nature portfolio

Corresponding author(s): Sagar P. Bapat

Last updated by author(s): Aug 27, 2026

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 were collected using a Cytek Aurora™ CS System with Cytek SpectroFlo software (v4.0.1).
Data analysis	Flow cytometry data were analyzed using FlowJo software (v10 and v11, FlowJo LLC). Bulk RNA-seq reads were aligned using STAR (v2.7.11b); differential expression and visualization were performed in R (v4.6.1) using DESeq2 (v1.50.2). Lesional CD4+ T cell scRNA-seq reads were processed using PIPseeker (v3.2, Fluent BioSciences); lesional immune-cell scRNA-seq reads were processed using Cell Ranger's multi pipeline (v10.1.0, 10x Genomics). Both scRNA-seq datasets were analyzed using Scanpy (v1.10.4), with plotting in matplotlib (v3.9.3) and seaborn (v0.13.2). snATAC-seq reads were processed using Cell Ranger's atac count pipeline (v10.1.0) and analyzed using ArchR (v1.0.3), with peak calling in MACS2 (v2.2.9.1). Publicly available human psoriasis scRNA-seq data were analyzed in R (v4.6.1) using Seurat (v5.5.1), with doublet removal via scDblFinder (v1.24.0) and cell-type scoring via decoupler's OmniPath module (v2.2.0). Histology scale bars were generated using ImageJ (v1.54r). Statistical analyses were performed using GraphPad Prism v10 and v11 (GraphPad Software). Custom code is available on GitHub at https://github.com/bapatlab/RNAseq_scRNAseq_snATACseq.

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

Raw and processed bulk RNA-seq data have been deposited in the NCBI Sequence Read Archive (SRA) under BioProject accession PRJNA1212208 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1212208). Raw and processed single-cell RNA-seq and single-nucleus ATAC-seq data have been deposited in the Gene Expression Omnibus (GEO) under accession GSE287431 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE287431). Publicly available human psoriasis scRNA-seq datasets analyzed in this study were obtained from the European Genome-phenome Archive (EGA) under accessions EGAS00001007373 (https://ega-archive.org/studies/EGAS00001007373) and EGAS00001005271 (https://ega-archive.org/studies/EGAS00001005271); access to EGA data is subject to Data Access Committee approval. Sequencing reads were aligned to the UCSC mm10 mouse reference genome (bulk RNA-seq and PIPseeker-processed lesional CD4+ T cell scRNA-seq) or the GRCm39 mouse reference genome assembly (RefSeq GCF_000001635.27; Cell Ranger-processed lesional immune-cell scRNA-seq and snATAC-seq). Cell-type scoring used the PanglaoDB database (https://panglaodb.se/) and the OmniPath resource (https://omnipathdb.org/) via decoupler. Custom code is available on GitHub (https://github.com/bapatlab/RNAseq_scRNAseq_snATACseq).

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex and gender information was not available for all samples included in the publicly available datasets analyzed in this study. No sex- or gender-based analyses were performed. All analyses were conducted using de-identified data obtained from previously published studies. Where available, participant demographic information is reported in the original publications (Liu et al., 2022; Wu et al., 2024).
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity, and other socially relevant groupings were not analyzed in this study. Such information was not required for the objectives of the present analysis and was not consistently available across the publicly available datasets used. No analyses were stratified by race or ethnicity.
Population characteristics	This study analyzed publicly available single-cell RNA-seq data from psoriasis vulgaris skin lesions generated in previously published studies (Liu et al., 2022; Wu et al., 2024). The present study did not recruit participants or collect new human data. Participant characteristics, inclusion criteria, and clinical metadata are described in the original publications.
Recruitment	No participants were recruited for the present study.
Ethics oversight	The present study used publicly available, de-identified human single-cell RNA-seq datasets and therefore did not require additional institutional review board approval. Ethical approval, informed consent procedures, and oversight for participant recruitment and sample collection are described in the original publications (Liu et al., 2022; Wu et al., 2024).

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

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 formal statistical power calculations were performed. Sample sizes were chosen based on standard practice in the field for comparable in vivo mouse models of diet- and imiquimod-induced skin inflammation, consistent with prior published studies from our group and others using similar models (Bapat et al., 2022, Nature; Sivasami et al., 2023, Immunity), and were informed by pilot experiments in our laboratory that established the expected magnitude and variability of the phenotypes measured. Based on this precedent and pilot data, group sizes of 5–10 mice per condition were used to optimize detection of consistent, reproducible differences between experimental and control groups.
Data exclusions	Data were excluded for failed experiments, including reasons like loss-of-confidence in controls, experimentalist errors, technical errors, and inadequate cell number recovery for analyses.
Replication	All in vivo experiments were conducted with at least two independent cohorts, except for histological analyses which were conducted once in a repeat study. Unless otherwise noted, data from one instance of the repeated experiments is represented in this manuscript. Bulk and single-cell RNA-Seq experiments were conducted once using multiple biological samples per group (as indicated in figure legends).

Randomization	When possible, mice were randomly assigned to experimental or control groups. Mice in a given study were age- and sex-matched whenever possible.
Blinding	The pathologist analyzing histology was self-blinded to mouse genotype, dietary regimen, and treatment. Otherwise, investigators were not blinded to mouse genotype, dietary regimen, or treatment during 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 and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

The following antibodies were used for flow cytometry: Fc Block (2.4G2, BD, No. 553141, 1:200), CD45.2 (BV785, clone 104, BioLegend, No. 109839, 1:200), CD197/CCR7 (BV421, clone 4B12, BioLegend, No. 120120, 1:200), CD11c (Pacific Blue, clone N418, BioLegend, No. 117322, 1:200), CD11b (Pacific Blue, clone M1/70, BioLegend, No. 101224, 1:200), CD44 (BV570, clone IM7, BioLegend, No. 103037, 1:200), TCRγδ (BV650, clone GL3, BD, No. 563993, 1:200), CD62L (APC, clone MEL-14, TONBO, No. 20-0621-U025, 1:200), CD69 (FITC, clone H1.2F3, BioLegend, No. 104506, 1:200), Ly6G (PE/Cyanine5, clone 1A8, BioLegend, No. 127672, 1:200), CD3ε (BV711, clone 145-2C11, BioLegend, No. 100349, 1:200), CD4 (PE/Cyanine7, clone RM4-5, BioLegend, No. 100528, 1:200), CD8α (BV605, clone 53-6.7, BioLegend, No. 100744, 1:200), Ki-67 (Brilliant Ultraviolet 737, clone SolA15, Invitrogen, No. 367-5698-82, 1:400), RORγt (PE-CF594, clone Q31-378, BD, No. 562684, 1:400), FOXP3 (PerCP-eFluor 710, clone FJK-16s, Invitrogen, No. 46-5773-82, 1:400), IL-17A (Alexa Fluor 700, clone TC11-18H10.1, BioLegend, No. 506914, 1:400), IL-17A (BV421, clone TC11-18H10.1, BioLegend, No. 506925, 1:400), IL-17F (PE, clone 9D3.1C8, BioLegend, No. 517008, 1:400), CD121a (clone 35F5, BD, No. 564387, 1:400), CD121a (clone JAMA-147, BioLegend, No. 113505, 1:400), IFNγ (clone XMG1.2, BioLegend, No. 505806, 1:400), and IL-22 (clone Poly5164, BioLegend, No. 516409, 1:400). eBioscience Fixable Viability Dye eFluor780 (Invitrogen, No. 65-0865-14, 1:1000) was used to distinguish live from dying or dead cells.

For in vivo antibody-mediated depletion studies, the following antibodies were used: anti-mouse CD4 (clone GK1.5, Bio X Cell, No. BE0003), rat IgG2b isotype control (clone LTF-2, Bio X Cell, No. BE0090), anti-mouse Ly6G (clone 1A8, Bio X Cell, No. BE0075-1), and rat IgG2a isotype control (clone 2A3, Bio X Cell, No. BE0089).

For thick-section 3D confocal imaging, the following antibodies were used: rabbit anti-dsRed (Takara/Clontech, No. 632496, polyclonal, 1:400), rat anti-CD49f–AF488 (clone GoH3, BioLegend, No. 313608, 1:200), anti–α-smooth muscle actin–CF405S (clone 1A4, Biotium, No. BNC040665, 1:100), and goat anti-FABP5 (R&D Systems, No. AF1476-SP, polyclonal, 1:400). Secondary antibodies conjugated to Alexa Fluor 555 or Alexa Fluor 594 (Thermo Fisher Scientific) were used as appropriate.

Validation

All flow cytometry antibodies were obtained from BioLegend, BD Biosciences, Invitrogen/eBioscience, or TONBO Biosciences. For each catalog number listed above, the manufacturer's product datasheet confirms reactivity with mouse and validation for flow cytometry, per each vendor's internal quality-control program (BioLegend Quality Control, biolegend.com/en-us/quality/quality-control; BD Biosciences Quality and Reproducibility, bdbiosciences.com/en-us/products/reagents/flow-cytometry-reagents/research-reagents/quality-and-reproducibility; Thermo Fisher/Invitrogen Antibody Verification, thermofisher.com/us/en/home/life-science/antibodies/invitrogen-antibody-validation.html). Antibodies used for intracellular cytokine and transcription factor staining (Ki-67, RORγt, FOXP3, IL-17A, IL-17F, IFNγ, IL-22) are additionally validated by each manufacturer specifically for intracellular flow cytometry applications in mouse and have extensive prior use in the published literature for these targets.

For in vivo antibody-mediated depletion, anti-mouse CD4 (clone GK1.5, Bio X Cell #BE0003) is validated by the manufacturer specifically for in vivo CD4+ T cell depletion in mouse and has been cited in published depletion studies. Anti-mouse Ly6G (clone 1A8, Bio X Cell #BE0075-1) is validated by the manufacturer for in vivo neutrophil depletion in mouse and was originally characterized as a selective, non-cross-reactive Ly6G-specific depleting clone by Daley et al. (J. Leukoc. Biol., 2008). Rat IgG2b (clone LTF-2, Bio X Cell #BE0090) and rat IgG2a (clone 2A3, Bio X Cell #BE0089) isotype controls are manufacturer-validated, isotype-matched non-reactive controls for use with rat IgG2b and IgG2a antibodies, respectively, in mouse in vivo studies.

For immunofluorescence, rabbit anti-dsRed (Takara #632496) is validated by the manufacturer for detection of DsRed and DsRed-derived fusion proteins by immunofluorescence, with lot-specific validation provided in the manufacturer's certificate of analysis. Rat anti-CD49f–AF488 (clone GoH3, BioLegend #313608) is validated by the manufacturer for both flow cytometry and immunofluorescence applications in mouse. Anti–α-smooth muscle actin–CF405S (clone 1A4, Biotium #BNC040665) uses a widely characterized clone validated across species, including mouse, for immunofluorescence detection of smooth muscle actin. Goat anti-

FABP5 (R&D Systems #AF1476-SP) is validated by the manufacturer for reactivity with mouse FABP5 by immunohistochemistry/ immunofluorescence.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	All mice were on a C57BL/6 background and housed at the University of California, San Francisco (UCSF). Strains used were C57BL/6J (JAX No. 000664), B6.SJL-Ptprca Pepcb/BoyJ (JAX No. 002014), Rag1-/- (JAX No. 002216), Tcra-/- (JAX No. 002116), B6.129S2-H2dlAb1-Ea/J (MHC IIΔ/Δ) (JAX No. 003584), B2m-/- (JAX No. 002087), Tcrd-/- (JAX No. 002120), Cd4Cre (JAX No. 022071), and Nlrp3-/- (JAX No. 021302), all purchased from The Jackson Laboratory; Il1r1fl/fl and Cd4CreERT2 Ai14 mice were provided by the Scharschmidt Lab at UCSF. All mice used were male. Mice were 6 weeks of age at the start of dietary feeding (6–7 weeks of age at the start of the diet regimen for experiments involving diet-induced obesity, as detailed in Methods).
Wild animals	No wild animals were used in the study.
Reporting on sex	All mice used for the studies were male.
Field-collected samples	No field collected samples were used in the study.
Ethics oversight	All procedures involving animals were performed in accordance with protocols approved by the Institutional Animal Care and Use Committee (IACUC) of UCSF.

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

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

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	For skin flow cytometry, dissected mouse ear skin was separated into dorsal and ventral halves and digested in RPMI-1640 with 2% fetal calf serum, 1x Penicillin-Streptomycin-Glutamine, 0.2 mg/mL Liberase (Roche), 0.2 mg/mL DNase I (Sigma), and 0.5 mg/mL Hyaluronidase (Worthington) for 30 min, then minced into 1–2 mm^3 pieces and digested for an additional 30 min. The digest was passed through a 40 µm mesh, and the flow-through was centrifuged at 500 RCF for 5 min to pellet the stromal vascular fraction, which was washed once in RPMI and either stained directly or first stimulated with PMA and ionomycin in the presence of brefeldin A (Cell Activation Cocktail, BioLegend) for 1.5 h at 37 °C prior to intracellular cytokine staining. For lung flow cytometry, dissected lung tissue was finely minced and digested for 1 h in the same digestion buffer formulation described above, passed through a 40 µm mesh, and the flow-through was centrifuged at 500 RCF for 5 min; the pellet was washed once in RPMI and stimulated with PMA/ionomycin/brefeldin A as above prior to cytokine staining. For both tissues, cells were then Fc-blocked, surface-stained, and where applicable fixed, permeabilized, and stained intracellularly as described under Antibodies used, and analyzed on a Cytek Aurora™ CS System.
Instrument	Cytek Aurora System

Software	Cytek SpectroFlo software
Cell population abundance	CD4+ T cells were FACS-sorted from mouse ear skin (gating on live CD45.2+ CD3ε+ CD4+ cells) for scRNA-seq library preparation, with post-sort purity confirmed by re-analysis to be >90%. A total of 2,103 CD4+ T cells were recovered from LFD samples and 5,232 from HFD samples prior to QC filtering (1,769 and 4,450, respectively, after doublet and contamination removal). For the lesional immune-cell scRNA-seq dataset, 27,738 total cells were recovered (12,748 LFD, 14,990 HFD) following the Chromium Flex fixed-RNA profiling workflow. For adoptive transfer experiments, CD4+ T cells were isolated from spleens of WT mice using a magnetic bead-based CD4+ T Cell Isolation Kit (Stemcell), with post-isolation purity of >90% confirmed by flow cytometry prior to transfer.
Gating strategy	Gating strategies are shown in Extended Data Fig. 1b and Extended Data Fig. 9m. For skin immune cell analysis (Extended Data Fig. 1b), cells were gated on FSC-A/SSC-A to exclude debris and FSC-H/FSC-A to exclude doublets, followed by exclusion of viability dye-positive (dead) cells. Conventional T cells (Tconv) were defined as CD45+ CD3εInt CD4+ FOXP3-; regulatory T cells (Treg) as CD45+ CD3εInt CD4+ FOXP3+; TH17 cells as Tconv cells expressing RORγt and competent for IL-17A, IL-17F, and IL-22; γδ T cells as CD45+ CD3εInt γδTCR+; and neutrophils as CD45+ CD3ε- CD11b+ Ly6G+. For the tissue-resident memory (Trm) T cell panel (Extended Data Fig. 9m), cells were gated as above through live CD45+ CD3εInt cells, then gated on CD4 vs. CD8α to identify CD4+ T cells, SSC-H vs. FOXP3 to retain FOXP3-negative Tconv, CD62L vs. CCR7 to identify the CD62Llow CCR7low subset, and CD44 vs. CD69 to identify the CD44high CD69+ tissue-resident memory phenotype. Boundaries between positive and negative populations were defined using fluorescence-minus-one (FMO) controls.

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