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Last updated by author(s): Oct 27, 2020

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 cytometric analyses were performed with a BD FACSVerse , Violet(2), Blue(4), Red(2) Quantitative PCR was performed with Applied Biosystems QuantStudio™ 3 Real-Time PCR System Pseudovirus luciferase activity was measured with BioTek Synergy H1 Hybrid Multi-Mode Microplate Reader
Data analysis	Flow cytometric data were analysed with FlowJo v10.7.1 All other data were analysed and graphed using GraphPad Prism 8

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

All data related to Fig. 1a, b, Fig. 2b, c, e, f, h, i, Fig. 3, Extended Fig. 1a, d, Extended Fig. 3a, c-f, Extended Fig. 5, Extended Fig. 6b are all included in Resource data and publicly available.

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 sample size calculation was performed in advance. Rather numbers of mice analyzed were based on previous studies and on the numbers required to obtain statistical significance (Ref 14; Channappanvar et al, PMID: 31355779).
Data exclusions	No data were excluded.
Replication	All experiments were repeated at least twice with the same results. However, because of a shortage of mice, some measurements of immune parameters were performed once, with four mice/group.
Randomization	Mice used in this study are inbred. Mice of the same gender and age were distributed randomly into different groups.
Blinding	All observational data (Fig. 2 and extended Fig. 5) and histology analyses (Fig. 1c-j, Extended Fig. 1c, d, Extended Fig. 2, Extended Fig. 4 and Extended Fi. 6a) were obtained by blinded personnel and analyzed in a blinded fashion by a pathologist, to avoid subjective bias.

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	For flow cytometry: Anti-mouse CD3e-BV421 (clone 145-2C11, Cat. No.: 562600), Anti-mouse CD16/32 (clone 93, Cat. No.:101302), Anti-mouse CD4-PercP (clone RM4-5, Cat. No.: 550954), Anti-mouse CD8-APCCy7 (clone 53-6.7, Cat. No.: 100714), Anti-mouse CD220-APC (clone RA3-6B2, Cat. No.: 553092), Anti-mouse Ly6C-PerCP (clone HK1.4, Cat. No.: 128028), anti-mouse Ly6G-FITC (clone 1A8, Cat. No.: 127606), Antimouse CD11b-BV510 (clone M1/70, Cat. No.: 101263), Anti-mouse CD11c-BV421 (clone N418, Cat. No.: 117343), Anti-mouse CD64-PE-Cy7 (X54-5/7.1, Cat. No.: 139314), all from Biolegend, San Diego, CA; Antimouse CD103-APC (clone 2E7, Cat. No.: 17-1031-80), Anti-mouse TNF-FITC (clone MP6-XT22, Cat. No.: 11-7321-82), Anti-mouse IFN-γ-APC (clone XMG1.2, Cat. No.: 25-7311-82), all from eBioscience, San Diego, CA. For IHC: Rabbit monoclonal antibody recognizing SARS-CoV-2 N protein (Cat. No.:40143-R019), Sino Biological US Inc.
Validation	All antibodies were obtained commercially. Specificity and sensitivity were validated by the manufacturers.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Calu-3 (ATCC HTB-55) and Vero E6 cells (ATCC CRL-1586)
Authentication	None of the cells were formally authenticated although they remained sensitive to infection with SARS-CoV-2.

Mycoplasma contamination	Negative for Mycoplasma
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	7-8 weeks old Male and female C57/BL6 K1 8-hACE2 mice
Wild animals	none
Field-collected samples	none
Ethics oversight	All studies approved by the Institutional Animal Care and Use Committee at the University of Iowa.

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	The convalescent plasma donor was a 58 year old female who had molecularly confirmed COVID-19 more than 4 weeks prior to their donation. Following the donation, she tested positive for HLA antibodies so the plasma was not eligible for administration to patients and was diverted to research. Antibody testing (EUROIMMUN SARS-COV-2 ELISA (IgG)) performed on this donor was 9.8, well above the cutoff of 1.1 for a positive result. Neutralization titer using a luciferase-expressing SARS-CoV-2 S protein pseudovirus assay showed that the neutralization IC50 titer was 1:1,480. Control plasma was obtained from an expired plasma unit collected prior to COVID-19 spread in our area.
Recruitment	Written informed consent was obtained from subjects to obtain plasma for participation in this study.
Ethics oversight	High titer convalescent and control plasma was collected with subject consent under IRB (#202003554) and (#201402735) approved protocols respectively that allow use of samples for research.

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	Mice were anesthetized with ketamine/xylazine before dissection for lung harvest. Lungs were perfused transcardially and minced into smaller pieces with a pair of surgical scissors. The minced lungs were left in digestion buffer (1 mg/ml collagenase D (Roche) and 0.1 mg/ml DNase I (Roche)) at 37°C for 30 minutes. Digested tissue was passed through a 70 µm cell strainer and cells were pelleted by centrifugation at 330 RCF for 5 minutes. Cell pellet was resuspended in either FACS buffer or RPMI for peptide stimulation. Fc receptors on cells were blocked and cells were subsequently fixed with Cytofix/ cytoperm followed by intracellular IFNγ and TNF staining after peptide stimulation. Cells were pelleted and resuspended in FACS buffer for analysis.
Instrument	BD FACSVerse , Violet(2), Blue(4), Red(2)
Software	FlowJo v10.7.1
Cell population abundance	Total CD4 T cell frequency in lungs ranged from 3.87% to 8.57% of live single cells (Virus-specific CD4+ T cell frequency in lungs ranged from 0% to 11.15% of CD4 T cells). 0% frequency was found in uninfected mice. Total CD8 T cell frequency in lungs ranged from 1.96% to 11.83% of live single cells (Virus-specific CD8+ T cell frequency in lungs ranged from 0% to 9.37% in CD8 T cells). 0% frequency was found in uninfected mice. B cell frequency in lungs ranged from 4.33% to 11.52% of live single cells Total DC frequency in lungs ranged from 2.10% to 18.32% of live single cells CD103+ DC frequency in lungs ranged from 0.04% to 14.53% of live single cells PMN frequency from lungs ranged from 0.17% to 4.58% of live single cells

Inflammatory monocyte/macrophage frequency in lungs ranged from 0.75% to 18.90% of live single cells
Alveolar macrophage frequency in lungs ranged from 7.65% to 13.5% of live single cells

Gating strategy

Lymphocytes were gated using SSC-A vs FSC-A .Single cells were gated using FSC-A vs FSC-H. B and T cells were gated using B220 and CD3, respectively, as B220+ and CD3+ populations from the single cell population. CD8+ and CD4+ T cells were gated after selection of CD3+ T cell populations. AM and DC were gated on CD11c vs CD64 from the single cell gate as CD11c + CD64+ and CD11c+ CD64- populations respectively. CD103+ DC were gated on the DC population using FCS-A vs CD103. Neutrophils were gated using Ly6G vs CD11c on the single cell gate and were identified as Ly6G+ CD11c intermediate populations. IMMs were gated on the single cell population using Ly6C vs CD11b (Ly6C+CD11b+ population).

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