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Corresponding author(s): Michael Farrar

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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	Flow cytometry data was collected using Fortessa and LSR II cytometers and cell sorting was performed on FACS Aria II sorters; FACSDiva (v8.0) was used to collect flow cytometry data. 10X Genomics platform was used to capture cells and generate libraries for scRNA-seq and scATAC-seq. Illumina NovaSeq instrument was used for sequencing.
Data analysis	Graphpad Prism 9, FlowJo (10.6.2), CellRanger (v 3.1.0), Seurat R package (v 3.0.3, v4.0.1), Gene set enrichment analysis (GSEA v4.0) used annotations from MSigDB (v 7.0) and completed using "enricher" from clusterProfiler R package (v 3.14.0), Signac (v1.5.0), EnsDb.Mmusculus.v79 (R v2.99.0), chromVAR (v1.16), smoove (v0.2.8), dittoSeq (v0.1.2), Trimmomatic (v 0.39), bwa mem software (v0.7.17), Picard MarkDuplicates (v 2.25.5), IntervalStats (v 1.0.1), trackviewer (v1.30.0), bcl2fastq (v2.2.0)

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 data supporting this study are available within the paper and supplementary information file. A reporting summary is also available. Mouse genome mm10 was used as reference sequence (https://www.ncbi.nlm.nih.gov/assembly/GCF_000001635.20/). Single-cell RNA-Seq and single-cell ATAC-seq data were deposited at

Gene Expression Omnibus, with the following accession code: GSE208656 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc= GSE208656). Whole genome sequencing data was deposited at SRA with the following accession code: PRJNA860179 (http://www.ncbi.nlm.nih.gov/bioproject/860179). STAT5 ChIP-Seq peaks data were obtained from GSE86878 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE86878) and H3K27ac ChIP-seq peaks data were obtained from cistrome.org via project GSM1463433. IMMGEN RNA-Seq count data was from GSE124829. Landscape in silico analysis was performed from lisa.cistrome.org. Human B-ALL NCOR1 and NCOR2 mutation and RNA-seq data were obtained from StJude ProteinPaint (https://pecan.stjude.cloud/proteinpaint). Source data are provided with this paper.

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	Sample size for experiments was not predetermined and were chosen based on statistical significant derivation and sufficient reproducibility. The sample size used for each experiment is indicated in the figure legends and/or main text.
Data exclusions	Excluded data includes single-cell RNA-seq and single-cell ATAC-seq data with filtered cells that did not meet minimum quality thresholds. For single-cell RNA-seq, hashtag based doublets were also used to exclude doublets from final analysis.
Replication	All flow cytometry data were derived from at least two independent experiments. The number of experiments performed is indicated in the figure legends.
Randomization	Mice for phenotyping (WT and NCOR-knockouts), scRNAseq, scATACseq and whole genome sequencing were selected based on their genotypes for age-matched cohorts. Otherwise, animals and samples were randomly selected for experiments.
Blinding	Investigators were not blinded to the genotype of mice (WT, NCOR1 KO, NCOR1/2 DKO) to ensure appropriate genotypes were used in each experiment and for comparison of phenotypic differences. Bioinformaticists were also not blinded to sample origin to identify transcriptomic and accessibility differences between the genotypes.

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

scRNA-seq hashtag and CITE-Seq antibodies

anti-mouse TotalSeq-A0301 (M1/42) Hashtag 1 antibody, BioLegend, 155801, 1:50
anti-mouse TotalSeq-A0302 (M1/42) Hashtag 2 antibody, BioLegend, 155803, 1:50
anti-mouse TotalSeq A0303 (M1/42) Hashtag 3 antibody, BioLegend, 155805, 1:50
anti-mouse TotalSeq A0304 (M1/42) Hashtag 4 antibody, BioLegend, 155807, 1:50
anti-mouse TotalSeq A0305 (M1/42) Hashtag 5 antibody, BioLegend, 155809, 1:50
anti-mouse TotalSeq A0306 (M1/42) Hashtag 6 antibody, BioLegend, 155811, 1:50
anti-mouse TotalSeq-A0103 B220/CD45R (RA3-6B2), BioLegend, 103263, 1:50
anti-mouse TotalSeq-A0093 CD19 (6D5), BioLegend, 115559, 1:50
anti-mouse TotalSeq-A0113 CD93 (AA4.1), BioLegend, 136513, 1:50
anti-mouse TotalSeq-A0097 CD25 (PC61), BioLegend, 102055, 1:50
anti-mouse TotalSeq-A450 IgM (RMM-1), BioLegend, 406535, 1:50

TotalSeq-A0951 PE Streptavidin, 405251, 1:50

Flow cytometry antibodies

anti-mouse B220-BUV395 (RA3-6B2), BDBiosciences, 563793, 1:100
anti-mouse B220-Pacific Blue (RA3-6B2), BDBiosciences, 558108, 1:100
anti-mouse CD11c-APCef780 (N418), ThermoFisher, 47-0114-82, 1:100
GhostRed780 Tonbo Biosciences, 13-0865, 1:1000
anti-mouse Ter119-APCef780 (TER-119), ThermoFisher, 47-5921-82, 1:100
anti-mouse NK1.1-APCef780 (PK136), ThermoFisher, 47-5941-82, 1:100
anti-mouse Ly6G-APCef780 (RB6-8C5), ThermoFisher, 47-5931-82, 1:100
anti-mouse CD4-APCef780 (GK1.5), ThermoFisher, 47-0041-82, 1:100
anti-mouse CD8-APCef780 (53-6.7), ThermoFisher, 47-0081-82, 1:100
anti-mouse CD43-Biotin (S7), BDBiosciences, 553269, 1:100
anti-mouse CD43-FITC (S7), BDBiosciences, 561856, 1:100
anti-mouse CD19-BV605 (6D5), BioLegend, 115540, 1:100
anti-mouse CD93-PE (12-5892-82), eBioscience, 1:100
anti-mouse IgM-APC (115-136-075), Jackson Immuno Research, 1:100
anti-mouse IgM-APC (RMM-1), BioLegend, 406509, 1:100
anti-mouse IgM-FITC (eB121-15F9), eBioscience, 11-5890-85, 1:100)
anti-mouse CD62L-APC (MEL-14), Tonbo Biosciences, 20-0621-U100, 1:100
anti-mouse CD25-BV421 (BDB562606), BDBiosciences, 1:100
anti-mouse CD24-PerCP-Cy5.5 (562360), BDBiosciences, 1:100
anti-mouse CD249/BP1-BV786, (740882), BDBiosciences, 1:100
anti-mouse CD90.2-FITC (35-0903-U100), Tonbo Biosciences, 1:100
anti-mouse CD3-APC (20-0031-U100), Tonbo Biosciences, 1:100
anti-mouse Lambda-FITC (1175-02), SouthernBiotech, 1:100
anti-mouse Kappa-PE (1175-09), SouthernBiotech, 1:100
anti-mouse IKAROS-PE (653304), BioLegend, 1:100
anti-mouse Ki67-BV421 (652411), BioLegend, 1:100
anti-mouse NCOR1 (5948S), Cell Signaling, 1:100
anti-mouse BIM (2933T), Cell Signaling, 1:100
anti-mouse pSTAT5 (A17016B.Rec), BioLegend, 936904, 1:100
Goat anti-Rabbit IgG-PE, Abcam, ab72465, 1:100
Donkey anti-Rabbit IgG-PE (12-4739-81), eBioscience, 1:100
anti-mouse IL7R-BV421 (A7R34), BioLegend, 135023, 1:100
Streptavidin-BV421 BioLegend, 405225, 1:100

Validation

All antibodies used were commercially available antibodies validated by and used per manufacturer's instructions listed in the technical datasheets listed on the website of manufacturers. In addition, all antibodies were tested before use either with this work or based on previous literature usage. Antibodies were validated based on the use of positive and negative controls.

Animals and other organisms

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

Laboratory animals

All animals used in this study were bred and housed at University of Minnesota in pathogen-free facilities. Breeding and experimental protocols for mice were approved by the Institutional Animal Care and Use Committee (IACUC 2010-38515A and IACUC 1904-36975A) at University of Minnesota. All animals were housed in a dark/light cycle of 10 hrs/14 hrs. Light cycle was from 6 AM to 8 PM. Ambient temperature was maintained at 22°C and the humidity of the room ranged from 30-40%. Ncor1FL/FL mice were provided by E. Olson (UT-Southwestern) and J. Auwerx (École Polytechnique Fédérale, Lausanne, Switzerland). Tg(IghelMD4)4Ccg/J (MD4-transgene) mice were provided by M. Jenkins (Univ. of Minnesota). Cd79a-Cre mice were obtained from T. Bender (University of Virginia) and backcrossed for 30 generations to the C57Bl/6 background. Stat5b-CA mice were previously described. Ncor2 conditional knockout mice were generated using a flip-excision system. A retroviral vector containing a splice acceptor followed by lacZ reporter gene and poly A sequence and flanked by FRT and loxP sequences was used to insert the gene trap vector between exon 1 and 2 of the Ncor2 gene in mouse embryonic stem cells; embryonic stem cells were injected into blastocysts to make gene trapped mice. These mice were bred with mice expressing constitutive FLPe, inverting the cassette, allowing for normal gene splicing. Mice with the inverted cassette were bred to Cd79a-Cre, allowing for conditional knockout of Ncor2 in B cells. A schematic describing this mouse model is shown in Extended Data Figure 1a. For all NCOR-knockout phenotyping experiments, animals used were between 6- to 13-week old C57BL/6 male and female mice with appropriate age and sex matched controls. For the single-cell RNA-seq experiment, 8-week-old male C57BL/6 mice were used for WT (n = 2), NCOR1 KO (n = 2), and NCOR1/2 DKO (n = 2) samples. For the single-cell ATAC-seq experiment, 9-12 week old male and female C57BL/6 mice were used for WT (n = 1), NCOR1 KO (n = 1) and NCOR1/2 DKO (n = 1) samples. Stat5b-CA, Stat5b-CA x Cd79a-Cre x Ncor1FL/+, and Stat5b-CA x Cd79a-Cre x Ncor1FL/FL mice ranged from 103-304 days old at time of analysis and included male and female C57BL/6 mice.

Wild animals

This study did not involve wild animals

Field-collected samples

This study did not involve field-collected samples

Ethics oversight

Animal experiment protocols were approved by Institutional Animal Care and Use Committees (IACUC 2010-38515A and IACUC 1904-36975A) at the University of Minnesota

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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	Bilateral femurs, tibias and the spleen were harvested from mice. The femurs and tibias were flushed with FACS buffer (1X PBS with 2% fetal bovine serum (Sigma Aldrich, 12133C), 0.1% sodium azide (Ricca, 7144.8-16) and 0.5 mM ethylenediaminetetraacetic acids (EDTA; Fisher Scientific, S3113), pH 7.4). The spleen was mechanically grinded between the rough sides of frosted glass slides. Cells were then filtered through a 70 µm mesh filter and centrifuged at 350 x g for 5 minutes. Cells were incubated and centrifuged at 350 x g for 5 minutes in ACK lysis buffer (0.15M ammonium chloride (Fisher, A661), 10 mM potassium bicarbonate (Fisher, P184), 1mM EDTA (Fisher Scientific, S3113)). Cells were then washed and centrifuged at 350 x g and resuspended in 2 mL of FACS buffer. Counting was performed on a hemocytometer (Fisher Scientific. 02-671-10).
Instrument	Fortessa, Aria II; LSR II
Software	FACSDiva 8.0 (BDBiosciences), FlowJo (10.7.1), Prism 9 (GraphPad Software)
Cell population abundance	Cell sorting was performed with the FACS Aria II cytometer. For single-cell RNA-seq, 20,000 Dump-B220+CD43+ cells and 20,000 Dump-B220+CD43- cells were sorted from each mouse (n = 6 total from WT, NCOR1 KO and NCOR1/2 DKO). All cells were sorted into a single 15 mL conical tube. For single-cell ATAC-seq, 50,000 Dump-B220+CD43+ and 50,000 DUmp-B220 +CD43- cells were sorted from WT, NCOR1 KO and NCOR1/2 DKO mice. For whole genome sequencing, we sorted 300,000 CD19+B220+ cells from WT and NCOR1/2 DKO bone marrow cells.
Gating strategy	For the single-cell RNA and ATAC-sequencing experiments, lymphocytes were identified by SSC-A vs FSC-A, then singlets with FSC-H, FSC-W and SSC-H and SSC-W. Singlets were then gated on B220-Pacific Blue positive cells and negative for Dump-APCef780 (CD11c, Ter119, NK1.1, Ly-6G, CD4, CD8a, Dead). Cells were then sorted on CD43+ and CD43- . For B cell development phenotyping, Hardy fractions were used to assess B cell development stages (Rumfelt et. al, 2006). In short, cells were gated on SSC-A vs FSC-A for lymphocytes then singlets were gated on SSC-A vs SSC-W. Cells were then gated on CD43+ vs CD43-. The CD43+ fraction was divided into pre-pro-B (CD24-BP1-), pro-B (CD24+BP1-), and pro-B/pre-B (CD24 +BP1+) using CD24 and BP1. The CD43- population was subdivided into small pre-B (B220lowIgM-), immature B (B220lowIgM +), and mature B (B220highIgM+).

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