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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	No software was used for data collection
Data analysis	Droplet libraries were processed using 10x Genomics Cell Ranger 4.0.0. Reads were aligned to the GRCh38 human genome. Scrublet (v0.2.3 version) was used for the identification of doublets, on each separate sample using the raw counts. The python package scanpy was used for analysis

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

All data accession codes have been provided.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	The present study involved the Discovery cohort, two separate validation cohorts and samples used for the functional experiments. As male individuals have been associated with increased severity of COVID-19 we selected samples from male individuals for our discovery cohort. Subsequently, our validation cohorts were comprised by both male and female subjects.
Population characteristics	Patients were recruited according to the disease status. No other covariate characteristics were taken into consideration.
Recruitment	118 individuals were enrolled in the study of who 95 were COVID-19 patients and 23 controls. Ethics approval was obtained from the Ethics Committee of Evangelismos General Hospital (approval number: 360, Study title: COVID-19 and Immunological profile) and all procedures were carried out according to the Declaration of Helsinki. A written informed consent was obtained from all patients or the patient's next of kin.
Ethics oversight	Ethics Committee of Evangelismos General Hospital, Athens, Greece.

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	The sample size was not pre-determined. For this study, all available samples at the time were processed.
Data exclusions	Doublets and low quality cells were excluded from analysis.
Replication	sc-RNA seq findings from the discovery cohort were validated by Real-time PCR amplification and Flow cytometric analysis in two separate cohorts (Validation Cohort A and Cohort B)
Randomization	No randomizing of patients was performed.
Blinding	Not applicable for this study.

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

Methods

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

Antibodies

Antibodies used	Mouse anti-Human CD45, APC-H7, 2D1/560178, BD Pharmigen. Mouse anti-Human CD64, PC7, 10.1/561191, BD Pharmigen.

anti-human CD15 (SSEA-1), APC, HI98/301908, BioLegend.
Anti-human CD55 FITC, JS11KSC2.3/IM2725, Immunotech/Bechman Coulter.
Anti-Hu CD45 Pacific Orange, 2D1/PO-160-T100, exbio.
Anti-Hu CD3 Pacific Blue, 10.1/561191, exbio.
Anti-Hu CD4 PerCP-Cy, MEM-241 / T9-359-T100 , exbio.
Anti-Hu CD8 APC-Cy, APC-Cy, MEM-31 / T4-207-T100, exbio.
Anti-Hu CD19 PE-Cy, LT19 / T7-305-T100, exbio.
Anti-Hu CD55 FITC,MEM-118/1F-230-T100, exbio.

Validation

The following antibodies were validated at the amount of 5 µl per 100 µl of whole blood sample:
Mouse anti-Human CD45, APC-H7, 2D1/560178, BD Pharmigen.
Mouse anti-Human CD64, PC7, 10.1/561191, BD Pharmigen.
anti-human CD15 (SSEA-1), APC, HI98/301908, BioLegend.

The following antibodies were validated at the amount of 4 µl per 100 µl of whole blood sample:
Anti-Hu CD45 Pacific Orange, 2D1/PO-160-T100, exbio.
Anti-Hu CD3 Pacific Blue, 10.1/561191, exbio.
Anti-Hu CD4 PerCP-Cy, MEM-241 / T9-359-T100 , exbio.
Anti-Hu CD8 APC-Cy, APC-Cy, MEM-31 / T4-207-T100, exbio.
Anti-Hu CD19 PE-Cy, LT19 / T7-305-T100, exbio.

Anti-human CD55 FITC, JS11KSC2.3/IM2725, Immunotech/Bechman Coulter for detection of CD55 on monocytes was validated at 10 µl per 100 µl of whole blood sample.

Anti-Hu CD55 FITC,MEM-118/1F-230-T100, exbio for detection of CD55 on T and B cells was validated at 20 per 100 µl of whole blood sample.

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	100 µl of whole blood sample were added to the correct amounts of antibodies.
Instrument	FACS Canto II flow cytometer (BD Biosciences)
Software	FACSDiva software (version 8.0.1) for Monocyte facs analysis and FlowJo version 8 for CD4 and CD8 T cell and B cells facs analysis.
Cell population abundance	Sorting was not performed.
Gating strategy	For CD55 expression on monocytes, CD45 cells were gated and CD64 were selected for gating of CD55 positive cells. For CD55 expression on CD4 and CD8 T cells and B cells CD45 cells were gated for selection of CD4, CD8 and CD16 populations. CD4CD55, CD8CD55 and CD16CD55 were then gated.

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