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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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ 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
<i>Give P values as exact values whenever suitable.</i> |
| ☐ | ☒ 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

Data analysis

Confocal and STED super-resolution microscopy
Confocal images were processed, 3D rendered and analyzed with Leica Application Suite X software (LASX; version 3.5.5.19976)
STED images were de-convolved with Huygens Professional software (Scientific Volume Imaging B. V.; version 19.10)
Surface plasmon resonance analysis
Binding kinetics were determined by fitting of the experimental curves with the Langmuir 1:1 model according to standard procedures; data analyses were performed with Biacore™ Insight Evaluation Software v2.0.15.12933
Molecular modeling
The binding site of mannose molecules was determined aligning the MBL2 structure to the crystal structure of rat mannose protein A (PDB code 1KX1). Reference distances (~ 40 Å) between mannose molecules were computed in PYMOL (version 1.5.0.5, <https://pymol.org/2/>). Putative binding sites of MBL2 with SARS-CoV-2 were computed using the program ALMOST (version 2.2.0). Almost is available for the most common Unix-based operating systems, including Linux and Mac OS X. Almost is distributed free of charge under the GNU Public License, and is available both as a source code and as a binary executable from the project web site at <http://www.open-almost.org>.
Genetics
For genetic studies, case-control allele-dose association tests were performed using used for data plink (version 1.07 and version 1.9). Haplotype analysis was performed using beagle (version 3.3 and version 5.1) and R (version 4.5). All of them are freely available.
Statistical analysis
Prism GraphPad software (version 8.0, www.graphpad.com) and R (version 4.5, <https://www.r-project.org/>) were used for the statistical analyses.

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 supporting the findings of this study are present in the main text and/or in supplementary information. Additional data are available from the corresponding authors. For genetic studies, the dataset for cases is publicly available at the European Bioinformatics Institute (www.ebi.ac.uk/gwas) under accession numbers GCST90000255 and GCST90000256 [12], whereas the dataset for controls is deposited in the Genotypes and Phenotypes database (dbGaP; <https://www.ncbi.nlm.nih.gov/gap/>), under the phs000294.v1.p1 accession code [50].

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

Sample size was not pre-determined by statistical analysis. In the infection experiments with the cell lines, three independent experiments in triplicate were performed, whereas with the human primary respiratory cells we obtained 3 independent donors which were sufficient to determine the permissivity to SARS-COV-2 infection, as in the infected untreated condition, viral titers increased by 4 log₁₀ from 24 h to 72 h post-infection.

For studies on human data, all available data were used and no calculation was performed on sample-size.

In addition, our sample sizes are similar to those reported in previous publications^{12,65,71}.

Data exclusions

GraphPad Prism software was used to analyze the data. ROUT test or Rosner's test were applied to identify outliers. No outliers were identified and all data were included in the statistical analysis concerning Figures 1-5 and extended Data Figures 1, 2, 4. For Figure 6c and d, 3 outliers were excluded, based on Rosner's test.

Replication

Two-four experiments per type were performed with reproducible results. All replicates were used for the analysis.

Randomization

For experiments with cells, randomization was not necessary, since all groups derived from the same cell culture.

Blinding

For binding assays, IF and infection experiments, blinding was not considered relevant because the analysis was not operator-dependent.

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used

For ELISA binding assay and complement deposition assay the following primary antibodies were used: rabbit polyclonal IgG anti human PTX3 (produced in-house, Lot 23, 1:5000); rabbit polyclonal IgG anti-human C1q (Dako, Cat. A0136, Lot 20071886, 1:5000);

recombinant rabbit monoclonal IgG anti-human MBL (clone EPR18381-156, Abcam, Cat. Ab190834, Lot GR3189741-3, 1:5000); mouse monoclonal IgG anti-human PTX2/SAP (clone 910119, R&D Systems, Cat. MAB1948, Lot CIVT0115061, 1:5000); rabbit polyclonal IgG anti-human CRP (Merck, Cat. 235752, Lot 3179228, 1:5000); rabbit polyclonal IgG anti-human SC5b-9 (Complementech, Cat. A227, Lot 5e, 1:2000); mouse monoclonal IgG anti-human CL-K1 (clone Hyb-15, 1:2000; produced in-house and provided by Peter Garred); mouse monoclonal IgG anti-human Ficolin-2 (clone FCN219, 1:2000; produced in-house and provided by Peter Garred). The following secondary antibodies were used: HRP-linked donkey anti-rabbit IgG (GE Healthcare, Cat. NA934V, Lot 12219044, 1:5000); HRP-linked sheep anti-mouse IgG (GE Healthcare, Cat. NA931V, Lot 16982037, 1:5000). For confocal image analysis and STED super-resolution microscopy, the following primary antibodies were used: rabbit polyclonal IgG anti-SARS-CoV-2 Spike protein (Proteintech, Cat. 28867-1-AP, Lot 88993, 1:500); mouse monoclonal IgG anti-human Cytokeratine-14 (clone LL02, Pro-Sciences, Cat. 33-168, Lot 26009-2102, 1:200); rat monoclonal IgG anti-human MBL (clone 8G6, Hycult Biotech, Cat. HM1035, 1:100); rat monoclonal IgG anti-human MBL (clone 14D12, Hycult Biotech, Cat. HM1038, 1:100). The following secondary antibodies were used: donkey anti-rabbit IgG Alexa Fluor 488 (ThermoFisher Scientific, Cat. A-21206, 1:2000); donkey anti-rat IgG Alexa Fluor 594 (ThermoFisher Scientific, Cat. A-21209, 1:2000); donkey anti-mouse IgG Alexa Fluor 647 (ThermoFisher Scientific, Cat. A-31571, 1:2000).

Validation

Primary antibodies used for ELISA, binding assays, complement deposition assays and microscopy analysis are commercially available and validated by vendors for human proteins. References are reported for each of them in the manufacturer's website. Rabbit polyclonal IgG anti-human PTX3 was produced in-house by immunizing rabbits with recombinant human PTX3 and purified by immunoaffinity on PTX3-conjugated Sepharose-CNBr columns. The antibody was validated for ELISA in our laboratory (Brunetta et al., Nat. Immunology, 2021.(22)19-24). Mouse monoclonal IgG anti-human CL-K1 and anti-human Ficolin-2 were produced in-house and validated for ELISA (Bayarri-Olmos R et al., Front. Immunol. 9:2238. doi: 10.3389/fimmu.2018.02238; Munthe-Fog et al., Scand J Immunol. 2007 Apr;65(4):383-92).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Eukaryotic cell lines:

Source:

Vero, BS CL101, Istituto Zooprofilattico, Brescia, Italy

Vero E6, ATCC CRL-1586

HEK-293T, ATCC CRL-3216

Calu-3, NovusPharma

Expi293F, cat A14527, ThermoFisher Scientific

Primary cells

Primary bronchial epithelial cells were isolated from mainstem human bronchi, derived from individuals undergoing lung transplant.

Authentication

Cells were verified by gene expression analysis. Species were confirmed by isozyme analysis (NP, G6PD, PEPB, MD and AST). Bronchial epithelial cells are not in the database of commonly misidentified cell lines.

Mycoplasma contamination

Cells in use in our laboratories are routinely checked for mycoplasma contamination. Only mycoplasma-free cells were used.

Commonly misidentified lines (See ICLAC register)

No commonly misidentified cell lines were used in the study.

Human research participants

Policy information about studies involving human research participants

Population characteristics

For association analyses, we investigated a total of 2,000 individuals. These included: i) 332 patients with severe COVID-19, which was defined as hospitalization with respiratory failure and a confirmed SARS-CoV-2 viral RNA PCR test from nasopharyngeal swabs. Patients were recruited from intensive care units and general wards at two hospitals in the Milan area, i.e., the Humanitas Clinical and Research Center, IRCCS, in Rozzano, Italy (140 patients); and San Gerardo Hospital, in Monza, Italy (192 patients); ii) 1,668 controls from the general Italian population with unknown COVID-19 status. The analysis of MBL plasma levels was performed in a cohort of 40 patients. We included all males and non-pregnant females, 18 years of age or older, admitted to Humanitas Clinical and Research Center (Rozzano, Milan, Italy) between March and April, 2020 with a laboratory-confirmed diagnosis of COVID-19. For all subjects, data about age and sex were collected, and used as covariates in the association analyses. All samples were genotyped using Affymetrix 6.0 GeneChip (data available at: Genotypes and Phenotypes database, dbGaP; <https://www.ncbi.nlm.nih.gov/gap/>, under the phs000294.v1.p1 accession code) or the Illumina Global Screening Array (data available at: the European Bioinformatics Institute, www.ebi.ac.uk/gwas under accession numbers GCST90000255 and GCST90000256). An extensive quality control step was performed before proceeding with the imputation process. In the post-imputation steps, we only retained those SNPs with $R^2 \geq 0.6$ and minor allele frequency (MAF) $\geq 1\%$, and considered for the downstream association analysis only those SNPs localized in the MBL2 region (the gene +/-500 kb). The final set of analyzed variants comprised 3,425 SNPs. HECB isolation. The UOC Genetica Medica of the IRCCS Istituto Giannina Gaslini houses a large collection of primary bronchial cells banked as frozen aliquots in the frame of the Primary Bronchial Cell Repository supported by the Italian Cystic Fibrosis Foundation. Epithelial cells are obtained from mainstem human bronchi, derived from individuals undergoing lung transplant. Among the donors there are subjects undergoing lung transplantation for pathologies like cystic fibrosis, emphysema, pulmonary hypertension, idiopathic fibrosis, sarcoidosis, bronchiectasis, COPD, alpha-1 antitrypsin deficiency or surfactant dysfunction. For the present study, primary cells from 3 individuals were chosen: BE37: 67-yr male; emphysema

BE63: 63-yr old female; idiopathic fibrosis
BE177: 64-yr old male; idiopathic fibrosis

Recruitment

Cases are all characterized by a severe form of COVID-19, defined as hospitalization with respiratory failure. This comprises the use of oxygen supplementation or mechanical ventilation (supplemental oxygen therapy only, noninvasive ventilatory support, invasive ventilatory support, or extracorporeal membrane oxygenation). Information about the SARS-CoV-2 infection status in the control participants is not known, however this concern is mitigated by the fact that the presence of susceptible persons in the control group would only bias the tests toward the null.

Ethics oversight

Approvals for the project were obtained from the relevant ethics committees (Humanitas Clinical and Research Center, reference number, 316/20; the University of Milano-Bicocca School of Medicine, San Gerardo Hospital, reference number, 84/2020). Written informed consent was obtained from the study patients at each center. The collection of bronchial epithelial cells and their study to investigate airway epithelium physiopathology were specifically approved by the Ethics Committee of the Istituto Giannina Gaslini following the guidelines of the Italian Ministry of Health (registration number: ANTECER, 042-09/07/2018). Each patient provided informed consent to the study using a form that was also approved by the Ethics Committee. Viral isolation from clinical samples and use for research purposes was approved by San Raffaele Hospital IRB within the COVID-19 Biobanking project "COVID-Biob" (34 /int/2020 19/March/2020. ClinicalTrials.gov Identifier: NCT04318366). Each patient provided informed consent.

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