

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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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 Excel 2016(Microsoft), Image J version 1.8.0, FV31S-SW viewer version 2.4 (Olympus)

Data analysis Histological staining images acquired with FV-31S-SW software and were analyzed by Image J. All statistical data were analyzed with Prism 9 GraphPad or Prism 7 GraphPad .

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 results in this study are available within the paper and its Supplementary Information. The raw and analyzed datasets generated during the study are too large to be publicly shared, but they are available for research purposes from the corresponding authors upon reasonable request.

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](https://www.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 statistical methods were used to predetermine the sample size. To proceed with statistical analysis, more than three animals or repeats were performed.
Data exclusions	No data was excluded.
Replication	All experiments were repeated from at least three independent tests, and all attempts at replication were successful.
Randomization	All samples was randomly assigned, and analyzed together in each experiment.
Blinding	Data acquisition and analysis were performed by investigators blinded to the groups.

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		Methods	
n/a	Involved in the study	n/a	Involved in the study
☐	☒ Antibodies	☒	☐ ChIP-seq
☐	☒ Eukaryotic cell lines	☐	☒ Flow cytometry
☒	☐ Palaeontology and archaeology	☒	☐ MRI-based neuroimaging
☐	☒ Animals and other organisms		
☒	☐ Human research participants		
☒	☐ Clinical data		
☒	☐ Dual use research of concern		

Antibodies

Antibodies used	RBD primary antibody (40592-T62, Sino Biological, PA, USA), CD63 (PA5-100713, Thermo Fisher Scientific, MA, USA), CD86-APC (565479, BD Biosciences, CA, USA), CD40-PE (553791, BD Biosciences, CA, USA), CD80-APC (A14724, Invitrogen, MA, USA), CD11b (53-0112-82, eBioscience, CA, USA), Phalloidin-iFluor 488 (ab176753, Abcam, Cambridge, United Kingdom), CD4-FITC (100406, Biolegend, CA, USA), CD8-FITC (ab22504, Abcam, Cambridge, United Kingdom), IFN-γ-PE (507806, Biolegend, CA, USA), IL-4-PE (504103, Biolegend, CA, USA), IL-17a-APC (17-7177-81, Invitrogen, MA, USA), CD205 (DDX0020P100, Fisher Scientific, PA, USA), IgA-HRP (ab97235, Abcam, Cambridge, United Kingdom), IgG1-HRP (ab97240, Abcam, Cambridge, United Kingdom), IgG2a-HRP (A-10685, Thermo Fisher Scientific, MA, USA), IgE-HRP (ab99574, Abcam, Cambridge, United Kingdom), Primary rabbit anti-SARS-N antibody (NB100-56576, Novus Biologicals, CO, USA), CD3 (ab16669, Abcam, Cambridge, United Kingdom), MPO (PA5-16672, Thermo Fisher Scientific, MA, USA), MX1 (MABF938, Millipore Sigma, Burlington, USA), goat anti-rabbit HRP secondary antibody (ab6721, Abcam, Cambridge, United Kingdom), goat anti-mouse HRP secondary antibody (ab6789, Abcam, Cambridge, United Kingdom), AF-488-CD206 (sc-376108 AF488, Santa Cruz Biotechnologies, Texas, USA), Alexa Fluor®568-Iba-1 (ab221003, Abcam, Cambridge, United Kingdom), goat anti-rabbit Alexa Fluor® 647 (ab150079, Abcam, Cambridge, United Kingdom), FITC-pan-CK (ab78478, Abcam, Cambridge, United Kingdom)
Validation	RBD: https://cn.sinobiological.com/antibodies/cov-spike-40592-t62 CD63: https://www.thermofisher.com/antibody/product/CD63-Antibody-Polyclonal/PA5-100713 CD86-APC: https://www.bdbiosciences.com/en-us/products/reagents/flow-cytometry-reagents/research-reagents/single-color-antibodies-ruo/apc-r700-rat-anti-mouse-cd86.565479 CD40-PE: https://www.bdbiosciences.com/en-us/products/reagents/flow-cytometry-reagents/research-reagents/single-color-antibodies-ruo/pe-rat-anti-mouse-cd40.553791 CD80-APC: https://www.thermofisher.com/antibody/product/CD80-Antibody-clone-1G10-Monoclonal/A14724 CD11b: https://www.thermofisher.com/antibody/product/CD11b-Antibody-clone-M1-70-Monoclonal/53-0112-82 Phalloidin-iFluor 488: https://www.abcam.com/phalloidin-ifluor-488-reagent-ab176753.html CD4-FITC: https://www.biolegend.com/en-us/products/fits-anti-mouse-cd4-antibody-248

CD8-FITC: <https://www.abcam.com/fitc-cd8-alpha-antibody-kt15-ab22504.html>
 IFN- γ -PE: <https://www.biolegend.com/en-us/products/pe-anti-rat-ifn-gamma-antibody-1547>
 IL-4-PE: <https://www.biolegend.com/en-us/products/pe-anti-mouse-il-4-antibody-893>
 IL-17a-APC: <https://www.thermofisher.com/antibody/product/IL-17A-Antibody-clone-eBio17B7-Monoclonal/17-7177-81>
 CD205: <https://www.fishersci.com/shop/products/dec-205-cd205-nldc-0-1-mg/ddx0020p100>
 IgA-HRP: <https://www.abcam.com/goat-mouse-iga-alpha-chain-hrp-ab97235.html>
 IgG1-HRP: <https://www.abcam.com/goat-mouse-igg1-hrp-ab97240.html>
 IgG2a-HRP: <https://www.thermofisher.com/antibody/product/Goat-anti-Mouse-IgG2a-Secondary-Antibody-Polyclonal/A-10685>
 IgE-HRP: <https://www.abcam.com/rat-monoclonal-23g3-mouse-ige-epsilon-chain-hrp-ab99574>
 SARS-N: https://www.novusbio.com/products/sars-nucleocapsid-protein-antibody_nb100-56576
 CD3: <https://www.abcam.com/cd3-antibody-sp7-ab16669.html>
 MPO: <https://www.thermofisher.com/antibody/product/Myeloperoxidase-Antibody-Polyclonal/PA5-16672>
 MX1: https://www.emdmillipore.com/US/en/product/Anti-MxA-clone-M143-CL143,MM_NF-MABF938
 goat anti-rabbit HRP secondary antibody: <https://www.abcam.com/goat-rabbit-igg-hl-hrp-ab6721.html>
 goat anti-mouse HRP secondary antibody: <https://www.abcam.com/goat-mouse-igg-hl-hrp-ab6789.html>
 AF-488-CD206: <https://www.scbt.com/p/cd206-antibody-d-1?requestFrom=search>
 Alexa Fluor®568-Iba-1: <https://www.abcam.com/alexa-fluor-568-iba1-antibody-epr61362-ab221003.html>
 goat anti-rabbit Alexa Fluor® 647: <https://www.abcam.com/goat-rabbit-igg-hl-alexa-fluor-647-ab150079.html>
 FITC-pan-CK: <https://www.abcam.com/pan-cytokeratin-antibody-c-11-fitc-ab78478.html>

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)

Lung spheroid cells were generated from healthy human whole lung samples from the Cystic Fibrosis and Pulmonary Diseases Research and Treatment Center at the University of North Carolina at Chapel Hill.
 Primary small airway epithelial cells (PCS-301-010) and primary bronchial/tracheal epithelial cells (PCS-300-010) were purchased from ATCC (Manassas, VA, USA)
 A549 lung carcinoma cells expressing human ACE2 and TMPRSS2 (a549-hace2tpsa) were purchased from Invivogen (San Diego, CA, USA)
 C57BL/6 Dendritic cells (1129-4807AU20) were purchased from Cellero (Lowell, MA, USA)

Authentication

Primary small airway epithelial cells and primary bronchial/tracheal epithelial cells were authenticated by ATCC. A549 cells were authenticated by Invivogen and C57BL/6 dendritic cells were authenticated by Cellero, respectively. No further authentication was performed. Lung spheroid cells were authenticated by our previous reported cell surface markers (Stem Cells Transl. Med. 4, 1265-1274, 2015).

Mycoplasma contamination

Mycoplasma testing (PCR method) is routinely performed in the lab, and all cell lines were tested negative for mycoplasma contamination.

Commonly misidentified lines (See [ICLAC](#) register)

No misidentified cell lines were used in the study.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals

Seven-eight weeks old male and female CD1 mice (CrI:CD1(ICR)) were obtained from Charles River Laboratory (Wilmington, MA, USA)
 Six to eight weeks old male and female Syrian golden hamsters were obtained from Envigo

Wild animals

The study did not involve wild animals

Field-collected samples

This study did not involve field-collected samples.

Ethics oversight

The mice study was performed under guidelines of the North Carolina State University, Institutional Animal Care and Use Committee(IACUC), under approved IACUC # 19-806-B
 The hamster study were approved by the Bioqual Institutional Animal Care and Use Committee (IACUC), under approved IACUC# 20-091P

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

Cells were washed with MACS flow buffer (Miltenyi Biotec, Bergisch Gladbach, Germany) and permeabilized with BD Cytofix/Cytoperm (BD Biosciences, San Jose, CA, USA) prior to incubation with antibodies against CD86-APC (565479; BD Biosciences, San Jose, CA, USA), CD40-PE (553791; BD Biosciences, San Jose, CA, USA), and CD80-APC (A14724; Invitrogen, Waltham, MA, USA). Samples were gated with CD11b (53-0112-82; eBioscience, San Diego, CA, USA).

Instrument

BD LSR-II Flow Cytometer and CytoFLEX Flow Cytometry

Software

BD FACSDiva Software and FCS Express V6

Cell population abundance

Provided in Supplementary Figs. 9-11

Gating strategy

Unstained cells were used as negative control and FSC-A/SSC-A was used to gate singlets, followed by setting up a gate that 99%-100% unstained cells as negative.

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