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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 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	Western blots were visualized by chemiluminescence on an Amersham Imager 600 (GE Healthcare). Flow cytometry samples were run on a LSR Fortessa (BD Biosciences) running BD FACSDiva v8.0.
Data analysis	Statistical comparisons were made using GraphPad Prism 7 (GraphPad Software) or SigmaPlot 14.0. RNAseq data from TCGA, GTEx, CCLE, and other studies were aligned to the cancer-tissue transcriptome assembly using GNU v3 parallel and Salmon v0.12.0. Splice junctions were visualised using the Integrative Genome Viewer v2.4.19. RNAseq reads were adapter trimmed and filtered for minimal 35nt sequences using Trimmomatic v0.39. Single cell RNA-seq reads were mapped with HISAT2. We used the DropSeq:picard toolbox (v2.3.0) to recapitulate processing of HCL samples as documented on 'https://github.com/ggjlab/HCL'. Amplicon sequencing reads were quality and adapter trimmed in pairs using cutadapt v1.18 and aligned with STAR v2.7.1a. Phylogenetic alignments were conducted with the MUSCLE aligner. Flow cytometry data were analyzed with FlowJo v10 (Tree Star Inc.). All code used in this study has been previously described and cited within the Methods and is also available by request to the authors (G.K.).

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 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

Data supporting the findings of this study are available within the article and its supplementary information files and from the corresponding author upon reasonable request. Publicly available data were downloaded from the following databases: The Cancer Genome Atlas (TCGA) Research Network (http://cancergenome.nih.gov), The Genotype-Tissue Expression (GTEx) Project (https://gtexportal.org/home); and the Broad Institute Cancer Cell Line Encyclopedia (CCLE) consortium (https://portals.broadinstitute.org/ccle). Additionally, RNA-seq data from individual studies (GSE147507 and GSE134355) were downloaded from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo). Source data are provided with this paper.

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 determined empirically, based on the variability of the assays in our previous work. For example, the variability of NHBE cells to interferon treatment was based on prior results published in Major et al., (PMID: 32527928) and the transcriptional variability (determined by RT-qPCR) of CV-1, R9ab and MCA-38 cell cultures was based on prior results published in Ng et al., (PMID: 31729316).
Data exclusions	No data were excluded.
Replication	To ensure reproducibility, all experiments included 2-3 technical replicates within each independent experiment and most experiments (indicated in the article) were repeated at least twice (independent biological replicates). All attempts at replication for all experiments were successful.
Randomization	Not applicable – the biological samples tested here were homogeneous cell lines and no pre-experiment differences required random allocation.
Blinding	Not applied – the behavior of the biological samples tested here (cell lines) is unaffected by the an unblinded design.

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	The following primary antibodies were used: anti-human ACE2 (ab15348, Abcam), anti-FLAG (F1804-50UG, clone M2, Sigma-Aldrich), HRP-conjugated anti-mouse IgG (#7076, Cell Signaling Technology) or anti-rabbit IgG (#7074, Cell Signaling Technology) and HRP-conjugated anti-human actin (ab49900, Abcam).
Validation	Antibodies were validated by the manufacturers. The anti-ACE2 rabbit polyclonal antibodies were validated by the manufacturer

Validation	using a variety of human, mouse and rat cell lines and primary tissues (https://www.abcam.com/ace2-antibody-ab15348.html). Specific binding can be blocked with a human ACE2 peptide. The anti-FLAG antibody monoclonal antibody M2 is widely used (over 5,000 publications) (https://www.sigmaaldrich.com/catalog/product/sigma/f1804).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HHEK293T (ATCC), A549 (ATCC), SCC-4 (ATCC), SCC-25 (ATCC), Vero (ATCC), CV-1(ATCC), MDCK (originally provided by Dr John McCauley, The Francis Crick Institute), R9ab (ATCC) and MCA-38 cells (originally provided by Dr. Giorgio Trinchieri, NCI, Bethesda, MD) were obtained from and verified as mycoplasma free by the Cell Services facility at the Francis Crick Institute. Primary human bronchial epithelial cells were purchased from Lonza.
Authentication	Established cell lines were validated by DNA fingerprinting by the Cell Services facility at the Francis Crick Institute
Mycoplasma contamination	Established cell lines were verified as mycoplasma-free by the Cell Services facility at the Francis Crick Institute
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study.

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	HEK293T cells were trypsinized into a single cell suspension and used directly for flow cytometry.
Instrument	Samples were run on a LSR Fortessa (BD Biosciences).
Software	Data were collected using FACSDiva v8.0 (BD Biosciences) and analyzed with FlowJo v10 (Tree Star Inc.).
Cell population abundance	HEK293T cells are a homogeneous cell line.
Gating strategy	HEK293T cells are a homogeneous cell line and only the proportion of cells expressing GFP was enumerated. No additional gating was used.

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