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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.

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 acquired using SpectroFlo software v2.2.
Data analysis	Flow cytometry data were analyzed using FlowJo v10 and Prism v8. ELISA, ELISpot, and neutralization data were analyzed using Prism v8. Sequence data were analyzed using blastn v2.11.0, pRESTO v0.6.2, cd-hit-est v4.8.1, IgBLAST v1.17.1, IMGT/GENE-DB release 202113-2, Change-O v1.0.2, TIgGER v1.0.0, igraph v1.2.5, and SHazaM v1.0.2.

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. 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

Antibody sequences are deposited on GenBank under the following accession numbers: MW926396–MW926407, MW926409–MW926430, MW926432–MW926441, MZ292481–MZ292510, available from GenBank/EMBL/DDBJ. Bulk sequencing reads are deposited on Sequence Read Archive under BioProject PRJNA731610. The IMGT/V-QUEST database is accessible at http://www.imgt.org/IMGT_vquest/. Other relevant data are available from the corresponding author upon 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

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 determine sample size. 41 total participants were enrolled based on recruitment, of whom 14 provided axillary LN samples
Data exclusions	No data were excluded
Replication	Human samples were collected from 41 participants. For ELISA, ELISpot, and neutralization assays, results were from one experiment performed in duplicate. Flow cytometry experiments were performed once
Randomization	Different experimental groups were not used.
Blinding	No blinding was done for convenience; subjective measurements were not made.

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
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	total Ig (goat polyclonal, Jackson ImmunoResearch 109-005-064), IgG-HRP (goat polyclonal, Jackson ImmuoResearch 109-035-088), IgA-HRP (goat polyclonal, Jackson ImmuoResearch 109-035-011), IgM-HRP (goat polyclonal, Caltag H15007), mouse IgG-HRP (goat polyclonal, Sigma 12-349), murine anti-S mAbs: SARS2-2, SARS2-11, SARS2-16, SARS2-31, SARS2-38, SARS2-57, and SARS2-71 (Diamond laboratory, Washington University School of Medicine), IgG-BV480 (goat polyclonal, Jackson Immunoresearch 109-685-098), PD-1-BB515 (EH12.1, BD Horizon 564494), IgA-FITC (M24A, Millipore CBL114F), CD45-A532 (HI30, Thermo 58-0459-42), Bcl6-PE (K112-91, 561522, BD Pharmingen), CD38-BB700 (HIT2, 566445, BD Horizon), Blimp1-A700 (646702, IC36081N, R&D), CD19-BV421 (HIB19, 302234), FoxP3-BV421 (206D, 320124), CD20-Pacific Blue (2H7, 302320), CD27-BV510 (O323, 302836), CD8-BV570 (RPA-T8, 301038), IgM-BV-605 (MHM-88, 314524), HLA-DR-BV650 (L243, 307650), Ki-67-BV711 (Ki-67, 350516), CD19-BV750 (HIB19, 302262), Tbet-BV785 (4B10, 644835), CD3-FITC (HIT3a, 300306), CD71-FITC (CY1G4, 334104), IgD-PE (IA6-2, 348204), CD71-PE (CY1G4, 334106), CXCR5-PE-Dazzle 594 (J252D4, 356928), IgD-PE-Cy5 (IA6-2, 348250), CD4-PerCP (OKT4, 317432), CD14-PerCP (HCD14, 325632), IgD-PerCP-Cy5.5 (IA6-2, 348208), CD38-PE-Cy7 (HIT2, 303516), CD71-PE-Cy7 (CY1G4, 334112), CD19-APC (HIB19, 302212), CD4-Spark 685 (SK3, 344658), CD20-APC-Fire750 (2H7, 302358), CD3-APC-Fire810 (SK7, 344858); all Biolegend.
Validation	All commercial antibodies were validated by their manufacturers as detailed in their product information and titrated in the lab for the indicated assay by serial dilution. We validated mAbs generated in our lab in preliminary ELISAs to SARS-CoV-2 spike, bovine serum albumin, and anti-Ig.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Expi293F (Thermo), Vero E6 (CRL-1586, American Type Culture Collection), Vero-TMPRSS2 (Ding laboratory, Washington University School of Medicine), Vero-hACE2-TMPRSS2 (Graham laboratory, VRC/NIH)
Authentication	All cell lines grew and performed as expected. Expression of TMPRSS2 on Vero-TMPRSS2 was validated by flow cytometry [ref. 17]. No additional specific authentication was performed.
Mycoplasma contamination	Vero lines were tested monthly for mycoplasma and were negative. Expi293F lines were not tested.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used

Human research participants

Policy information about studies involving human research participants

Population characteristics	Study participants demographics are detailed in Extended Data Table 1
Recruitment	Study participants were recruited from the St. Louis metropolitan area by the Washington University Clinical Trials Unit. Potential self-selection and recruiting biases are unlikely to affect the parameters we measured.
Ethics oversight	The study was approved by the Washington University IRB

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	Fine needle aspirates of axillary LNs were flushed from needles with 3 mL of RPMI supplemented with 10% FBS and 100 U/mL penicillin/streptomycin, followed by three 1 mL rinses. Red blood cells were lysed with ammonium chloride buffer, washed twice with PBS supplemented with 2% FBS, 2mM EDTA and immediately used or cryopreserved in 10% DMSO in FBS. Blood samples were collected in EDTA tubes, and peripheral blood mononuclear cells (PBMCs) were enriched by density gradient centrifugation over Ficoll 1077 (GE) or Lymphopure (BioLegend). The residual red blood cells were lysed with ammonium chloride lysis buffer, and cells were immediately used or cryopreserved in 10% dimethylsulfoxide in FBS.
Instrument	Cytek Aurora
Software	Flow cytometry data was acquired using Cytek SpectroFlo and analyzed using FlowJo (Treestar) v10.
Cell population abundance	Single cell sorts and bulk sorts directly into lysis buffer were not amenable to post-sort purity analysis.
Gating strategy	Gating strategies are shown in Extended Data Figure 2

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