annotated to RefSeq using the R subread package. Whole-genome sequencing data aligned to human genome hg-19 was retrieved from the European Genome Archive and used to generate unmapped bam files using picard tools RevertSam according to GATK best practice. Bam files were aligned to human genome hg38 using BWA mem. Somatic alterations were called from matched tumor-normal pairs using Manta followed by Strelka2, and annotated by VEP (https://github.com/nf-core/sarek). FishHook (https://github.com/mskilab/fishHook) was used to model background mutational processes. All study and public Hi-C data used have been pre-processed with the hic-bench pipeline. FRAP data were analyzed using ImageJ (v1.51j) and FRAP Profiler plugin (http://worms.zoology.wisc.edu/research/4d/4d.html)

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 sequencing datasets generated in this study are available at GEO (GSE143293). No restriction of data availability.

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	For high throughput NG, mass spec experiments, a minimum of three independent biological replicates were used where possible (ChIP-seq, ATAC-seq, RNA-seq, Cut and Run). Two biological replicates were used for HiC and Single cell RNA-seq. Sample size for in vivo experiments were chosen based on our prior experience for detecting statistically significant differences compared to control animals (Béguelin et al Cancer Cell, Vol37, Issue 5, Pages 655-673). Sample size for in vitro experiments were determined with preliminary experiments with a minumum of 2 samples per group, and full cohort experiments repeated at least twice.
Data exclusions	No samples were excluded.
Replication	All findings were reproducible. Confirmation of reproducibility was assessed with at least three independent experiments for in vivo and at least two independent experiments for in vitro assays, and in the case of high throughput NGS analysis, through the use of sample sized that provided comprehensive genome-wide coverage of chromatin changes.
Randomization	Sex-matched littermates were randomly assigned to experimental arms. Samples were allocated to groups according to genotype.
Blinding	Studies were not blinded and group allocation was done before data collection as only one investigator ran the experiments.

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	For immunoblotting, the following primary antibodies were used: D4J5Q, anti-H1E, Cell-Signaling 41328; AE-4, anti-H1, Millipore 05-457; C36B11 anti-H3 K27me3, Cell Signaling 9733; C75H12 anti-H3 K36me2, Cell Signaling 2901; AC22 anti-Ezh2, Cell Signaling 3147; 29D1 anti-NSD2, Millipore Mabe191; rabbit polyclonal anti-KLF5, Proteintech 21017-1-AP; 6C5 anti-GAPDH, Ab8245) For ChIP, the following primary antibodies were used: anti-H3 K27me3, C36B11 - Cell Signaling 9733 (20 micrograms), anti-H3 K36me2, C75H12 - Cell Signaling 2901 (20 micrograms). For CutandRun, the following antibodies were used: ant-H3K9me2 (Millipore 05-1249), anti-H3K9me3 (Abcam 176916), and anti-H3K4me3 (Epicypher 13-0041) (0.5ug each).
Validation	anti-H3 K27me3 and anti-H3 K36me2 antibodies have been extensively validated in literature, including Weinberg et al., 2019

Nature; Papillon-Cavanagh et al., Nat Genet 2017; Lu et al., Science 2016. Cut and Run antibodies are validated to SNAP-ChIP nucleosome standards (S1hah et al., Mol Cell 2018).D4J5Q and AE-4 anti-H1 antibodies have been validated in mouse knock-out and human shRNA-treated knock-down cells. C36B11, C75H12, Ac22 and 29D1 have been validated in human and mouse knock-out and transgenic cell lines (using ChIP-qPCR in wild type and loss-of-function (K27M, K36M, knock-ou, Ezh2 knock-out) backgrounds.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	NIH-3T3 (CRL-1658) purchased from ATCC; Kc167 (RRID:CVCL_Z834) cells were purchased from Drosophila Genomics Resource Center
Authentication	Cell lines were not specifically authenticated for these studies
Mycoplasma contamination	Cell line was tested negative for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used in this study

Animals and other organisms

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

Laboratory animals	The study involved H1c-/-/e-/- mice and littermate controls (C57BL/6J) that were age- and sex-matched (tested within 8-10-weeks old). Bone-marrow recipient mice were female, 8-weeks old and C57BL/6J strain with donor bone marrow (CD45.1 and CD45.2) pooled from sex-matched, 8-10-week old mice. VavP-Bcl2 (C57BL/6J), crossed with H1c-/-/e-/-, were used sex-matched 8-week old mice as bone-marrow donors for lymphomagenesis and survival studies.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	Animal care was in strict compliance with institutional guidelines established by Weill Cornell Medicine, the Guide for the Care and Use of Laboratory Animals (National Academy of Sciences 1996) (Silverman et al., 2006), and the Association for Assessment and Accreditation of Laboratory Animal Care International. All mice were followed until any one of several criteria for euthanizing were met, including severe lethargy, more than 10% body weight loss, and palpable splenomegaly that extended across the midline, in accordance with our Weill Cornell Medicine Institutional Animal Care and Use Committee (IACUC)–approved animal protocols.

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=GSE143293 Publicly available
Files in database submission	GSM4256478 Sample_1_GCB_WT_repl1_RNAseq GSM4256479 Sample_2_GCB_WT_repl2_RNAseq GSM4256480 Sample_3_GCB_WT_repl3_RNAseq GSM4256481 Sample_4_GCB_WT_repl4_RNAseq GSM4256482 Sample_5_GCB_H1_DKO_repl1_RNAseq GSM4256483 Sample_6_GCB_H1_DKO_repl2_RNAseq GSM4256484 Sample_7_GCB_H1_DKO_repl3_RNAseq GSM4256485 Sample_8_GCB_WT_H3K27me3_repl1_ChIPseq GSM4256486 Sample_9_GCB_WT_H3K27me3_repl2_ChIPseq GSM4256487 Sample_10_GCB_WT_H3K27me3_repl3_ChIPseq GSM4256488 Sample_11_GCB_H1 DKO_H3K27me3_repl1_ChIPseq GSM4256489 Sample_12_GCB_H1 DKO_H3K27me3_repl2_ChIPseq GSM4256490 Sample_13_GCB_H1 DKO_H3K27me3_repl3_ChIPseq GSM4256491 Sample_14_GCB_WT_H3K36me2_repl1_ChIPseq GSM4256492 Sample_15_GCB_WT_H3K36me2_repl2_ChIPseq GSM4256493 Sample_16_GCB_WT_H3K36me2_repl3_ChIPseq GSM4256494 Sample_17_GCB_H1 DKO_H3K36me2_repl1_ChIPseq GSM4256495 Sample_18_GCB_H1 DKO_H3K36me2_repl2_ChIPseq GSM4256496 Sample_19_GCB_H1 DKO_H3K36me2_repl3_ChIPseq GSM4256497 Sample_20_GCB_WT_Input_repl1_ChIPseq

GSM4256498 Sample_21_GCB_WT_Input_repl2_ChIPseq
GSM4256499 Sample_22_GCB_WT_Input_repl3_ChIPseq
GSM4256500 Sample_23_GCB_H1 DKO_Input_repl1_ChIPseq
GSM4256501 Sample_24_GCB_H1 DKO_Input_repl2_ChIPseq
GSM4256502 Sample_25_GCB_H1 DKO_Input_repl3_ChIPseq
GSM4363364 Sample_26_GCB_WT_repl1_HiC
GSM4363365 Sample_27_GCB_WT_repl2_HiC
GSM4363366 Sample_28_GCB_H1_DKO_repl1_HiC
GSM4363367 Sample_29_GCB_H1_DKO_repl2_HiC
GSM4523349 Sample_30_GCB_WT_repl1_ATACseq
GSM4523350 Sample_31_GCB_WT_repl2_ATACseq
GSM4523351 Sample_32_GCB_WT_repl3_ATACseq
GSM4523352 Sample_33_GCB_WT_repl4_ATACseq
GSM4523353 Sample_34_GCB_H1_DKO_repl1_ATACseq
GSM4523354 Sample_35_GCB_H1_DKO_repl2_ATACseq
GSM4523355 Sample_36_GCB_H1_DKO_repl3_ATACseq
GSM4523356 Sample_37_GCB_H1_DKO_repl4_ATACseq
GSM4523357 Sample_38_GCB_WT_H3K4me3_CutAndRun
GSM4523358 Sample_39_GCB_WT_H3K9me2_CutAndRun
GSM4523359 Sample_40_GCB_WT_H3K9me3_CutAndRun
GSM4523360 Sample_41_GCB_H1_DKO_H3K4me3_CutAndRun
GSM4523361 Sample_42_GCB_H1_DKO_H3K9me2_CutAndRun
GSM4523362 Sample_43_GCB_H1_DKO_H3K9me3_CutAndRun
GSM4523363 Sample_44_GCB_WT_H3K27Ac_rep1_ChIPseq
GSM4523364 Sample_45_GCB_WT_H3K27Ac_rep2_ChIPseq
GSM4523365 Sample_46_GCB_WT_H3K27Ac_rep3_ChIPseq
GSM4523366 Sample_47_GCB_H1_DKO_H3K27Ac_rep1_ChIPseq
GSM4523367 Sample_48_GCB_H1_DKO_H3K27Ac_rep2_ChIPseq
GSM4523368 Sample_49_GCB_H1_DKO_H3K27Ac_rep3_ChIPseq
GSM4752544 Sample_DKO2-GCB-3_10X_SingleCell
GSM4752545 Sample_WT4-GCB-1_10X_SingleCell
GSM4752546 Sample_WT5-GCB-2_10X_SingleCell
GSM4752547 Sample_DKO6-GCB-4_10X_SingleCell

Genome browser session
(e.g. UCSC)

Not applicable - visualized data using IGV

Methodology

Replicates

For ChIP-seq experiments with primary mouse GC B-cells, three biological replicates (n=3)per group were tested. For CutandRun experiments with primary mouse GC B-cells, two biological replicates (n=2) per group were tested. For HiC experiments with primary mouse GC B-cells, two biological replicates per group were tested. For ATAC-seq with primary mouse GCB-cells, at least three biological replicates (n=3) per group were tested. For Single Cell RNA-seq with primary mouse GC B-cells, two biological replicates per group were tested.

Sequencing depth

ChIP-seq experiments: 75 bp single-end
1-WT-H3K27me3, total number reads: mm10, 18,627,064; dm6, 23,345,945
2-WT-H3K27me3, total number reads: mm10, 15,809,793; dm6, 21,688,452
3-WT-H3K27me3, total number reads: mm10, 18,663,073; dm6, 21,202,327
1-H1DKO-H3K27me3, total number reads: mm10, 20,042,774; dm6, 26,505,971
2-H1DKO-H3K27me3, total number reads: mm10, 17,020,424; dm6, 25,308,467
3-H1DKO-H3K27me3, total number reads: mm10, 16,444,400; dm6, 23,322,436
1-WT-H3K36me2, total number reads: mm10, 19,010,885; dm6, 2,397,743
2-WT-H3K36me2, total number reads: mm10, 18,804,732; dm6, 2,275,684
3-WT-H3K36me2, total number reads: mm10, 16,474,978; dm6, 1,760,707
1-H1DKO-H3K36me2, total number reads: mm10, 27,599,022; dm6, 2,585,188
2-H1DKO-H3K36me2, total number reads: mm10, 22,605,400; dm6, 2,310,040
3-H1DKO-H3K26me2, total number reads: mm10, 28,325,523; dm6, 2,900,788
1-WT-H3K27Ac, total number reads: mm10, 22,811,922; dm6, 8,933,764
2-WT-H3K27Ac, total number reads: mm10, 23,571,881; dm6, 8,717,785
3-WT-H3K27Ac, total number reads: mm10, 26,129,676; dm6, 9,378,885
1-H1DKO-H3K27Ac, total number reads: mm10, 18,992,351; dm6, 6,909,044
2-H1DKO-H3K27Ac, total number reads: mm10, 16,722,924; dm6, 7,466,262
3-H1DKO-H3K27Ac, total number reads: mm10, 21,355,372; dm6, 8,752,978

CutAndRun experiments:
1-WT-H3K4me3, total number reads: mm10, 3,815,224
2-WT-H3K4me3, total number reads: mm10, 5,541,738
1-H1DKO-H3K4me3, total number reads: mm10, 4,812,484
2-H1DKO-H3K4me3, total number reads: mm10, 5,854,955
1-WT-H3K9me2, total number reads: mm10, 6,981,537
2-WT-H3K9me2, total number reads: mm10, 6,448,278
1-H1DKO-H3K9me2, total number reads: mm10, 7,147,881
2-H1DKO-H3K9me2, total number reads: mm10, 6,496,731

1-WT-H3K9me3, total number reads: mm10, 7,617,674
2-WT-H3K9me3, total number reads: mm10, 9,044,632
1-H1DKO-H3K9me3, total number reads: mm10, 7,585,753
2-H1DKO-H3K9me3, total number reads: mm10, 8,276,380

ATAC-seq experiment:
DKO1-GCB: 75,394,476
DKO2-GCB: 68,819,276
DKO3-GCB: 63,692,712
WT1-GCB: 79,495,180
WT2-GCB: 68,697,976
WT3-GCB: 73,202,966

Hi-C number of intra-chromosomal reads used for downstream reads ('ds.accepted intra'):
WT_H1_1, total number of reads: 216,296,915
WT_H1_2, total number of reads: 222,714,033
H1DKO_1, total number of reads: 246,312,138
H1DKO_2, total number of reads: 237,201,022

Single cell-RNA seq:
WT4-GCB: 283,715,494
WT5-GCB: 237,596,846
DKO2-GCB: 210,177,503
DKO6-GCB: 257,475,313

Antibodies

For ChIP, the following primary antibodies were used: anti-H3 K27me3, C36B11 - Cell Signaling 9733 (20micrograms), anti-H3 K36me2, C75H12 - Cell Signaling 2901 (20micrograms)

Peak calling parameters

Peaks were called using SICER algorithm:
GCB_WT_K27me3_pooledSicer: 24,131
GCB_H1DKO_K27me3_pooledSicer: 13,603
GCB_WT_K36me2_pooledSicer: 29,466
GCB_H1DKO_K36me2_pooledSicer: 35,553
GCB_WT_K27ac_pooledSicer: 10,522
GCB_H1DKO_K27ac_pooledSicer: 16,790
GCB_WT_K4me3_pooledSicer: 13,393
GCB_H1DKO_K4me3_pooledSicer: 14,761
GCB_WT_K9me2_pooledSicer: 77,330
GCB_H1DKO_K9me2_pooledSicer: 90,670
GCB_WT_K9me3_pooledSicer: 103,436
GCB_H1DKO_K9me3_pooledSicer: 73,051

ATAC-seq peaks were called:
Sample_30_GCB_WT_repl1_ATACseq: 141,700
Sample_31_GCB_WT_repl2_ATACseq: 143,301
Sample_32_GCB_WT_repl3_ATACseq: 147,478
Sample_34_GCB_H1_DKO_repl1_ATACseq: 157,608
Sample_35_GCB_H1_DKO_repl2_ATACseq: 150,869
Sample_36_GCB_H1_DKO_repl3_ATACseq: 134,151

Data quality

Resulting FASTQ files were aligned to mouse mm10 and Drosophila dm6 genomes using bwa-mem function of the BWA suite. Individual sequencing experiments were assessed for their percent of mapped reads (to mm10 and dm6) to ensure proper coverage. ChIPseq data was normalized to dm6 spike-in reads using CompChIPseq algorithm. H3K27me3 and H3K36me2 ChIPseq peaks were called using the SICER algorithm on pooled BAM files from all respective replicates. Loci showing differences in ChIPseq abundance were determined by calculating the Comp-ChIPseq normalized read count within the union of peaks from both genotypes using the multiBigwigSummary function of the deepTools package.

For Hi-C, mapped reads were filtered by the GenomicTools tools-hic filter command integrated in HiC-bench for known artifacts of the Hi-C protocol. The filtered reads include multi-mapped reads ('multihit') read-pairs with only one mappable read, duplicated read-pairs, low mapping quality reads, read-pairs resulting from self-ligated fragments, and short-range interactions, resulting from read-pairs aligning within 25kb. For the downstream analyses, all the accepted intra-chromosomal read-pairs ('ds.accepted intra') were used.

Software

ChIP-seq reads were aligned using bwa-mem function of the BWA suite. Peaks were called using the SICER algorithm. Read density tracks were visualized using the Integrative Genomics Viewer (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	Single cell suspensions from mouse spleens were separated by Ficoll gradient centrifucation and stained using fluorescent labeled anti mouse antibodies, incubated on ice in the dark for 30min, then washed 2x with BS with .5% BSA and 5mM EDTA and resuspended in 200ul washing buffer for acquisition
Instrument	BD FACS Canto II
Software	FlowJo v10
Cell population abundance	Sorted human and murine GC B cells were confimed to be >90% following each sorting.
Gating strategy	For selection of single cells, cells were first gated based on FSC-H/FSC-A, then DAPI/FSC-A followed by FSC-A/SSC-A gating. For Sorting: lymphocytes were further gated on APC-B220 positive population on a SSC-A/APC-A dotplot. GC B cells were gated on GL7+FAS+ populations on a BV421-A/PE-Cy7 boxplot (Log axes). For regular flow: live B cells were selected as B220-APC+ cells on APC-A/SSC-A dotplot followed by gating GC B cells either as GL7-FITC+/FAS-PE+ or CD38-APC negative /FAS-PE positive on dotplot with logarithmic axes.

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