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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	Sequencing data was collected using a NovaSeq S4.
Data analysis	Reads were aligned against hg19 (Ensembl: Homo_sapiens.GRch37.74; which included the complete genome sequences for all SARS-CoV-2 strains sequenced from California before March 24, 2020) using Drop-seq Tools (v.1.13) using STAR_2.5.4. Count matrices were assembled with dropEst_0.6.8. R version 3.6.1 was used for downstream analysis with the following packages: Seurat_3.1.1, sctransform_0.2.0, ggplot2_3.2.1, Matrix_1.2-17, reshape2_1.4.3, tidyverse_1.3.0, nichenetr_0.1.0, pheatmap_1.0.12, scater_1.13.27, SingleR_0.99.13, ggpubr_0.2.3, FlexDotPlot_0.1.1, ggrepel_0.8.1, Hmisc_4.2-0, factoextra_1.0.5, circlize_0.4.8, Matrix.utils_0.9.7, SummarizedExperiment_1.15.9, SingleCellExperiment_1.7.11, dplyr_0.8.3, plyr_1.8.4. Python version 3.7.4 was used with packages: scvelo_0.1.23, scanpy_1.4.4, anndata_0.6.22, pandas_0.25.1, matplotlib_3.1.1 Ingenuity Pathway Analysis (Qiagen) was used for gene pathway enrichment analysis and upstream regulator discovery.

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

Processed count matrices with de-identified metadata and embeddings are available for download from the Covid-19 Cell Atlas (https://www.covid19cellatlas.org/#wilk20) hosted by the Wellcome Sanger Institute. Processed data is also available for viewing and exploration on the publicly accessible cellxgene platform by the

Chan Zuckerberg Initiative at https://cellxgene.cziscience.com/d/Single_cell_atlas_of_peripheral_immune_response_to_SARS_CoV_2_infection-25.cxg/. Raw sequencing data are available at the NCBI Gene Expression Omnibus (accession number GSE150728). Requests for additional materials can be made via email to the corresponding authors.

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	7 patients with confirmed COVID-19 (1 patient sampled twice); 6 healthy controls. Sample size was not pre-determined; all available specimens were processed for sequencing.
Data exclusions	Cells with fewer than 1,000 or more than 15,000 unique transcript reads were removed from analysis as low quality cells or potential doublets. Any cell that contained more than 75 genes per 100 sequenced UMIs were removed as potential doublets. These cells would add unwanted noise to downstream analysis. Any cell from which >20% of sequencing reads aligned to either mitochondrial genes or ribosomal RNA (RNA18S5 and RNA28S5) were also removed from analysis, as these have been shown to be low quality cells. All exclusion criteria were pre-established for this data analysis.
Replication	Given the small number of available specimens, we were unable to perform technical replicates on individual samples.
Randomization	Samples were not allocated into experimental groups.
Blinding	Blinding to COVID-19 status was not possible as the patient-derived vs. control-derived samples were acquired from different locations.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	All available demographic characteristics for COVID-19 patients and healthy controls are listed in Table 1 and Extended Data Table 1. The seven patients profiled were male, aged 20 to >80 years of age. We collected samples between two and sixteen days following symptom onset; healthy controls were asymptomatic, four male and two female, and aged 30–50 years.
Recruitment	Eligible participants were adults (age >18 yo) admitted to Stanford Hospital (wards or ICU) with RT-PCR-confirmed SARS-CoV-2. All patients with documented COVID-19 in Stanford hospital were offered enrollment.
Ethics oversight	This study was approved by the Stanford Institutional Review Board IRB-28205 and IRB-26571.

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