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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	FACSDiva (BD), Image Capture Engine V602 (AMT), StepOne software v2.3 (Applied Biosystems), Quantity One (BioRad), Nanodrop 2000 (ThermoFisher).
Data analysis	FlowJo v7.6.5 (Treestar), GSEA (Broad), ArrayStar (DNAStar), ImageJ (NIH), Object J plugin (NIH), Venn Diagram Plotter (PCNL), EulerAP3v3 (Micallef et al), Excel (Microsoft), Illustrator CC (Adobe), Photoshop (Adobe), Prism 7 (GraphPad), DREME 5.0.1 (Bailey), UCSC Genome Browser, FastQC (0.11.3), Bowtie (1.1.1), MACS v1.4 (Zhang et al), Deeptools (2.5.3), R package ChIPseeker (1.14.1), BEDtools suite (v2.25.0), SRA Toolkit (NIH), Morpheus (Broad)

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 data that support the findings of this study are available from the corresponding author upon request. The microarray and ChIP-sequencing data is deposited in the GEO repository under accession code GSE125730.

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 calculation was performed, but previous experience and pilot experiments led us to typically use greater than or equal to 6 mice per group to prove or disprove statistically significant differences.
Data exclusions	One Bhlhe40+/+ and one Bhlhe40-/- microarray sample from in vivo IL-4c-simulated large peritoneal macrophages were excluded based upon global gene expression differences from the other replicates. However, analysis with these samples included did not affect the conclusions drawn. This non-pre-established exclusion was based on an unbiased assessment of global gene expression differences. Exclusions of animals were rare, and only due to evidence of unrelated injury or sickness. This is a pre-established policy in our lab.
Replication	As described in the figure legends, experiments were replicated multiple times. Controls were included and, when possible, complementary methods were used to confirm findings. Replication of experiments confirmed our results. Microarrays were not repeated, but biological replicates were used. Chip-seq experiments were not repeated, but samples were pooled from multiple mice.
Randomization	Within each experiment, mice of different genotypes were assigned to experimental groups in an age- and gender-matched manner. Groups of age- and sex-matched mice were then randomly allocated between treatment groups. When possible, animals of different genotypes were littermate controls and/or were cohoused. This was done so that differences in age, gender, and microbiota would not be confounding covariates in our analyses.
Blinding	Electron microscopy analysis was performed in a blinded fashion. Other analyses could not be blinded as treatment and analysis was performed by the same individuals

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

See supplementary table 1.
Beta actin polyclonal 4967 7 Unconjugated Cell Signaling Technologies Immunoblotting 1/5000
Dec1 (Bhlhe40) polyclonal NB100 C-1 Unconjugated Novus Biologicals ChIP-Seq 10 µg/sample
BrdU Not available "51-23619L, from 552598 kit" Multiple APC BD Flow cytometry 1/100-1/200
CD11b M1/70 35-0112 C0112083017353 FITC Tonbo Flow cytometry 1/400
CD11b M1/70 101216 and 25-0114 Multiple PE/Cy7 BioLegend, Tonbo Flow cytometry 1/400
CD11b M1/70 101212 Multiple APC BioLegend Flow cytometry 1/400
CD11b M1/70 101226 and 25-0112 Multiple APC/Cy7 BioLegend, Tonbo Flow cytometry 1/400
CD11c N418 117312 Multiple AF647 BioLegend Flow cytometry 1/200
CD11c N418 117324 and 25-0114 Multiple APC/Cy7 BioLegend, Tonbo Flow cytometry 1/200
CD16/32 2.4G2 BE0008 Multiple Unconjugated BioXCell Flow cytometry (Fcblock) 1/200
CD19 1D3 65-0193 Multiple PerCP/Cy5.5 Tonbo Flow cytometry 1/200
CD19 1D3 115530 Multiple APC/Cy7 BioLegend Flow cytometry 1/200
CD45 30-F11 557659 Multiple APC/Cy7 BD Flow cytometry 1/200
CD45 30-F11 563891 Multiple BV510 BD Flow cytometry 1/200

CD45.1 A20 110706 Multiple FITC BioLegend Flow cytometry 1/200
CD45.1 A20 110728 C045308151653 PE Tonbo Flow cytometry 1/200
CD45.1 A20 110728 and 65-0453 Multiple PerCP/Cy5.5 BioLegend, Tonbo Flow cytometry 1/200
CD45.1 A20 110722 and 75-0453 Multiple PB, V450 BioLegend, Tonbo Flow cytometry 1/200
CD45.1 A20 110704 B197550 Biotin BioLegend Flow cytometry 1/200
CD45.2 104 109806 Multiple FITC BioLegend Flow cytometry 1/200
CD45.2 104 50-0454 C0454011717503 PE Tonbo Flow cytometry 1/200
CD45.2 104 109814 Multiple APC BioLegend Flow cytometry 1/200
CD45.2 104 80-0454 C0454040314802 RF710 Tonbo Flow cytometry 1/200
CD45.2 104 109804 Multiple Biotin BioLegend Flow cytometry 1/200
CD64 X54-5/7.1 139306 Multiple APC BioLegend Flow cytometry 1/200
CD102 (ICAM2) 3C4 (MIC2/4) 105606 Multiple FITC BioLegend Flow cytometry 1/200
CD102 (ICAM2) 3C4 (MIC2/4) 105612 Multiple AF647 BioLegend Flow cytometry 1/200
CD102 (ICAM2) 3C4 (MIC2/4) 105604 B201603 Biotin BioLegend Flow cytometry 1/200
CD115 AFS98 50-1152 Multiple PE Tonbo Flow cytometry 1/200
CD115 AFS98 135513 Multiple BV421 BioLegend Flow cytometry 1/200
CD115 AFS98 135507 B204156 Biotin BioLegend, Tonbo Flow cytometry 1/200
CD226 10E5 128803 NA FITC BioLegend Flow cytometry 1/200
CD226 10E5 128806 Multiple PE BioLegend Flow cytometry 1/200
CD301 (Clec10a) LOM-14 145706 Multiple PE/Cy7 BioLegend Flow cytometry 1/200
CDK2 78B2 2546 8 Unconjugated Cell Signaling Technologies Immunoblotting 1/1000
CDK4 DCS31 sc-56277 K0818 Unconjugated Santa Cruz Immunoblotting 1/1000
CDK6 DCS83 3136 2 Unconjugated Cell Signaling Technologies Immunoblotting 1/2000
Cyclin D1 92G2 2978 12 Unconjugated Cell Signaling Technologies Immunoblotting 1/1000
Cyclin D2 D52F9 3741 5 Unconjugated Cell Signaling Technologies Immunoblotting 1/1000
Cyclin D3 DCS22 2936 5 Unconjugated Cell Signaling Technologies Immunoblotting 1/2000
E2F2 EPR8622 ab138515 GR3207895-1 Unconjugated Abcam Immunoblotting 1/1000
Embigin-1 G7.43.1 12-5839 Multiple PE eBioscience/Invitrogen Flow cytometry 1/200
F4/80 BM8.1 123110 and 20-4801 Multiple PE BioLegend, Tonbo Flow cytometry 1/200
F4/80 BM8.1 65-4801 C4801012916653 PerCP/Cy5.5 Tonbo Flow cytometry 1/200
F4/80 BM8.1 50-4801 123116 APC BioLegend, Tonbo Flow cytometry 1/200
I-A/I-E (MHC-II) M5/114.15.2 107635 Multiple BV510 BioLegend Flow cytometry 1/200-1/400
I-A/I-E (MHC-II) M5/114.15.2 107620 Multiple PB BioLegend Flow cytometry 1/200-1/400
I-A/I-E (MHC-II) M5/114.15.2 80-5321 Multiple RF710 Tonbo Flow cytometry 1/200-1/400
IL-4 11B11 I-1071 0814L365 Unconjugated Leinco In vivo IL-4c treatment NA (see methods)
IL-4 11B11 BE0045 Multiple Unconjugated BioXCell In vivo IL-4c treatment NA (see methods)
Ki67 SolA15 46-5698 Multiple PerCP/e710 eBioscience Flow cytometry 1/200
Ly6C HK1.4 128006 Multiple FITC BioLegend Flow cytometry 1/200
Ly6C HK1.4 128012 Multiple PerCP/Cy5.5 BioLegend Flow cytometry 1/200
Ly6C HK1.4 128026 Multiple APC/Cy7 BioLegend Flow cytometry 1/200
Ly6C HK1.4 128033 Multiple BV510 BioLegend Flow cytometry 1/200
Ly6C HK1.4 128014 Multiple PB BioLegend Flow cytometry 1/200
Lyve-1 ALY7 53-0443 Multiple AF488 eBioscience Flow cytometry 1/200
Lyve-1 ALY7 50-0443 E12123-1637 eF660 eBioscience Flow cytometry 1/200
pHH3 D2C8 3458 Multiple AF647 Cell Signaling Technologies Flow cytometry 1/200
RELMα polyclonal 500-P214 Multiple Unconjugated Peprotech Flow cytometry 1/200
Siglec-F E50-2440 552126 Multiple PE BD Flow cytometry 1/200
TIM4 RMT4-54 (54) 12-5866 Multiple PE eBioscience Flow cytometry 1/200
TIM4 RMT4-54 (54) 130010 Multiple PE/Cy7 BioLegend Flow cytometry 1/200
TIM4 RMT4-54 (54) 130007 B218029 AF647 BioLegend Flow cytometry 1/200
Goat αRabbit polyclonal A11034 1705912 AF488 Life Technologies Flow cytometry 1/200
Goat αRabbit polyclonal A21245 1700082 AF647 Life Technologies Flow cytometry 1/200
"Mouse αRabbit IgG light chain" polyclonal 211-032-171 116819 HRP Jackson ImmunoResearch Laboratories Immunoblotting 1/10000
"Goat αMouse IgG light chain" polyclonal 115-035-174 139280 HRP Jackson ImmunoResearch Laboratories Immunoblotting 1/10000
Streptavidin NA 50-4317 C4317042116503 PE Tonbo Flow cytometry 1/400
Streptavidin NA 405214 B249755 PerCP/Cy5.5 BioLegend Flow cytometry 1/400
Streptavidin NA 405206 B207311 PE/Cy7 BioLegend Flow cytometry 1/400
Streptavidin NA 405207 B145530 APC BioLegend Flow cytometry 1/400
Streptavidin NA 47-4317 E08466-1635 APC/e780 ebBioscience Flow cytometry 1/400
Streptavidin NA 561419 2104987 V500 BD Flow cytometry 1/400
Streptavidin NA 560797 36864 V450 BD Flow cytometry 1/400
7-AAD NA "51-2359KC from 552598 kit" Multiple NA BD, BioLegend Flow cytometry 1/20
DAPI NA 428801 B212123 NA BioLegend Flow cytometry final 3 µM
Po pro 1 NA V35123 1543354 NA LIfe Technologies Flow cytometry 1/1000

Validation

We validated all antibodies with appropriate controls (i.e. BrdU staining used BrdU-negative mice and omission of the DNase treatment step as controls). Notably, staining for cell cycle related molecules (Ki67, RELMa, BrdU, pHH3, CDKs, cyclins) and alternative activation markers (RELMa, Clec10a) were validated by comparison of naive mice with IL-4c-stimulated mice or H. polygyrus-infected mice. All antibodies were obtained from highly reputable vendors, who conducted comprehensive quality control testing, and are cited in numerous other publications.

Animals and other organisms

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

Laboratory animals	C57BL/6 (Taconic), B6.SJL (CD45.1, Taconic or Jackson), Il10-/- (B6.129P2-Il10tm1Cgn/J, Jackson), LysM-Cre (B6N.129P2(B6)-Lyz2tm1(cre)Ifo/J, Jackson), Bhlhe40-/- (10 generations backcrossed to the C57BL/6 background, Lin et al., 2014; Sun et al., 2001), Bhlhe40GFP (Lin et al., 2016), and Bhlhe40fl/fl (Huynh et al., 2018) mice. Animals of both sexes were used. Mice were used between the ages of 8-20 weeks.
Wild animals	the study did not involve wild animals
Field-collected samples	the study did not involve field-collected samples
Ethics oversight	All procedures involving animals were conducted following the National Institutes of Health guidelines for housing and care of laboratory animals, and they were performed in accordance with institutional regulations after protocol review and approval by the Institutional Animal Care and Use Committee of The Washington University in St. Louis School of Medicine (protocol 20160094, Immune System Development and Function). Washington University is registered as a research facility with the United States Department of Agriculture and is fully accredited by the American Association of Accreditation of Laboratory Animal Care. The Animal Welfare Assurance is on file with Office for Protection from Research Risks–National Institutes of Health.

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=GSE125730
Files in database submission	FASTQ lpm_naive_input.2667_5.R1.fq.gz lpm_naive_bhlhe40.2667_5.R1.fq.gz lpm_il_4c_input.2667_5.R1.fq.gz lpm_il_4c_bhlhe40.2667_5.R1.fq.gz BW naïve_input_depth_norm.bw naïve_bhlhe40_depth_norm.bw il4c_input_depth_norm.bw il4c_bhlhe40_depth_norm.bw BED lpm_naive_light_peaks.bed lpm_il_4c_light_peaks.bed xlsx naïve_LPM_Bhlhe40_bound_peaks.xlsx IL-4c_stimulated_LPM_Bhlhe40_bound_peaks.xlsx
Genome browser session (e.g. UCSC)	No longer applicable

Methodology

Replicates	4 samples were sequenced: Bhlhe40 ChIP from naive LPMs, input DNA from naive LPMs, Bhlhe40 ChIP from in vivo IL-4c-stimulated LPMs, and input DNA from IL-4c-stimulated LPMs
Sequencing depth	lpm_il_4c_bhlhe40 62873288 reads. Uniquely mapped reads 49195324. Read length 50, single end lpm_il_4c_input 70681704 reads. Uniquely mapped reads 55503874. Read length 50, single end lpm_naive_bhlhe40 41734788 reads. Uniquely mapped reads. 31711416 Read length 50, single end lpm_naive_input 72572802 reads. Uniquely mapped reads 57014420. Read length 50, single end
Antibodies	anti-Dec1 (Bhlhe40) antibody (NB100-1800, Lot C1; Novus Biologicals)
Peak calling parameters	Read mapping for all samples: bowtie -p 4 -St -m 1 -v 3 --best --strata INDEX GENOME READS OUTFILE IL-4c LPM peak calling command line

	macs callpeak -t lpm_il_4c_bhlhe40.2667_5.R1_mm10.bam -c lpm_il_4c_input.2667_5.R1_mm10.bam -f BAM -g mm -n lpm_il_4c naive LPM peak calling command line macs callpeak -t lpm_naive_bhlhe40.2667_5.R1_mm10.bam -c lpm_naive_input.2667_5.R1_mm10.bam -f BAM -g mm -n lpm_naive Called peaks were also required to have fold-enrichment ≥5 and reads from unmapped regions (chrUn_xxxxx) were excluded.
Data quality	All peaks were >/=5 fold enriched and FDR <5%
Software	DREME 5.0.1 (Bailey), UCSC Genome Browser, FastQC (0.11.3), Bowtie (1.1.1), MACS v1.4 (Zhang et al), Deeptools (2.5.3), R package ChIPseeker (1.14.1), BEDtools suite (v2.25.0), SRA Toolkit (NIH)

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	Peritoneal and pleural cells were collected from body cavities by lavage. Bone marrow was collected by flushing hind limb femurs and tibias. Blood was collected by submandibular bleeding into EDTA or lithium heparin tubes. Lungs, liver, spleen, and kidney were excised, placed in Iscove's Modified Dulbecco's Medium (IMDM) containing 5% fetal bovine serum (FBS), minced finely, and digested at 37 °C for an hour with mechanical disruption with a stirbar and enzymatic digestion (lung and kidneys, 4 mg/ml collagenase D (Roche); spleen, 0.25 g/ml collagenase B (Roche) and 30U/ml DNase I (EMD); liver, 4 mg/ml collagenase D and 30U/ml DNase I). Isolations of microglia(Lin et al., 2016) and small intestinal lamina propria cells(Bando et al., 2018) were performed as described. After digestion, enzymes were inactivated with 5 mM EDTA and samples were incubated on ice for 5 minutes. All cells were passed through a 70 µm cell strainer before analysis. If necessary, tissues were treated with ACK lysis buffer to lyse red blood cells. Cells were counted with a hemocytometer using 3% acetic acid (naïve peritoneum and pleura) or trypan blue (all others).
Instrument	FACSCanto II, LSRFortessa, LSRFortessa X20, FACSAria II, and LSR II (BD)
Software	FACSDiva (BD), FlowJo (Treestar)
Cell population abundance	All sorted populations were confirmed as highly pure by post-sorts (>90%)
Gating strategy	Gating of cell populations was as follows (all analysis pre-gated on FSC/SSC and a FSC-W/FSC-A singlet gate). Blood monocytes were gated as Ly6G-CD115+ and then divided by Ly6C expression. Peritoneal and pleural macrophages were gated as CD115+CD11b+, then divided into ICAM2+MHC-IIint large macrophages and ICAM2-MHC-II+ small macrophages. Thioglycollate-elicited macrophages were gated as CD115+CD11b+ICAM2lo. Liver Kupffer cells were gated as CD45+CD11bloF4/80hi, and in some contexts as Ly6C-. Kidney macrophages were gated as CD45+Ly6C-CD11b+F4/80hi. AMs were gated as CD45+Siglec-F+CD11c+, and in some contexts as F4/80+CD11b-. Red pulp macrophages were gated as F4/80hi and negative or low for other markers (CD11blo, MHC-IIlo, or CD11clo). Microglia were gated as CD45intCD11b+. Small intestinal lamina propria macrophages were gated as CD45+Ly6C-F4/80+CD64+MHC-II+. Peritoneal B cells were gated as CD115-MHC-II+CD19+. Analysis of cells from the Bhlhe40GFP+ reporter mouse used viability dyes (Po pro 1 or 7-AAD) when necessary to exclude dead cells.

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