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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 *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 *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 *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	FACSDiva v8.0.1; Summit v5.2; ImageJ v1.48; AxioVision v4.8.2; Leica Applications Suite v4.9; QuantStudio v1.2; StepOne v2.1
Data analysis	FlowJo v9.9; Prism v6.0h; Excel v14.7.7; Photoshop CS6; Seurat v2.0; STAR v.2.4.0j; CellRanger v2.1; GeneProf (2017); GSEA v3.0; Ingenuity Pathway Analysis (Summer Release 2015); Morpheus (https://software.broadinstitute.org/morpheus); Interferome (http://www.interferome.org)

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

The RNA sequencing data reported in this study are available at the Gene Expression Omnibus under accession codes GSE97405 (bulk) and GSE108233 (single-cell).

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

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	In most cases we assumed a minimum of 4 mice would be required to recognize differences between genotypes or conditions, based upon historical experiments in other contexts. A minimum number of animals were used to conform with NIH guidelines.
Data exclusions	For the bulk RNA sequencing experiment, two granuloma data sets were excluded due to low unique mapping rates and failure to group by tissue in principle components analysis and hierarchical clustering.
Replication	All experiments were replicated at least twice with similar findings, except single cell RNAseq due to prohibitive cost. We also did not replicate Diphtheria Toxin treatment of wild type mice for Sca-1 induction (Extended Data Figure 6a,b) due to clear and expected results for this reviewer requested control. These are noted in the text under "Statistics".
Randomization	Samples were randomly assigned.
Blinding	Investigators were not blinded to group allocation because treatments and data collection were performed by the same people.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☐	☒ Unique materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☐	☒ Research animals
☒	☐ Human research participants

Unique materials

Obtaining unique materials	Lgr5(DTRGFP) mice can be used with permission from Genentech.

Antibodies

Antibodies used	CD45 (Biolegend #103106, Clone 30-F11, various lot #s) CD326/EpCAM (Biolegend #118210, Clone G8.8, various lot #s) CD44 (Biolegend #103018, Clone IM7, various lot #s) Sca-1 (Biolegend #108134, Clone D7, various lot #s) TCRβ (Biolegend #109218, Clone H57, various lot #s) γδTCR (Biolegend #109218, Clone GL3, various lot #s) NK1.1 (Biolegend #108728, Clone PK136, various lot #s) CD90.2 (Biolegend #140318, Clone 53-2.1, various lot #s) CD11b (Biolegend #301332 Clone M1/70, various lot #s) Gr1 (Biolegend # 108428, Clone RB6-8C5, various lot #s) GFP (Aves #GFP-1020, Clone NA (Polyclonal), Lot# GFP697986) GFP (Abcam #ab13790, Clone NA (Polyclonal), Lot# GR236651-8)Ki67 (Thermo# RM-9106, Clone Sp6, various lot #s) E-Cadherin (Cell Signaling Technology #3195, Clone 24E10, Lot# 13) Sca-1 (Biolegend #122502, Clone e13-161.7, Lot# B186579) Muc2 (Santa Cruz #SC-15334, Clone NA (Polyclonal), various lot #s, no longer available) MMP7 (R&D Systems #AF2967, Clone NA (Polyclonal), Lot #YLS0214071)
Validation	Validation statements available from manufacturers: GFP, (Aves #GFP-1020, http://www.aveslab.com/wp-content/uploads/GFP-10201.pdf) GFP (Abcam #ab13790, http://www.abcam.com/gfp-antibody-ab13970.html) Ki67 (Thermo #RM-910, https://www.thermofisher.com/order/catalog/product/RM-9106-R7) E-Cadherin (Cell Signaling Technology #3195, https://www.cellsignal.com/products/primary-antibodies/e-cadherin-24e10-rabbit-mab/3195) Sca-1 (Biolegend #122502, https://www.biolegend.com/en-us/products/purified-anti-mouse-ly-6a-e-sca-1-antibody-3892) Muc2 (Santa Cruz #SC-15334, No longer available from Santa Cruz) MMP7 (RD #AF2967, https://resources.rndsystems.com/pdfs/datasheets/af2967.pdf) CD11b (BioLegend #301332, https://www.biolegend.com/en-us/products/brilliant-violet-605-anti-human-cd11b-antibody-8493) CD326/EpCAM (BioLegend #118210, https://www.biolegend.com/en-us/products/alexa-fluor-488-anti-mouse-cd326-ep-cam-antibody-4972) CD44 (BioLegend #103018, https://www.biolegend.com/en-us/products/alexa-fluor-647-anti-mouse-human-cd44-antibody-3098) CD45 (BioLegend 103106, https://www.biolegend.com/en-us/products/pe-anti-mouse-cd45-antibody-100) CD90.2 (BioLegend #140318, https://www.biolegend.com/en-us/products/brilliant-violet-605-anti-mouse-cd90-2-thy-1-2-

antibody-7866)
Gr1 (BioLegend #108428, https://www.biolegend.com/en-us/products/percp-cy5-5-anti-mouse-ly-6g-ly-6c-gr-1-antibody-4286)
NK1.1 (BioLegend #108728, https://www.biolegend.com/en-us/products/percp-cy5-5-anti-mouse-nk-1-1-antibody-4289)
Sca-1 (BioLegend, #108134, https://www.biolegend.com/en-us/products/brilliant-violet-605-anti-mouse-ly-6a-e-sca-1-antibody-8664)
TCRβ (BioLegend, #109218, https://www.biolegend.com/en-us/products/alexa-fluor-647-anti-mouse-tcr-beta-chain-antibody-3272)
γδTCR (BioLegend #118108, https://www.biolegend.com/en-us/products/pe-anti-mouse-tcr-gamma-delta-antibody-2421)

Research animals

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

Animals/animal-derived materials	Male and female mice aged 6–14 weeks, weighing 20-30 grams, were used for all experiments, except those analyzing fetal tissue. Lgr5DTRGFP mice were from Genentech. Wild-type (C57BL/6J), Lgr5GFP-CreERT2/+ (B6.129P2-Lgr5tm1(cre/ERT2)Cle/J), Rosa26RFP/+ (B6;129S6-Gt(ROSA)26Sortm14(CAG-tdTomato)Hze/J), IFNγ reporter (B6.129S4-Ifngtm3.1Lky/J), IFNγ-null (B6.129S7-Ifngtm1Ts/J), IFNγ receptor-flox (Ifngr1loxP/loxP; C57BL/6N-Ifngr1tm1.1Rds/J), and Vil1-Cre (B6.Cg-Tg(Vil1-cre)997Gum/J) mice were from The Jackson Laboratory (Bar Harbor, Maine).

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ Magnetic resonance imaging

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	The duodenum was dissected, flushed extensively with cold PBS, and the mesenteric tissue was removed. For whole tissue preps, Peyer's patches were removed and tissue was turned inside-out. For recovery of punch biopsies tissue was fileted open longitudinally. In both cases, tissue was shaken in three changes of 20 ml cold PBS and washed for 20 minutes at 37°C in two changes of 20 ml Ca2+/Mg2+-free HBSS containing 5 mM DTT, 10 mM HEPES, and 2% FCS, followed by 20 ml of Ca2+/Mg2+-replete HBSS containing 10 mM HEPES and 2% FCS. For punch biopsies, granuloma and non-granuloma tissue was dissected with a 1 mm punch tool under low-power magnification. Tissues were digested for 30 minutes at 37°C in 5 ml (whole tissue) or 2 ml (punch biopsies) Ca2+/Mg2+-replete HBSS containing 10 mM HEPES, 2% FCS, 30 µg/ml DNaseI (Roche), and 0.1 Wünsch/ml LibTM (Roche), and whole tissue was homogenized in C tubes using a gentleMACS tissue dissociator (Miltenyi). Homogenate or punch biopsies were passed through a 100 µm filter with assistance of a 3 ml syringe plunger, and enumerated for staining equivalent numbers for flow cytometry or sorting. Fc Block (anti-CD16/32), doublet exclusion, and DAPI exclusion were used in all cases.
Instrument	Becton Dickinson Fortessa; Beckman Coulter MoFlo XDP
Software	FACSDiva v8.0.1; FlowJo v9.9; Summit v5.2
Cell population abundance	In all cases, sorted cells were checked for purity by running a fraction of the sorted material on a cytomtery, including fresh DAPI to exclude dead cells. Prior to determination of purity, events were gated for FSC x SSC to exclude bubbles and debris in the sample collection tube, and only DAPI(lo) events were considered. Sorted samples generally had a purity >90%. Samples that were obviously outliers for the frequency of DAPI+ events or of obviously low purity were removed from downstream analysis, on a case-by-case basis.
Gating strategy	For gating of intestinal epithelial populations, data were generally gated in a linear fashion as follows: 1) time x FSC to exclude events influenced by initial sampling by the cytometer and by exhaustion of the sample, 2) FSC x SSC chosen to includes epithelial cells, 3) FSC-height x FSC-area to exclude doublets, 4) DAPI x FSC to exclude DAPI+ events, 5) CD45 x SSC to exclude CD45+ events, 6) CD326 x CD44 to include CD326+ events, 7) CD326 x CD44 to include CD326+ CD44+ events, 8a) Sca-1 x Lgr5, and/or 8b) Sca-1 x SSC, and/or 8c) Lgr5 x SSC. See Extended Data Figure 2a. For gating of intestinal neutrophils, data were generally gated in a linear fashion as follows: 1) time x FSC to exclude events influenced by initial sampling by the cytometer and by exhaustion of the sample, 2) FSC x SSC chosen to includes epithelial cells,

3) FSC-height x FSC-area to exclude doublets, 4) DAPI x FSC to exclude DAPI+ events, 5) CD45 x SSC to include CD45+ events, 6) Gr1 x SSC to included Gr1+ events, 7) CD11b x SSC. See Extended Data Figure 4a.

For gating of intestinal lymphoid populations, data were generally gated in a linear fashion as follows: 1) time x FSC to exclude events influenced by initial sampling by the cytometer and by exhaustion of the sample, 2) FSC x SSC chosen to includes epithelial cells, 3) FSC-height x FSC-area to exclude doublets, 4) DAPI x FSC to exclude DAPI+ events, 5) CD45 x SSC to include CD45+ events, 6) TCRb x gdTCR to gate abT cells, gdT cells, and non-T cells, 7) of non-T cells, NK1.1 x CD90.2, 8) Great x SSC. See Extended Data Figure 4b.

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