nature portfolio

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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	BD FACSDiva V9 and FACS Canto II were used for acquisition of the flow cytometry data. Seahorse Wave Desktop v2.6.0 was used for acquisition of the extracellular flux data. StepOne V2.3 was used for acquisition of the qRT-PCR data. Skanlt Software 7.0.0.50 was used for acquisition of the growth curves and biofilm data. SoftMax Pro v7.0.3 was used for acquisition of the carbon source assimilation data. E-MAVEN v0.10.0 and MAVEN 2011.6.17 were used for acquisition of metabolomics data.
Data analysis	E-MAVEN v0.10.0 and MAVEN 2011.6.17 were used to quantify metabolite signals. FlowJo v10 was used for cell gating and signal quantification. scRNA-Seq data was analyzed with R programming and Seurat. Statsistical analyses were performed with Graph Prism, V10.1.1. Codes/Scripts used in this study are included in this manuscript under “MucA and DNPPS bioinformatic analysis”. Scripts and files used in this study are available on Zenodo (ID: 16945235).

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

To ensure access to data and materials associated to this study, readers can contact Dr. Sebastián A. Riquelme (sr3302@cumc.columbia.edu). The transcriptomic datasets used in this study are available in public repositories. The transcriptomic datasets included in this analysis are as follows: 1) Primary cells/cell lines: GSE35391, GSE268909, GSE127696, GSE138167, GSE154905, GSE154802; 2) Human scRNA-Seq: GSE193782; 3) mouse scRNA-Seq: GSE203352. All data generated during this study are included in this article as the Source Data file. Source data are provided with the paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	NA
Reporting on race, ethnicity, or other socially relevant groupings	NA
Population characteristics	NA
Recruitment	NA
Ethics oversight	NA

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	Sample sizes were determined by power analysis based on effect sizes observed in previous experiments, with a statistical power of 80% and a significance level of 0.05.
Data exclusions	A few data points were excluded based on pre-established criteria using the ROUT detection method with a Q = 1%.
Replication	To ensure reproducibility, both biological and technical replicates were included where appropriate. Biological replicates consisted of independent mice, independently established cell cultures, and/or experiments performed on different days using independent samples and controls. The number of independent experiments and biological replicates for each experiment is provided in the corresponding figure legends. All replication attempts were successful.
Randomization	Samples and animals were randomly allocated into experimental groups.
Blinding	Blinding was not performed during data acquisition or analysis because the study involved objective experimental measurements in cell culture and animal models.

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
☒	☐ Plants

Methods

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

Antibodies

Antibodies used: Antibody used in this study includes: anti-mouse CD45 AF700 (Biolegend, Cat 103128), anti-mouse CD11c Bv605 (Biolegend, Cat 117333), anti-mouse SiglecF (BD Bioscience, Cat 562680), anti-mouse CD11b AF594 (Biolegend, Cat 101254), anti-mouse MHC II APC/Cy7 (Biolegend, Cat 107628), anti-mouse Ly6C Bv421 (Biolegend, Cat 128032), anti-mouse Ly6G PerCP/Cy5.5 (Biolegend, Cat 127616), anti-mouse Epcam FITC (Biolegend, Cat 118208), anti-mouse F4/80 (Biolegend, Cat 123114), anti-DHODH (Proteintech, Cat 14877-1-AP), anti-PTEN antibody [EPR9941-2], anti-CFTR (sc-376683).

Validation: Target specificity and functional validation for each antibody was performed by the manufacturer, and validation statements for each antibody can be found on the manufacturer's website.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): 1. Primary HBEC were obtained from UNC Marsico Lung Institute. Sex: Both Male and Female derived cells were used for the study.
2. IB3-1 and C38 cells were obtained from Dr. Zeitlin (National Jewish Health) and Dr. Alice Prince (Columbia University).
3. 4T1 (WT/WT), 4T1 DHODH KO and Rescue cell lines were provided by Dr. Jiri Neuzil (Czech Academy of Sciences, Czech Republic, and Griffith University, Australia).

Authentication: Cell identity was verified by the provider and western blot assays.

Mycoplasma contamination: Cell lines used were negative for Mycoplasma contamination.

Commonly misidentified lines (See ICLAC register): NA

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals: All animal assays were performed following institutional guidelines at Columbia University Irving Medical Center. Mice experiments were approved by protocol IACUC AABE8600. 8–10-week-old C57bl/6 (000664) WT mice (20-25grs) were obtained from The Jackson Laboratories. These mice were housed in humidity-controlled conditions at 18-23 degrees Celsius, with 12 hour light/dark cycles.

Wild animals: No wild animals were used in this study.

Reporting on sex: Equal numbers of males and females mice were used in each animal experiment (50/50).

Field-collected samples: No field-collected samples were used in this study

Ethics oversight: All animal experiments were approved by the Columbia University Institutional Animal Care and Use Committee (IACUC) and conducted in accordance with approved protocol AABE8600.

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

Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA

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 the cells harvested from infected mice: bronchoalveolar lavage fluid (BAL) was collected by intratracheal lavage and lung tissue was collected and homogenized through 40 um cell strainers. Red blood cells were lysed hypotonically in ACK lysis buffer, and the remaining cells were extracellularly stained in buffered saline and fixed. Samples were immediately analyzed or stored at 4C in the dark.
Instrument	BD LSRII and BD Fortessa were used for the analysis of the human and mouse immune cell population.
Software	BD FACSDiva v9 was used for data acquisition and FlowJo v10 was used for data analysis.
Cell population abundance	No post-sort fractions were collected in this study. All populations were analyzed as percentage and total cell number.
Gating strategy	Cells were gated using forward scatter and side scatter. Single cells were gated using forward scatter (area and height), live cells were gated using forward scatter and DAPI. Gating strategy was based on a set of commonly used markers validated by our scRNA-Seq studies: “recruited neutrophils 1” were gated as DAPI-CD45+Epcam-CD11bhighSiglecF-CD11c-MHCII-F4/80-Ly6G+Ly6C+; “recruited monocytes 1” as DAPI-CD45+Epcam-CD11bhighSiglecF-CD11c-MHCII-F4/80-Ly6G-Ly6Clow; “recruited monocytes 2” as DAPI-CD45+Epcam-CD11bhighSiglecF-CD11c-MHCII-F4/80-Ly6G-Ly6Chigh; “resident neutrophils” as DAPI-CD45+Epcam-CD11bhighSiglecF-CD11c-MHCII-F4/80-Ly6G+Ly6Clow; and “recruited monocytes 2” as DAPI-CD45 +Epcam-CD11blowSiglecF-CD11c-MHCII-F4/80-Ly6G-Ly6Chigh.

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