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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 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	Sequencing is performed on Hi-Seq2000 of Illumina in single end read mode with read length of 50 bp (RNAseq), or in paired end read mode with read length of 150 nucleotides (ChIPseq, DNase-seq, CUT&RUN and Hi-C). Flow cytometry data were collected on FACSVerse cytometer.
Data analysis	For nextgen sequencing data, the following was used: Juicer(v1.21.01), hiclib(v0.8.0 https://github.com/mirnylab/hiclib-legacy), WashU Epigenome Browser, UCSC Genome Browser, FastQC (v0.11.4), Cutadapt(v3.4), Trim Galore(0.6.4_dev), bowtie2(v2.2.5), samtools(v.1.7), Picard(v.2.21.6, http://broadinstitute.github.io/picard/), bedtools(v.2.30.0), MACS2(v2.1.1), SICER(v1.1), R(4.0.4), deeptools(3.5.1), edgeR(v.3.28.1), chromVAR(v.1.12.0), motifmatchr(v.1.12.0), HOMER(v.4.11), Cuffdiff(v2.2.1), Tophat(v2.1.0), GSEA(v4.1.0), LiftOver tool. For HiCHub analysis, please refer the algorithm at https://github.com/WeiqunPengLab/HiCHub. Details were listed in the method section. Flow cytometry data were analyzed on FlowJo v10.2 (TreeStar) and statistical analysis performed on Prism v8.0 (GraphPad).

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 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 data reported in this paper are tabulated in the Supplementary Materials and archived on the GEO database under accession number GSE179775.

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	No sample size was predetermined through calculation. All multiomics data were collected from at least two independent experiments, in two-four replicates, which are sufficient to provide statistical power in nextgen sequencing data analysis.
Data exclusions	No data were excluded from analyses.
Replication	For all experiments, at least two biological replicates were analyzed in at least two independent experiments. All the replicates showed consistent reproducibility or distinct clusters in nextgen sequencing analyses.
Randomization	Mice are randomly selected from a pool of 6-12 weeks mice for phenotypic analysis or sorting for Hi-C or multiomics analyses.
Blinding	The investigators were not blinded to the group allocation during data collection or analysis. Blinding is not appropriate for biological assays because the investigators have to know the genotypes of donor cells. Blinding is not relevant for analysis of nextgen sequencing data.

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 in this studies were listed in Methods. Specifically: The fluorochrome-conjugated antibodies were as follows: anti-CD4 (RM4-5), anti-CD8 (53-6.7), anti-TCR (H57-597), anti-CD45.1 (A20), anti-CD45.2 (104), anti-CD62L (MEL-14), anti-IL-2R (TM-β1), anti-IL-7R (A7R34), anti-Eomes (Dan11mag), anti-CD25 (PC61.5), anti-CD69 (H1.2F3), anti-ICOS (C398.4A), and anti-CD44 (IM7) were from Thermo Fisher Scientific; anti-γc (TUGm2) and anti-PD1 (RMP1-30) from BioLegend; anti-Tcf1 (C63D9) and anti-Lef1 (C12A5) from Cell Signaling Technology; For immunoblotting: anti-pY694-STAT5a (clone: C11C5, Cell Signaling Technology), pS473-Akt (clone: 193H12, Cell Signaling Technology), total Stat5a (clone ST5a-2H2, ThermoFisher Scientific), and total Akt (C67E7, Cell Signaling Technology). anti-CTCF (JM10-61, Invitrogen/ThermoFisher Scientific) or anti-Tcf1 antibodies (C63D9, Cell Signaling Technology). anti-HA (C29F4, Cell Signaling Technology); For coIP: anti-FLAG M2 Magnetic Beads (MilliporeSigma), anti-FLAG antibody (clone M2, #F3165, MilliporeSigma), anti-Tcf1 rabbit polyclonal antibody (#14464-1-AP, ProteinTech), anti-CTCF rabbit polyclonal antibody (#07-729, MilliporeSigma); For CUT&RUN: anti-CTCF antiserum (Active Motif); For ChIP-seq: anti-CTCF rabbit polyclonal antibody from Millipore Sigma (#07-729, with human CTCF 659-675 peptides as immunogen), anti-CTCF rabbit monoclonal antibody from Cell Signaling Technology (D31H2, with a synthetic peptide from human CTCF as immunogen, precise location undisclosed), anti-CTCF mouse monoclonal polyclonal antibody form Santa Cruz Biotechnology (#sc-271514, clone B-5, with human CTCF 643-687 peptides as immunogen)
Validation	The antibodies are validated by the manufacturers, as appears on the manufacturers' websites.

Animals and other organisms

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

Laboratory animals	Laboratory animals used in this study are described in the "Methods" section. Specifically, C57BL/6J (B6), B6.SJL, Rag1−/−, hCD2-Cre, and Rosa26GFP mice were from the Jackson Laboratory, Tcf7FL/FLand Lef1FL/FL mice were previously generated in the authors' laboratory. CtcfFL/FL mice were provided by N. Galjart (Erasmus University Medical Center, the Netherlands) and A. Melnick (Weill Cornell Medicine). All compound mouse strains used in this work were from in-house breeding at the animal care facilities of University of Iowa and Center for Discovery and Innovation, Hackensack University Medical Center. All mice, if not specifically mentioned in this manuscript, were 6–12 weeks of age, and both sexes were used without randomization or blinding.
Wild animals	No wild animals were used in this study.
Field-collected samples	Study did not involve samples collected in the field.
Ethics oversight	All experiments are performed under the protocol approved by the Institutional Animal Use and Care Committees of the University of Iowa and Center for Discovery and Innovation, Hackensack University Medical Center.

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.*	Go to https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE192758 Enter token "udshmwuappydpgd" into the box
Files in database submission	WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep1 WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep2 WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep3 WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep4 Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep1 Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep2 Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep3 Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep4 WT naive CD8, IgG ChIP-seq
Genome browser session (e.g. UCSC)	https://genome.ucsc.edu/s/ShaoqiZhu/CD8HP

Methodology

Replicates	WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep1 GSM6042355 ChIP-seq WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep2 GSM6042356 ChIP-seq WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep3 GSM6042357 ChIP-seq WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep4 GSM6042358 ChIP-seq Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep1 GSM6042363 ChIP-seq Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep2 GSM6042364 ChIP-seq Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep3 GSM6042365 ChIP-seq Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep4 GSM6042366 ChIP-seq WT naive CD8, IgG ChIP-seq GSM6042371 ChIP-seq
Sequencing depth	Rreplicates total reads unique reads length of reads paired or single-end WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep1 22566785 12023762 100 paired-end WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep2 15212634 9083672 100 paired-end WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep3 26969353 15694071 100 paired-end WT naive CD8, CTCF ChIP-seq SantaCruz Ab, rep4 30135444 13375634 100 paired-end Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep1 30933509 13686174 100 paired-end Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep2 23355650 12270903 100 paired-end Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep3 26923428 14160988 100 paired-end Tcf1/Lef1-deficient CD8, CTCF ChIP-seq SantaCruz Ab, rep4 23035585 8626642 100 paired-end WT-NA-IgG1 22007897 3089587 100 paired-end WT-NA-IgG2 30755638 7705503 100 paired-end WT-Na-cst-igg 20969674 1830745 100 paired-end All reads are trimmed 50bp from the 3' end.
Antibodies	Antibody name: Anti-CTCF Antibody; Vendor: Santa Cruz; Catalog#:sc-271514X Lot#: J619
Peak calling parameters	Read mapping:

Peak calling parameters	i=sample_name; \ bowtie2 --mm -p 4 --no-unal --no-mixed --non-deterministic --no-discordant \ -x ~/ncbi/public/index/bowtie2index/mm9/mm9 \ -1 ${i}_R1_val_1.fq.gz \ -2 .${i}_R2_val_2.fq.gz \ -S ${i}.sam Peak calling: i=sample_name; \ macs2 callpeak -t ${i}_sorted_rmdup.bam \ -c WT-NA-IgG1_sorted_rmdup.bam \ WT-NA-IgG2_sorted_rmdup.bam \ WT-Na-cst-igg_sorted_rmdup.bam \ -f BAMPE -g mm -n ${i} -B -q 0.05 --fe-cutoff 2 --SPMR \ --outdir ../macs2_IgG #for separate replicates macs2 callpeak -t ${i}_sorted_rmdup.bam \ -c WT-NA-IgG1_sorted_rmdup.bam \ WT-NA-IgG2_sorted_rmdup.bam \ WT-Na-cst-igg_sorted_rmdup.bam \ -f BAMPE -g mm -n ${i} -B -q 0.05 --fe-cutoff 4 --SPMR \ --outdir ../macs2_IgG #for merged replicates bam files.
Data quality	Four replicates were performed for each genotype. Each replicate was processed, and all replicates had similar numbers of peaks called with MACS2. Peaks were called under stringent criteria: summit fold change ≥2 and FDR<0.05 (separate replicates); summit fold change ≥4 and FDR<0.05 (merged replicates)
Software	FastQC (v0.11.4), Trim Galore(0.6.4_dev), bowtie2(v2.2.5), samtools(v.1.7), Picard(http://broadinstitute.github.io/picard/), bedtools(v.2.30.0), MACS2(v2.1.1), R(4.0.4), deeptools(3.5.1), edgeR(v.3.28.1), chromVAR(v.1.12.0), motifmatchr(v.1.12.0), HOMER(v.4.11)

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	Mouse spleens and lymph nodes were collected, and single cell suspension was made following standard procedures.
Instrument	FACSAria (BD Biosciences) for cell sorting, and FACSVerse (BD Biosciences) for analysis.
Software	FACSDiva (BD Biosciences) software was used for data collection. FlowJo v10.2 was used for data analysis.
Cell population abundance	≥95% on sorted cells, which was determined by flow cytometry analysis on post-sorted cells.
Gating strategy	Live lymphocytes were gated the known location through FSC-A/SSC-A. Doublets were removed by using FSC-A/FSC-W. CD4 and CD8 T cells cells were gated on TCRb+ cells.

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