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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	MO Affinity Analysis (version 2.1.23333), Tecan Spark Control (version 2.1), Attune NxT Software (version 3.1.1243.0), Tanon Gelcap (version 5.22), QuantStudio Design & Analysis Software (version 1.51), Nikon NIS-Elements viewer (version 4.20), OpenSPR Software (version 3.11.6949.28944)
Data analysis	Flowjo (version 10.0.7), GraphPad Prism (version 8.0), Volocity Demo (Version 6.1.1), Microsoft Office Standard 2010 (version 14.0.4760.1000), Nikon NIS-Elements AR (version 4.00.12) , TraceDrawer (Version 1.8, Nicoya Lifesciences)

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

The data supporting the findings of this study are available from the corresponding authors upon written request.

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	No sample size calculations were performed. The sample size (n) of each experiment is provided in the corresponding figure captions in the main manuscript and supplementary information files. Sample sizes were chosen to support meaningful conclusions. (PubMed:32494007, 33082294)
Data exclusions	No data were excluded.
Replication	The MST, SPR or peptide-cholesterol binding assays were repeated at least three independent times, all attempts at replication were successful. All infection experiments were repeated at least two independent times, all attempts at replication were successful. The western blot and immunoprecipitation assays were repeated at least two independent times, all attempts at replication were successful. The confocal assays performed at least two independent times, whereas there are at least 3 images for each cell type, all attempts at replication were successful.. The qPCR was performed one time in triplicate all attempts at replication were successful. The flow cytometry assasys were repeated at least two independent times, all attempts at replication were successful.
Randomization	Allocation into non-treated or treated conditions was random.
Blinding	Technicians were not blinded to group allocation though they were not informed of expected treatment results before and during experimentation. Students blinded their experiments through random numbering of treatment groups and the code was unblinded after 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
☒	☐ 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	α-Tubulin for immunoblotting (Supplier:SigmaAldrich, Cat: T9026, clone: DM1A, Lot: 078M4796 V) Donkey-anti-rabbit antibody conjugated to Alexa Fluor 488 for FACS (Supplier: Biolegend, Cat: 406416, clone: poly4064, Lot: B310664) SR-B1 antibody for immunoblotting and immunohistochemistry (Supplier: abcam, Cat:ab217318, clone: EPR20190, Lot:GR325004814) ACE2 antibody for immunoblotting and immunohistochemistry (Supplier: abcam, Cat: ab108252, clone: EPR4435(2), Lot: GR145000-26) ACE2 antibody for FACS (Supplier: Proteintech, Cat: 21115-1-AP, Lot: 00087165) PE anti-His antibody for FACS (Supplier: Biolegend, Cat: 362603, clone: J095G46, Lot: B311762) APC anti-SR-B1 for FACS (Supplier: Biolegend, Cat: 363208, clone: m1B9, Lot: B246109) Spike antibody for immunoblotting (Supplier: Genetex, Cat: GTX632604, clone:1A9, Lot:42219) SARS-CoV-2 S1 antibody for confocal microscopy (Supplier: Sino biological, Cat: 40150-T62-COV2, Lot: HD14SE0223)
Validation	SARS-CoV-2 S1 antibody used in our studies are validated with presence and absence of infection controls. SR-B1 antibody for immunoblotting was validated in parallel western blotting confirmed bands at expected molecular weights, and depletion by siRNA of target. Optimal Ab concentration is titrated in-house by immunofluorescence, western blot, flow cytometry and imaging flow

cytometry, and referenced in the manuscript.
Further validation information of the antibodies by the manufacturer is as follows:
APC anti-SR-B1 for FACS (Supplier: Biolegend, Cat: 363208, clone: m1B9, Lot: B246109) - guaranteed for FACS on website (https://www.biolegend.com/fr-ch/products/apc-anti-human-cd36l1-scarb1-sr-bi-antibody-15058);
PE anti-His antibody for FACS (Supplier: Biolegend, Cat: 362603, clone: J095G46, Lot: B311762) - guaranteed for FACS on website (https://www.biolegend.com/en-us/products/pe-anti-his-tag-antibody-9861);
ACE2 antibody for FACS (Supplier: Proteintech, Cat: 21115-1-AP, Lot: 00087165) - guaranteed for FACS on website (https://www.ptglab.com/products/ACE2-Antibody-21115-1-AP.htm) and several published applications on website (https://www.ptglab.com/products/ACE2-Antibody-21115-1-AP.htm);
ACE2 antibody for immunoblotting and immunohistochemistry (Supplier: abcam, Cat: ab108252, clone: EPR4435(2), Lot: GR145000-26) - guaranteed on website (https://www.abcam.com/ace2-antibody-epr44352-ab108252.html) and several published applications on website (https://www.abcam.com/ace2-antibody-epr44352-ab108252.html);
Donkey-anti-rabbit antibody conjugated to Alexa Fluor 488 for FACS (Supplier: Biolegend, Cat: 406416, clone: poly4064, Lot: B310664) - guaranteed on website (https://www.biolegend.com/en-us/products/alexa-fluor-488-donkey-anti-rabbit-igg-minimal-x-reactivity-9380) and several published applications on website (https://www.biolegend.com/en-us/products/alexa-fluor-488-donkey-anti-rabbit-igg-minimal-x-reactivity-9380);
α-Tubulin for immunoblotting (Supplier:SigmaAldrich, Cat: T9026, clone: DM1A, Lot: 078M4796 V) - guaranteed on website (https://www.sigmaaldrich.com/catalog/product/sigma/t9026) and several published applications on website (https://www.sigmaaldrich.com/catalog/product/sigma/t9026).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	293T (CRL-3216), Vero E6 (CRL-1568), MDCK (CCL-34) and Hepa 1-6 (CRL-1830) cell lines were from the American Type Culture Collection (ATCC, Rockville, MD, USA). Huh-7 (0403) was from Japanese Collection of Research Bioresources.
Authentication	Cells are purchased from ATCC or Japanese Collection of Research Bioresources.
Mycoplasma contamination	293T, Vero E6, MDCK and Hepa 1-6 cell lines were from the American Type Culture Collection and Huh-7 was from Japanese Collection of Research Bioresources were authenticated by the distributor prior to shipping.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Immunohistochemical staining for ACE2 and SR-B1 was performed on the paraffin-embedded human normal organ tissue microarray. The human normal organ tissue microarray was purchased from Biomax (MNO661).
Recruitment	No human research participants were recruitment.
Ethics oversight	No human research participants were recruitment, and ethics statement was not needed.

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	Cells were harvested and resuspended in 100 µL phosphatebuffered saline (PBS) containing 0.2% bovine serum albumin and incubated with the antibodies in dark at room temperature. After 15 minutes, the cells were washed twice with PBS and analyzed on the flow cytometer. For cell surface ACE2 analysis, the cells were incubated with anti-ACE2 antibody for 30 minutes on ice before washing twice followed by incubation with a secondary Alexa Flour 488-conjugated anti-IgG Ab . After 15 minutes, the cells were washed twice with PBS and analyzed on the flow cytometer.
Instrument	Attune NxT Acoustic Focusing Cytometer (Invitrogen by Thermo Fisher Scientific)

Software	Attune NxT Software (version 3.1.1243.0) and Flowjo (version 10.0.7)
Cell population abundance	cell lines (100%)
Gating strategy	FSC-H vs. SSC-H - gated on cells FSC-H vs. FSC-W - gated on singlets SSC-H vs. corresponding dyes channel - gated positive on unstained negative control sample.

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