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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.

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	FACS DIVA, Living Image v4.5.5, CTL ImmunoSpot Series S five Versa ELISpot Analysis (S5Versa-02-9038), iQue Forecyt, NIS-Elements AR 4.40.00.
Data analysis	Graphpad Prism v8 was used for graph preparation and statistical analysis. FlowJo v10 was used to analyse flow-cytometry data. Chemdraw v17.1 was used to prepare chemical structures. Living Image v4.5.5 was used to quantify luminescence, CTL ImmunoSpot Series S five Versa ELISpot Analyzer (S5Versa-02-9038) was used to quantify spot-forming cells. Python v3.7 and Microsoft Excel were used to analyse antibody features. FIJI v 2.5.0 was used to prepare immunofluorescent microscopy images.

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 main data supporting the findings of this study are available within this paper and its Supplementary information. The raw and analysed datasets are too large to readily share publicly yet are available for research purposes from the corresponding author on reasonable request.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	The study did not involve human research participants.
Population characteristics	—
Recruitment	—
Ethics oversight	—

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	Power analysis was not performed. For the in vivo studies, we used 2–5 mice per group (n = 2 for the initial batch screening, owing to large sample sizes, and larger n numbers for subsequent studies, in line with similar group sizes reported in the literature).
Data exclusions	No data were excluded.
Replication	In general, the experiments were repeated to confirm the results. All attempts at replication were successful.
Randomization	Animal groups were randomized by body weight and/or age.
Blinding	The researchers performing batch-based screening and characterization of the immunostimulatory lipids were not blinded, as all data were quantitatively measured with standard equipment. Those performing vaccination experiments were blinded. In general, authors performing the analysis of the vaccination experiments were not blinded for the same reasons. Those performing serological analyses of FcR binding and antibody subclasses were blinded.

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

Methods

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

Antibodies

Antibodies used

CD3-APC/Cy7, anti-mouse, Biolegend(Cat#100221), 1/200 dilution; CD4-FITC, anti-mouse, BioLegend(Cat# 100405), 1/200 dilution; CD8a-APC, anti-mouse, BioLegend(Cat# 100711), 1/400 dilution, CD11b-PE/Cy7, anti-mouse, BioLegend(Cat#101215), 1/200 dilution; CD11c-AF488, anti-mouse, BioLegend(Cat# 117313), 1/300 dilution; CD21/CD35-FITC, anti-mouse, BioLegend(Cat# 123407), 1/200 dilution, B220-APC, anti-mouse, BioLegend(Cat# 103211), 1/800 dilution; CD40-APC, anti-mouse, BioLegend(Cat# 124611), 1/400 dilution; CD44-PE, anti-mouse, BioLegend(Cat# 103007), 1/400 dilution; CD45-BV421, anti-mouse, BioLegend(Cat# 103134), 1/300 dilution; CD62L-PerCP/Cy5.5, anti-mouse, BioLegend (Cat# 104431), 1:400 dilution; CD86-PE, anti-mouse, BioLegend(Cat# 159203), 1/400 dilution; CD16/32, anti-mouse, BioLegend(Cat# 101319), 1/50 dilution; HRP conjugated goat anti-mouse IgG, Cell Signaling (Cat# 7076S), 1/10,000 dilution; Goat Anti-Mouse IgG1, Human ads-PE, Southern Biotech (Cat #1070-09, 1:100); Goat Anti-Mouse IgG, Human ads-PE, Southern Biotech (Cat # 1030-09, 1:100); Goat Anti-Mouse IgG2a, Human ads-PE, Southern Biotech (Cat #1080-09), 1:100; Goat Anti-Mouse IgG2a, Human ads-PE, Southern Biotech (Cat #1090-09, 1:100); Goat Anti-Mouse IgG3, Human ads-PE, Southern Biotech (Cat #1100-09, 1:100); Goat Anti-Mouse IgA, Human ads-PE, Southern Biotech (Cat #1040-09, 1:100); Goat Anti-Mouse IgM, Human ads-PE, Southern Biotech (Cat #1020-09, 1:100); rabbit anti-RFP antibody (abcam, ab62341, 1:200); Dylight 594 goat anti-rabbit antibody (Vector Labs, DI-1594, 1:200); Alexa Fluor 647 anti-acetylated tubulin antibody (Santa Cruz, SC-23950, 1:200); Alexa Fluor 488 anti-Uteroglobin/SCGB1A1/CC10 antibody (Santa Cruz, SC-390313, 1:200)

Validation

All primary antibodies were bought from vendors (BioLegend, Cell Signaling, Santa Cruz, Abcam) and used for the specified suggested by the manufacturers (mouse-specific). Validations can be found in the manufacturer's website. In addition, many have literature references and species specifications on their websites. CD4, CD8, B220, CD11b, CD11c, CD21, CD44, CD45, CD62L, CD40, CD86, CD16/32 et. al are routinely used antibodies. Dilution factors were pre-determined in the lab. Flow data suggests clear isolation of the cell populations (Figs. S9, S13). Antibodies from Southern Biotech were validated by ELISA, FLISA and flow cytometry.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

THP1-Lucia ISG cells were from InvivoGen. THP1 and HEK293 cells were from ATCC. BMDCs were derived from female C57BL/6J mice and cultured in GM-CSF containing medium for 6 days.

Authentication

The cell lines were certified by the manufacturers.

Mycoplasma contamination

The cell lines tested negative for mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell lines were used.

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

Female C57BL/6J mice (BL6, 000664, 6–8 weeks) and B6.Cg-Gt(ROSA)26Sortm14(CAG-tdTomato)Hze/J mice (Ai14, 007914, 6–8 weeks) were obtained from the Jackson Laboratory.

Wild animals

This study did not involve wild animals.

Reporting on sex

Only female mice were used in this study.

Field-collected samples

The study did not involve samples collected from the field.

Ethics oversight

All procedures were performed under an animal protocol approved by the Massachusetts Institute of Technology Committee on Animal Care (CAC) and under the guidelines for animal care in an MIT animal facility.

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

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 splenocyte preparation, spleens were removed and passed through a 70-μm filter. Cell suspensions were treated with RBC lysis buffer followed by PBS neutralization before proceeding to antibody staining. BMDCs for analysis were prepared as described in Methods (section "IRF-inducible reporter monocyte and BMDC activation assay"). For lung cell preparation, a single-cell suspension of lung cells was generated using the Lung Dissociation Kit (Miltenyi Biotec), following the manufacturer's instructions. Cell suspensions were treated with RBC lysis buffer followed by PBS neutralization before proceeding to antibody staining. The full method is described in Methods (section "Flow cytometry and histology study of Ai14 mice").
Instrument	BD LSR II flow cytometer (BD Biosciences, San Jose, CA, USA).
Software	Collection via FACS DIVA and analysis via FlowJo.
Cell population abundance	Cell populations were generally distinct, and as many events were collected as possible from the starting sample.
Gating strategy	Cells were identified on the basis of FSC/SSC values. Single-color stains and FMO (fluorescence minus 1) were used to determine positive populations. Gating strategy is provided in Supplementary Figs. 9 and 13.

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