nature portfolio

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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	-MelTec TIC-Control software was used in the Toponome Image Cycler® MM3 to control the pipetting robot and the microscope system used for data acquisition. -DAB stainings were digitized using a whole slide scanner (Olympus VS120 or Leica Aperio GT 450 DX) -HE scans for spatical sequencing experiments were done with BZ-X800 Analyzer software -Excel 2016 was used for table generation
Data analysis	- The single-nucleus postmortem tissue dataset was processed using cellranger 3.0.1 and Seurat 3.1.4 - Ambient RNA removal was performed for each sample with SoupX 1.4.5 - ImageJ/Fiji version 1.52i was used to pre-process and normalize fluorescence images. - Image visualization was performed using Omero Server software 5.6, Omero figure 4.0.2 (https://github.com/ome/omero-figure) -To identify Interferon regulated genes (IRGs) and IRG signatures, we used Interferome v2.0126 (http://www.interferome.org/interferome/home.jspx) -Interferone score calculate using the AddModuleScore function in Seurat 3.1.4. -Synaptic gene identification was done using the genomic analysis tool SynGO (https://syngoportal.org/index.html) SynGO release 1.1 GTExv7 brain as reference set. -Monocle3 (https://github.com/cole-trapnell-lab/monocle3;112) was employed to determine the cluster and lineage relationships of the oligodedrocytes and OPCs. -Proteomics data , a tissue specific library was constructed using standard settings in library free mode with DIA-NN (version 1.7.16) further post processing was done in R (version 4.1.0) -Fastq output files of the sequenced library, including the spatial barcode, were aligned to the H&E image using Space Ranger software 1.3.0 further postprocessing was done with Seurat package (v4.0), R (version 4.1.0), R Studio (2022.07.1) and Loupe Browser v6

-The representative images shown in the figures were adjusted in brightness and contrast to different degrees in Adobe Photoshop or Adobe Illustrator (Creative Suite version 2021).
-GraphPad Prism 9.2.0 was use for statistics of Interferone related qPCR
-Cartoon images were partially created with Biorender.com

All software used for data acquisition and data analysis has already been published elsewhere. NO new codes have been generated.

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 single-nucleus RNA Sequencing (snRNA-seq) data generated in this study have been deposited in the European Genome-Phenome Archive under the accession number EGAS00001006442. The data are available under controlled access due to the sensitive nature of sequencing data, and access can be obtained by contacting the appropriate Data Access Committee listed for each dataset in the study. Access will be granted to commercial and non-commercial parties according to patient consent forms and data transfer agreements. We have an institutional process in place to deal with requests for data transfer. A response to requests for data access can be expected within 14 days. After access has been granted, the data is available for two years. The processed proteomic and clinical data are available in Supplementary table and Source data file 8129. The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE130 partner repository with the dataset identifier PXD038693. Raw image files of histological stainings, immunohistochemistry, MELC, and spatial transcriptomics generated in this study have been deposited publicly at Zenodo (10.5281/zenodo.7381807)28. The remaining data are available within the article, Extended or Source Data files.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Biological sex was assigned during autopsy according to the presence of the respective sex organs and reported as female or male. Gender was not considered due to the postmortem and retrospective study cohort design.
Reporting on race, ethnicity, or other socially relevant groupings	All relevant and availible medical population characteristics are provided in Source Data File 1. No self-reported data of socially relevant grouping was availible due to the postomortem nature of the study.
Population characteristics	The COVID-19 samples included in this study have been collected in the Department of Neuropathology of Charité - Universitätsmedizin Berlin as part of the COVID-19 autopsy Biobank and the National autopsy Network NATON.
Recruitment	From all clinical autopsies at Charité University medicine Berlin COVID-19 cases were selected according to availibility of cryo tissue and short postmortem-intervall. Patients with concomitant autoimmune diseases, tumors, or infarcts/bleedings in the selected regions were excluded. Controll donors were selected in the same time period accoring to sex, age and medical preconditions and treatments as indictaed in Source Data File 1. All control donors were tested for SARS-CoV-2 to exclude asymptomatic cases. All Autopsies were performed from spring 2020 to summer 2021. For the cerebrospinal fluid (CSF) dataset we performed a retrospective study on COVID-19 patients with lumbar puncture to rule out CNS pathologies such as autoimmune encephalitis or meningitis involving a total n = 38 with availible samples in the archive. No patients were excluded.
Ethics oversight	The study was approved by the local ethic committee at Charité (approval numbers: EA1/144/13, EA2/066/20, EA1/075/19, EA1/76/20) .

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	We did not use statistical methods to pre-determine sample size, but our sample sizes are similar to those reported in previous publications

Sample size	(transcriptome/proteome in lung in https://doi.org/10.1016/j.cell.2021.11.033 or transcriptome in brain https://doi.org/10.1038/s41586-019-0903-2) . Sample size was primarly determined by availibility of sufficient high-quality tissue of the respective anatomical region.
Data exclusions	Following standard procedures three samples (n = 1 mucosa D20 and n = 2 brainstem D12 and D8) were excluded from the proteomics post-processing analysis due to low quality (Source Data File 1, tab patients characteristics) assesed by peptide intensity.
Replication	All experiements have bees sucessfully replicated once.
Randomization	Randomization is not relevant to our study, as sample stratification was performed based on disease duration.
Blinding	Experimenters were blinded to disease group during analysis.

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
☒	☐ Plants

Methods

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

Antibodies

Antibodies used

The following primary and secondary antibodies were used for immunohistochemistry: Anti-SARS-CoV-2 antibody (Synaptic Systems) 1:2000 with Ventana Benchmark XT autostainer (Ventana, Tuscon, Arizona, USA) or rabbit anti–pSTAT1 (Y701) (clone D4A7,1:1000, heat mediated antigen retrieval with TrisEDTA, pH 8.0, cell signaling #7649). Manual pStat1 staining was developed with the Envision + System for mouse and rabbit (Dako) and stainings. All other staining were developed using the Ultra View Universal 3,3´-Diaminobenzidine (DAB) Detection Kit (Ventana, Roche) which contains both secondary antibodies (anti-rabbit and anti-mouse), DAB stain and counter staining reagent.
For immunofluorescence we used:
DAPI Roche Cat# 10236276001, N/A ´1:5000
Laminin Abcam ab11575 ´1:200
goat-anti-rabbit-A555 Invitrogen A21428 ´1:200
CD3-PE Miltenyi Biotec Cat# 130-113-139 ´1:50
CD4-PE Miltenyi Biotec Cat# 130-113-214, RRID:AB_2726025 ´1:50
CD8-PE Miltenyi Biotec Cat# 130-113-720, RRID:AB_2726261 ´1:50
PD1-PE Miltenyi Biotec Cat# 130-120-388, RRID:AB_2752074 ´1:50
CD163 Biolegend 326505 ´1:50
CD49a-PE Miltenyi Biotec Cat# 328304, RRID:AB_1236407 ´1:50
Granzyme B-PE Miltenyi Biotec Cat# 130-116-654, RRID:AB_2727639 ´1:50
CD45-PE Miltenyi Biotec Cat# 130-113-118, RRID:AB_2725946 ´1:50
CD31-PE R and D Systems Cat# FAB3567P, RRID:AB_2279388 ´1:50
HLA-DR,DP,DQ-PE Miltenyi Biotec Cat# 130-120-715, RRID:AB_2752176 ´1:50
GFAP Dako Z 0334 ´1:1000
SMA-FITC Abcam Cat# ab8211, RRID:AB_306359 ´1:50

Validation

Nucleocapsid antibody was validated in an independent study (https://doi.org/10.1016/j.ebiom.2022.104193). All other antibodies are commercially available and have been validated for flow cytometry and/or immunofluorescence/immunohistochemistry by the manufacturers. We have titrated all antibodies for the respective use and tested them in human tissues assessing by visual inspection the pattern of expression in the tissues, expression level, sub-cellular distribution and co-localization with other lineage-defining markers. Positive and negative tissue controls were used in all experiments.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*