nature portfolio

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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.

Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.
For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

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	qRT-PCR data were collected using QuantStudio 6/7 (Applied Biosystems). Immunofluorescence images were acquired with Zeiss LSM900-Airy confocal (Zeiss). H&E, in situ hybridization, and Toluidine blue staining images were captured using a Nikon Eclipse Ni-E fluorescence microscope (Nikon). Cell proliferation assay images were obtained with the IncuCyte ZOOM system (Sartorius). Flow cytometry data were analyzed with FACSVerse (BD Biosciences). Sequencing data were generated using NovaSeq 6000, X, and X Plus (Illumina). Western blot and chemokine array images were acquired using ChemiDoc MP (Bio-Rad).
Data analysis	Statistical analysis was performed using GraphPad Prism 9. Image quantification was conducted with ImageJ 1.53k and Zen 3.4. Bioinformatics analysis utilized R (v4.3.3), Cell Ranger (v7.1.0), Scanpy v1.10.2, Seurat (v5.1.0), DESeq2 (v1.44.0), DoubletFinder (v2.0.4), and SCTransform (v0.4.1).

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 raw and processed data have been deposited in the National Center for Biotechnology Information Gene Expression Omnibus (GEO) database under the following accession numbers: GSE287498 (10x single-cell RNA sequencing data of WT and Mir149EKO mice ear skin upon PBS or IL-23 injection), GSE274560 (human psoriasis epidermis bulk RNA sequencing data), and GSE254707 (single-cell RNA sequencing data of psoriasis epidermis).Previously published bulk RNA-seq data (Tweak-injection vs. Isotype Control-injection) can be accessed via GSE96957. Source data are provided with this paper, and additional data are available from the corresponding author upon request.

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 was not considered in the study design. Skin samples were collected from both female and male psoriasis patients.
Reporting on race, ethnicity, or other socially relevant groupings	The samples were collected from adult Caucasians. Race, ethnicity or socially relevant groupings were not considered in study design.
Population characteristics	Information on healthy donors and psoriasis patients who provided skin tissue samples is available from the corresponding author upon request.
Recruitment	The psoriasis patients and healthy donors were recruited at the Karolinska University Hospital, Stockholm, Sweden and at the clinics of the Swedish Psoriasis Association (Psoriasisföreningen), Region Stockholm, Sweden.
Ethics oversight	Human subject research was approved by the Stockholm local ethics committee with informed consent. The study was approved by the Stockholm Regional Ethics Committee and conducted in accordance with the Declaration of Helsinki.

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 power calculations were performed to determine sample size. Sample size was dictated by the availability of animal and clinical samples and based on prior experience with similar studies.
Data exclusions	Data from samples with poor cell/tissue viability or low RNA quality were excluded. In single-cell RNA-seq analysis, data were filtered based on quality control criteria (gene count: 200–5,000; <10% mitochondrial genes).
Replication	All animal and cell experiments were successfully replicated in 2–3 independent experiments with at least three biological replicates, unless stated otherwise in the figure legends or Methods.
Randomization	For in vitro studies, experimental conditions were randomly assigned. For in vivo studies, mice were randomly allocated to groups, including wild-type control and knockout groups.
Blinding	The investigators were blinded during data collecting and analysis.

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing	
Data exclusions	
Non-participation	
Randomization	

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing and spatial scale	
Data exclusions	
Reproducibility	
Randomization	
Blinding	

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	
Location	
Access & import/export	
Disturbance	

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	TWEAKR (FN14) – Rabbit monoclonal, 1:1000 (#4403S, CST, #ab109365, Abcam); Phospho-NF-κB p65 – Rabbit, 1:1000 (#3033S, CST); Total NF-κB p65 – Mouse, 1:1000 (#6956S, CST); β-Actin – Mouse (#SAB5500001, Sigma-Aldrich); Anti-BrdU – Mouse (#MA3-071, Invitrogen); Anti-CD45 – Rabbit (#ab10558, Abcam); Anti-Ki67 – Rabbit (#MA514520, Invitrogen); Anti-CD3 – Rat monoclonal (#ab11089, Abcam); Anti-F4/80 – Mouse (SP115, #ab111101, Abcam); Anti-CPA3 – Rabbit (Produced by Gunnar Pejler's lab); Secondary antibody: HRP-coupled anti-rabbit (#P039901-2, Dako); Alexa Fluor 594/488-conjugated (Invitrogen, Alexa Fluor 594); Counterstaining: WGA-Alexa Fluor 488 (1:200, #W11261, Invitrogen); DAPI (1:2000, #62247, Invitrogen).
Validation	

Antibody reactivates are validated by the literature or supplier as follows:
TWEAKR (FN14) – Rabbit monoclonal, 1:1000 (#4403S, Cell Signaling Technology; #ab109365, Abcam) https://www.cellsignal.com/products/primary-antibodies/tweak-receptor-fn14-antibody/4403?srsltid=AfmBOooKcFCFCn9WxDSbBxMUL-k8nAd5rATG0MjsoWFS32vQdviKxLOt https://www.abcam.com/en-us/products/primary-antibodies/tweakr-fn14-antibody-epr3179-ab109365?srsltid=AfmBOop5pPeAkiHVOMp-Zro1c99KMbKnbL9RXX_4sIJrMyopEtQn8XE7
Phospho-NF-κB p65 – Rabbit, 1:1000 (#3033S, Cell Signaling Technology) https://www.cellsignal.com/products/primary-antibodies/phospho-nf-kb-p65-ser536-93h1-rabbit-mab/3033
Total NF-κB p65 – Mouse, 1:1000 (#6956S, Cell Signaling Technology) https://www.cellsignal.com/products/primary-antibodies/nf-kb-p65-l8f6-mouse-mab/6956
β-Actin – Mouse (#SAB5500001, Sigma-Aldrich)
Anti-BrdU – Mouse (#MA3-071, Invitrogen) https://www.thermofisher.com/antibody/product/BrdU-Antibody-clone-BU-1-Monoclonal/MA3-071
Anti-CD45 – Rabbit (#ab10558, Abcam) https://www.abcam.com/en-us/products/primary-antibodies/cd45-antibody-ab10558?srsltid=AfmBOop4tQjH2cZ3w3IjcaYwuQIouNCpbaMTvQe_KV-DuvOlTtUKbCv5
Anti-Ki67 – Rabbit (#MA514520, Invitrogen) https://www.thermofisher.com/antibody/product/Ki-67-Antibody-clone-SP6-Recombinant-Monoclonal/MA5-14520
Anti-CD3 – Rat monoclonal (#ab11089, Abcam) https://www.abcam.com/en-us/products/primary-antibodies/cd3-antibody-cd3-12-ab11089?srsltid=AfmBOorQR4I6ArZ0seL8r9zwaTtWrBQ9xCXanXrjES2CACIyujZ96XTa
Anti-F4/80 – Mouse (SP115, #ab111101, Abcam) https://www.abcam.com/en-us/products/primary-antibodies/f4-80-antibody-sp115-ab111101
Anti-CPA3 – Rabbit (Produced by Gunnar Pejler's lab) https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/cpa3
Secondary antibody: HRP-coupled anti-rabbit (#P039901-2, Dako) https://www.agilent.com/store/en_US/Prod-P039901-2/P039901-2
Alexa Fluor 594/488-conjugated (Invitrogen) https://www.thermofisher.com/se/en/home/life-science/cell-analysis/fluorophores/alexa-fluor-488.html https://www.thermofisher.com/se/en/home/life-science/cell-analysis/fluorophores/alexa-fluor-594.html
Counterstaining: WGA-Alexa Fluor 488 (1:200, #W11261, Invitrogen) https://www.thermofisher.com/order/catalog/product/W11261
DAPI (1:2000, #62247, Invitrogen) https://www.thermofisher.com/order/catalog/product/62247

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Human adult primary keratinocytes (C0055C; Thermo Fisher) were cultured in Epilife medium supplement with Human Keratinocyte Growth Supplement (HKGS, 50015, Thermo Fisher) and lX Penicillin-Streptomycin.
Authentication	HEKa were obtained from Thermo Fisher
Mycoplasma contamination	The cells tested negative for Mycoplasma.
Commonly misidentified lines (See ICLAC register)	N/A

Palaeontology and Archaeology

Specimen provenance	N/A
Specimen deposition	N/A
Dating methods	N/A

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight

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

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	Experiments were conducted on in-house bred miR-149^flox (Cyagen) and K14-Cre transgenic mice (The Jackson Laboratory) on a C57BL/6J background. Mice were maintained under pathogen-free conditions at the Karolinska Institutet animal facility with standard housing conditions. All experiments used 8-10-week-old C57BL/6J mice.
Wild animals	No wild animals are used.
Reporting on sex	Both male and female mice were used.
Field-collected samples	N/A
Ethics oversight	All the mice were breed under pathogen-free conditions in Comparative Medicine Biomedicum (KMB) animal facility at Karolinska Institutet. All the mouse experiments were approved by committee on animal experimentation of Swedish Board of Agriculture (J ordbru ksverket).

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	N/A
Study protocol	N/A
Data collection	N/A
Outcomes	N/A

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☐	☐	Public health
☐	☐	National security
☐	☐	Crops and/or livestock
☐	☐	Ecosystems
☐	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☐	☐	Demonstrate how to render a vaccine ineffective
☐	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☐	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☐	☐	Increase transmissibility of a pathogen
☐	☐	Alter the host range of a pathogen
☐	☐	Enable evasion of diagnostic/detection modalities
☐	☐	Enable the weaponization of a biological agent or toxin
☐	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

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.*	N/A
Files in database submission	N/A
Genome browser session (e.g. UCSC)	N/A

Methodology

Replicates	N/A
Sequencing depth	N/A
Antibodies	N/A
Peak calling parameters	N/A
Data quality	N/A

Software

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 FACS analysis, ear skin from IL-23 or PBS-injected mice was dissected, cut into pieces, and digested with Liberase TL (100 µg/ml; Roche) and DNase I (0.5 mg/ml; Roche) in PBS with 0.2% FBS at 37°C for 2 hours at 700 rpm. The lysate was filtered through 70 µm filters (CellTrics, Sysmex) and washed with FACS buffer. Cells were blocked with rat anti-mouse CD16/32 (eBioscience) and stained for immune markers: neutrophils (Ly6G+CD11b+), macrophages (F4/80+CD11b+), and T cells (CD3+). Dead cells were labeled with the LIVE/DEAD Fixable Near-IR Dead Cell Stain Kit (Life Technologies).
Instrument	BD LSRFortessa Cell Analyser (BD Biosciences)
Software	All data were processed using FlowJo software version 10.5.0 (TreeStar).
Cell population abundance	Flow cytometry detected low immune cell abundance in healthy tissues, with recruitment to inflamed sites where they differentiate into proinflammatory states. Immune cell abundance in ear skin is reported as a percentage of total live/single cells, gated by CD45 (5.37%–10.2%), CD3 (3.43%–5.98%), CD11b/Ly6G (0.05%–0.39%), and F4/80/CD11b (1.49%–2.54%).
Gating strategy	Gating of CD45+,CD3+,CD11b/Ly6g+, F4/80+ was done as previously described (Martinez-Corral et al., 2020).

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

Magnetic resonance imaging

Experimental design

Design type	N/A
Design specifications	N/A
Behavioral performance measures	N/A
Imaging type(s)	N/A
Field strength	N/A
Sequence & imaging parameters	N/A
Area of acquisition	N/A

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software	N/A
Normalization	N/A
Normalization template	N/A
Noise and artifact removal	
Volume censoring	

Statistical modeling & inference

Model type and settings	N/A
Effect(s) tested	N/A

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016)

N/A

Correction

N/A

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

N/A

Graph analysis

N/A

Multivariate modeling and predictive analysis

N/A