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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. EM data were acquired using Leginon v3.2
Data analysis	Flow cytometry data were analyzed using FlowJo v10 and Prism v7 Clonal analyses were performed using pRESTO v0.5.10, blastn v2.7.1, IgBLAST v1.14.0, Change-O v0.4.3, Cell Ranger v3.1.0, and TIgGER v0.3.1 and visualized using circlize package v0.4.8. Clonal rank abundance distributions were produced using Alakazam v0.3.0 SHM frequency was calculated using SHazaM v0.1.11 Gene expression data from scRNAseq was processed and analyzed using Cell Ranger v3.1.0, biomaRt v2.42.0, and Seurat v3.1.1 Phylogenetic trees for responding B cell clones were constructed using IgPhyML v1.1.0 with the HLP19 model. EM data were analyzed using Appion (beta version), Relion v3.0, and UCSF Chimera v1.14 and visualized using Adobe Photoshop v13

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

Raw fastq files and associated RNA sequencing have been uploaded to the NCBI Gene Expression Omnibus (GEO) database under identifiers SRP251458 and GSE148633. Antibody sequences are deposited on GenBank under the following accession numbers: MT200037-MT200636, KEB[P-Z]00000000, KEC[A-Z]00000000,

KED[A-Z]00000000, and KEE[A-F]00000000, available from GenBank/EMBL/DDBJ. The template switch sequences, constant region primers, and isotype-specific internal constant region sequences that were used in these studies are available at: https://bitbucket.org/kleinstein/immcantation/src/master/protocols/AbSeq/. 3D reconstructions are deposited to the Electron Microscopy Data Bank (EMDB) under the following accession numbers: 21703, 21709, 21710, 21711, 21712, 21733, 21734, 21735, 21736, 21737, 21738, 21765, 21809, 21766, 21767, 21768, 21769, 21770, 21771, 21772, 21773, 21774, 21775, 21776, 21777, 21778, 21779, 21780, 21781, 21782, 21783 (participant 4 polyclonal immune complexes); 21739, 21740, 21741, 21742, 21743, 21744, 21745, 21746, 21747, 21748, 21749, 21750, 21784, 21785, 21786, 21787, 21788, 21789, 21790, 21791, 21792, 21793, 21794, 21795, 21796, 21797, 21798, 21799, 21800, 21801, 21802 (participant 5 polyclonal immune complexes); 21713, 21714, 21715, 21716, 21717, 21718, 21719, 21720, 21721, 21722, 21723, 21724, 21725, 21726, 21727, 21728, 21729, 21730, 21731, 21732, 21751, 21752, 21753, 21754, 21755, 21756, 21803, 21804, 21805, 21806, 21807, 21808 (participant 11 polyclonal immune complexes); 21757, 21758, 21759, 21760, 21761, 21762, 21763, 21764 (monoclonal immune complexes). Other relevant data are available from the corresponding author 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

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. 8 participants were enrolled in whom accessible axillary LNs could be located. Sample size for mouse experiments was determined to be adequate based on reproducibility of prior experiments and field standards to avoid unethical use of mice [refs. 2, 3, 13, 14].
Data exclusions	FNA samples were excluded as technical failures when live cell numbers recovered were below 10^4 and when the CD14+ fraction of CD45+ cells was higher than 10%, indicating blood contamination (Fig. 2f, Extended Data Fig. 2m). These criteria were established after collecting 30 FNA samples in preliminary experiments prior to the study described.
Replication	Human samples were collected from 8 participants and mouse experiments used 5-8 mice per experimental condition. All attempts at replication were successful.
Randomization	Different experimental groups were not used except in Fig. 4e. In this experiment, mice were age- and sex-matched and assigned to groups by cage.
Blinding	No blinding was done in this study; 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), IgM-bio (goat polyclonal, Invitrogen H15015), IgG-HRP (goat polyclonal, Jackson ImmuoResearch 109-035-088), IgG-Cy5 (goat polyclonal, Abcam ab97172), PD-1-BB515 (EH12.1, BD Horizon 564494), IgA-FITC (M24A, Millipore CBL114F), CD45-PerCP (2D1, BD Bioscience 347464), IgG-BV480 (goat polyclonal, Jackson Immunoresearch 109-685-098), IgD-SB702 (IA6-2, Thermo 67-9868-42), CD38-BV421 (HIT2, 303526), CD20-Pacific Blue (2H7, 302320), CD27-BV510 (O323, 302836), CD4-BV570 (OKT4, 317445), CD24-BV605 (ML5, 311124), streptavidin-BV650 (405232), CD19-BV750 (HIB19, 302262), CXCR5-PE-Dazzle 594 (J252D4, 356928), CD71-APC (CY1G4, 334108), CD14-A700 (HCD14, 325614), IgM-APC-Cy7 (MHM-88, 314520), Bcl6-PE (7D1, 358504), Ki-67-PE-Cy7 (Ki-67, 350526), CD71-FITC (CY1G4, 334104), CD19-PE (HIB19, 302254), IgD-PerCP-Cy5.5 (IA6-2, 348208), CD4-Alexa 700 (SK3, 344622), CD20-APC-Fire750 (2H7, 302358), CD38-BV605 (HIT2, 303532), CD19-BV421 (HIB19, 302234), CD71-PE (CY1G4, 334106), CD38-PE-Cy7 (HIT2, 303516); all Biolegend.
Validation	All commercial antibodies were validated as described in manufacturers' product information and titrated in the lab for the indicated assay by serial dilution. We validated mAbs generated in our lab in preliminary binding assays to QIV and anti-Ig

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Expi293F (Thermo)
Authentication	The cell line was not authenticated
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination. Growth rates were consistent with manufacturer's published data.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	6-8 week old female C57BL/6J mice were used
Wild animals	The study did not involve wild animals
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	The study was approved by the Washington University IACUC

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Study participants were healthy young adults aged 25-40 years old, 1 female, 7 males
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	PBMCs were isolated using Vacutainer CPT tubes, remaining RBCs were lysed with ammonium chloride lysis buffer, and cells were immediately used or cryopreserved in 10% DMSO in FBS. 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.
Instrument	Cytek Aurora
Software	Flow cytometry data was acquired using Cytek SpectroFlo software, and analyzed using FlowJo (Treestar) v10.
Cell population abundance	Single cell sorts and bulk sorts for clonal repertoire analysis directly into lysis buffer were not amenable to post-sort purity analysis.
Gating strategy	Gating strategies are shown in extended data figures

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