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Reporting Summary

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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	Fungal microbiome was analyzed using the Illumina MiSeq Next generation sequencing platform. All flow cytometry data were collected by FACS Diva Software. ELISA data were collected by softmax pro 6.4.
Data analysis	Fungal microbiome analysis performed with QIIME v1.9.1 and the R packages Phyloseq (1.26.1), and Vegan (2.5-5) in R version 3.5.2 . The dendrogram performed by SNPRelate R package and circlize R package . Flow cytometry data analyzed by FlowJo V10. Statistical analysis analyzed by R and Graphpad Prism V9.5.1 software.

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

16S and ITS sequencing data are available in the NCBI Sequence Read Archive (SRA) with the accession code PRJNA732432. The single-cell transcriptome and ATAC sequencing data have been deposited in NCBI Gene Expression Omnibus (GEO) under the accession number GSE196990.

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	Two-hundred sixteen plasma, 65 PBMC and 20 fecal samples were obtained from collections at Weill Cornell Medicine. Sample sizes were based on previous experience (Ref 29, 34) and were optimally utilized to extract as much information as possible based on resource availability to provide enough statistic robustness, reproducibility. For mouse, five or more mice per group were used in each experiment.
Data exclusions	No mice or human subject data were excluded from the analysis.
Replication	Findings in all ELISA experiments from human and mouse samples have been replicated from two independent experiments to confirm technical reproducibility. All mouse experiments in Fig.2,3 and 5 were performed at least twice.
Randomization	Randomization was not preformed with human samples as this is not an approach taken in observational studies. Patients were stratified by disease severity using disease severity scores, mild/moderate and severe. Disease scores were according with oxygen requirements with mild/moderate disease defined as SARS-CoV-2 infection and <6 liters noninvasive supplemental oxygen to maintain SpO2 >92%, and severe disease defined as SARS-CoV-2 infection requiring hospitalization and received >6 liters supplemental oxygen or mechanical ventilation. Mouse experiments were preformed by random assignation of age- and sex-matched mice in experimental groups at the beginning of each experiment.
Blinding	The investigators were blinded during sample and data collection in human study. In general, for mouse investigators were not blinded, as the investigator who planned the experiments, also performed them. However, we performed quantitative measurements and unbiased computational analyzes.

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

The staining antibodies for flow cytometry were purchased from Thermo Fisher Scientific, Biolegend or BD Biosciences. Dead cells were excluded with eBioscience Fixable Viability Dye eFluor 506 (Thermo Fisher Scientific, #65-0866-14, 1;1000) or Fixable Viability Stain 700 (BD Horizon, #564997,1;1000) during surface staining. Fluorophore-conjugated antibodies against human antigens: FITC-Cy7 anti-CD158e(NKB1)(DX9) (BD Pharmingen, #555966,1:80), PE anti-CD158b(CH-L) (BD Pharmingen, #559785,20), PerCP-Cy5.5 anti-CD158a (/h/g) (HP-MA4) (Invitrogen, #45-1589-42 ,80), PE-Vio770 anti- CD159a (NKG2A) (REA110) (Miltenyi Biotec, #130-113-567,80), APC anti-CD158i (KIR2DS4)(JJC11.6) (Miltenyi Biotec, #130-092-681,20), APC-H7 anti-CD3(SK7 (Leu-4)) (BD Biosciences, #641406,30), PE-Cy7 anti-CD3(SK7 (Leu-4)) (BD Biosciences, #341101,60), FITC anti-CD3(SK7 (Leu-4)) (BD Biosciences, #349201,20), BV421 anti-CD56 (NCAM16.2) (BD Horizon, #562751,400), V500C anti-CD45(2D1) (BD Biosciences, #647450,40), BV605 anti-CD16 (3G8) (BD Horizon, #563172,20), PE-Cy7 anti-CD19(J3-119) (Beckman Coulter / Immunotech, #IM3628U,40), PE-Cy7 anti-CD56(N901(NKH-1)) (Beckman Coulter / Immunotech, #A51078,100), APC anti-CD11b(D12) (BD Biosciences, #340936,40), APC-H7 anti-CD14(MphiP9) (BD Biosciences, #643077,40), CD124 anti-CD124(G077F6) (BioLegend, #355014,50), APC-H7 anti-CD8(SK1) (BD Biosciences, #64140,40), PE-Cy7 anti-CD4(SK1) (BD Biosciences, #348799,40), BV421 anti-CD19(HIB19) (BD Horizon, #562440,40), BV605 anti-CD5(UCHT2) (BD Horizon, #563945,100), APC-H7 anti-CD20(L27) (BD Biosciences, #641405,40), FITC anti-CD34 (AC136) (Miltenyi, #130-113-178,100), Pacific Blue anti-CD49f (Biolegend)(GoH3, #313620,200), PE anti-CD90 (5E10) (Biolegend, #328110,100), PE/cy7 anti-CD38 (HIT2) (Biolegend, #303516,100), APC/cy7 anti-CD45RA (HI100) (Biolegend, #304128,400) and lineage markers (

Biotin anti-CD20 (2H7) (Biolegend, #302350,1:100), Biotin anti-CD3 (SK7) (Biolegend, #344820,1:100), Biotin anti-CD16 (3G8) Biolegend, #302004, 1:100, Biotin anti-CD56 (5.1H11) Biolegend, #362536,1:100 and Biotin anti-CD14 (M5E2), Biolegend, #301826, 1:100)
Fluorophore-conjugated antibodies against mouse antigens: BUV395 anti-CD11b (M1/70) (BD Bioscience, #563553,1:400), BV605 anti-CD4 (RM4-5) (BioLegend, #100548, 1:200), BV650 anti-CD45 (30-F11) (BioLegend, #103151,1:200), BV711 anti-Ly-6G (1A8) (BioLegend, #127643
,1:200), and APC-Cy7 anti- TCRβ (H57-597) (BioLegend, #109220,1:200).The antibodies for immunofluorescence staining were used; Donkey anti-goat MPO (R&D System), Goat anti-rabbit Histone H3 (abcam), APC anti-Ly-6G (1A8) (BioLegend), donkey anti-goat 488 (Invitrogen) and donkey anti-rabbit 555 (Invitrogen).

Validation

All antibodies were well validated commercial clones and routinely QC'ed by the manufacturer. Please refer to the spec sheets on the respective vendors' website for technical information and detail by searching the catalog numbers provided above. Additionally, all antibody were titrated for optimal dilution in the assay and confirmed cell staining worked before experiments. Antibodies that were labeled/conjugated in house undergo quality control before its use for experiments.

Animals and other organisms

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

Laboratory animals	5-7-week-old wild-type SPF C57BL/6 mice (JAX:000664) and 129S1/SvImJ mice (JAX:0002448) were purchased from Jackson laboratory. All mice used in these experiments were housed with a 12-hr light/dark cycle per day at a temperature of 72±2℉, and 30-70% relative humidity.
Wild animals	No wild animals used in the study.
Field-collected samples	No field-collected samples used in the study.
Ethics oversight	Blood, fecal, lung and colon samples were obtained following Institutional-Review-Board-approved protocols from Weill Cornell Medicine and Icahn School of Medicine at Mount Sinai. All animal experiments were approved and are in accordance with the Institutional Animal Care and Use Committee guidelines at Weill Cornell Medicine and Icahn School of Medicine at Mount Sinai.

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	Demographic information is included in Extended Data Table 1,Table 2 and Table3.
Recruitment	Cohort1: Participants were recruited from patients hospitalized at New York Presbyterian Hospital from March to June 2020. Cohort2: Participants were recruited from the inpatient division of New York-Presbyterian Hospital and the Weill-Cornell Medicine pulmonary and post-ICU clinics between March 2020 and March 2021. Some subjects were followed after recovery from mCOVID-19 or sCOVID-19 and were partitioned into an early convalescent group (2-4 months following admission) and a late convalescent group (4-12 months following admission). Cohort3: Ten COVID-19 patients that were treated as inpatients at Weill Cornell Medicine New York Presbyterian Hospital, between January and April 2021. Sample size was not statistically predetermined. Ten SARS-CoV-2 negative individuals were used as uninfected controls. All patients were classified in mCOVID-19 and sCOVID-19 according with oxygen requirements with mCOVID-19 defined as SARS-CoV-2 infection and <6 liters noninvasive supplemental oxygen to maintain SpO2 >92%, and sCOVID-19 defined as SARS-CoV-2 infection requiring hospitalization and received >6 liters supplemental oxygen or mechanical ventilation.
Ethics oversight	This research was reviewed and approved by the Institutional Review Board of Weill-Cornell Medicine (New York Presbyterian and Lower Manhattan hospitals) (#IRB 20-03021645 and #IRB 20-03021671). Informed consents were obtained from all enrolled patients and healthcare workers by trained staff and records maintained in our research database for the duration of our study.

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	For human study, human peripheral blood was collected in Na-heparin. Polymorphonuclear leukocytes and monocytes were collected by density gradient centrifugation of PBMCs, erythrocytes were lysed with BD Pharm Lyse. Peripheral blood was washed in PBS, lysed in 1× BD Pharm Lyse, and washed again in PBS. PBMC cell suspensions were prepared with Ficoll-Paque following the manufacturer's protocol. Cells were stored briefly in storage media (10% heat-inactivated fetal bovine serum/1% L-glutamine/1% pen-strep) before staining with antibody cocktails for flow cytometry. For single-cell library preparation, frozen peripheral blood mononuclear cells (PBMCs) were thawed in a 37°C water bath and subsequently washed with RPMI before being centrifuged. An aliquot of the PBMCs was stained with 7-AAD (Biolegend) and CD34 microbeads (Miltenyi) and isolated using a magnetic column (Miltenyi) following the manufacturer's instructions. The positively-selected cells were then stained with a panel of antibodies, see method, and CD34+ cells were then sorted from the positive fraction, and viable PBMCs were sorted from the PBMC aliquot using a BD FACSAria cell sorter at ratios of 1:5-1:20. For mouse study, (1) Colons were isolated, opened longitudinally, washed and removed fecal contents and fat, and then cut into pieces. Such obtained tissues were rinsed thoroughly in Hank's Balanced Salt Solution (HBSS; Thermo Fisher Scientific) medium supplemented with 2 mM EDTA,15mM HEPES and 1mM DTT and gently shaken for 10 min at 37°C, followed washing, mincing and incubating in a RPMI medium containing 5% FBS, 0.5 mg/ml collagenase type VIII (Sigma), 5 U/ml DNase (Roche), 100 IU/ml penicillin and 100 µg/ml streptomycin (Thermo Fisher Scientific) for 60 min and filtered through a 70µm-nylon mesh cell strainer. After tissue dissociation the samples were re-suspended in a 40% Percoll solution (GE Healthcare), centrifuged at 950g for 20 min. Isolated cells at the bottom of the tube were resuspended in PBS containing 1% fetal bovine serum and used for flow cytometry analysis. (2) The middle and superior lobes of the right lung were harvested after perfusion and minced, then placed for 45 min at 37°C in 5 ml a RPMI medium containing 5% FBS, liberase (100 µg/ml; Roche) and deoxyribonuclease type 1 (DNase I) (50 µg/ml; Sigma), 100 IU/ml penicillin and 100 µg/ml streptomycin (Thermo Fisher Scientific). The cells were recovered by disruption through a 100-µm nylon cell strainer before being centrifuged at 300g for 5 min. Lysis of red blood cells was performed for 2 min at room temperature before a final centrifugation at 300 g for 5 min and resuspension of the remaining cell pellet in 2 ml of PBS containing 1% fetal bovine serum. (3)Blood samples were harvested by cardiac puncture from a euthanised mouse. Cell suspensions were washed with RBC lysis (BioLegend), followed centrifuging and resuspending in PBS containing 1% fetal bovine serum.
Instrument	Human and mouse samples were acquired on BD FACSCanto and LSRFortessa (BD Biosciences), respectively. CD34+ cells were then sorted from the positive fraction, and viable PBMCs were sorted from the PBMC aliquot using a BD FACSAria cell sorter.
Software	Flow cytometry data were collected by BD Diva and further analyzed by FlowJo V10 (TreeStar)
Cell population abundance	CD34+ cells were sorted from the positive fraction, and viable PBMCs were sorted from the PBMC aliquot at ratios of 1:5-1:20.
Gating strategy	All gating were determined after FSC/SSC gating on lymphocytes population. FSC-A vs FSC-H and SSC-A vs SSC-W gates were used to gate singlets. Only CD45 positive viable cells were included for further analysis. Additional gates to identify myeloid cell subsets are available in Extended Figure 1a,b and the previous paper (Rendeiro, A.F. et al.,Life Sci Alliance. 2020).

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