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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	HOMMER, HISAT, FlowJo v10.
Data analysis	R v3.4, LiblineaR R package v2.10-8, limma R package v3.32.5, doSNOW R package v1.0.16, foreach R package v1.4.4, raster R package v2.6-7, fields R package v9.6, sp R package v1.2-6.

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 upon request. 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 bulk RNA-seq datasets has been deposited in the Gene Expression Omnibus (GEO) database, under GEO accession numbers GSE113530 and GSE117975.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	80 female mice from 20 different lines of new developed Collaborative Cross and one C57BL/6J mouse were used for sequencing. Our analysis with 20 CC lines in Nachshon et al. 2016 (Frontiers in genetics, DOI: 10.3389/fgene.2016.00172) show that 20 lines should be sufficient to provide informative associations. We also used 13 mice from 6 CC lines for FACS validation; this number were chosen since CPM-inferred cell-to-phenotype correlations can be already observed with 13 mice.
Data exclusions	None
Replication	Not relevant, since our mice had a large variety of genetic backgrounds. However we did noticed that the gene expression profiles of mice from the same strain was usually more similar than the gene expression profiles of mice from different strains.
Randomization	Allocation of mice from each CC strain into the infected, PBS-control and untreated groups was random.
Blinding	Investigators were not blinded to group allocation. However, the main data contained a set of comprehensive gene expression profiles (with more than 20000 genes). We used the same method on each one of these full profiles and analyzed the results. We could not influence the results since initially we did not know the prediction for the samples. In the FACS analysis we mostly compared mice within each group and not between them.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Antibodies

Antibodies used	The following antibodies were used used for FACS: AF-700-anti-mouse I-A/I-E (BLG-107621; Biolegend) 1:50; PE-anti-mouse Ly-6G (BLG-127607; Biolegend) 1:100; FITC-anti-mouse Ly-6C (BLG-128005; Biolegend) 1:100; PE/Cy7-anti-mouse/human CD11b (BLG-101215 Biolegend) 1:100; APC-anti-mouse CD64 (FcγRI) (BLG-139305; Biolegend) 1:50; VioBlueAnti-mouse CD45 (130-102-430; Miltenyi) 1:100; anti-mouse CD16/32 (14-0161 eBioscience) 1:100.
Validation	All the antibodies used for the FACS were similar to the antibodies used by Yu, Y.-R.A., et al. (PloS 2016). We also tested non specific binding/background by comparing each antibody to its isotype control and unstained cells. All antibodies were previously validated and shown efficiency in mice; the relevant information from the manufacturers' websites: AF-700-anti-mouse I-A/I-E (BLG-107621; Biolegend): https://www.biolegend.com/en-us/products/alexa-fluor-700-anti-mouse-i-a-i-e-antibody-3413 PE-anti-mouse Ly-6G (BLG-127607; Biolegend): https://www.biolegend.com/en-us/products/pe-anti-mouse-ly-6g-antibody-4777

FITC-anti-mouse Ly-6C (BLG-128005; Biolegend):
https://www.biolegend.com/en-us/products/fitc-anti-mouse-ly-6c-antibody-4896

PE/Cy7-anti-mouse/human CD11b (BLG-101215 Biolegend):
https://www.biolegend.com/en-us/products/pe-cy7-anti-mouse-human-cd11b-antibody-1921

APC-anti-mouse CD64 (BLG-139305; Biolegend):
https://www.biolegend.com/en-us/products/apc-anti-mouse-cd64-fcgammari-antibody-7874

VioBlueAnti-mouse CD45 (130-102-430; Miltenyi):
https://www.miltenyibiotec.com/_Resources/Persistent/8fb245a80ee24b578ce3a5ccd6aaa4e97c130b83/DS_CD45-VioBlue%2Bmouse_30F11.pdf

anti-mouse CD16/32 (14-0161 eBioscience):
https://www.thermofisher.com/order/genome-database/generatePdf?productName=CD16/CD32&assayType=PRANT&detailed=true&productId=14-0161-81

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	All experiments were conduct on female mice of the new developed Collaborative Cross (CC). We used mice from 20 different CC lines (111A, 1488A, 1912A, 2126A, 21B, 2513A, 2750A, 3348A, 3912A, 4438A, 5000A, 5001A, 5003A, 5004A, 5010A, 5021A, 5022A, 5023A, 57B, 72A) and the C57BL/6J strain, all aged 7 to 10 weeks.
Wild animals	The study did not involved wild animals
Field-collected samples	The study did not involved samples collected from the field

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	Mice were sacrificed using CO2 asphyxiation and the lung tissue was dissociated into single-cell suspensions using lung dissociation kit (130-095-927 MACS, Miltenyi Biotec). 2x10^6 cells were taken to measure the portion of CD45 positive cells in the single cell suspension . CD45 positive cells were enriched using CD45 microbeads (130-052-301 MACS, Miltenyi Biotec) following Miltenyi protocol. Cells were stained for FACS analysis -We Used 2x10^6 cells per sample. Cells were incubated in blocking solution containing 5% normal mouse serum, 5% normal rat serum, and 1% FcBlock (eBiosciences, San Diego, CA) in PBS. Cells were then stained with antibodies on ice for 30 minute. After staining, cells were washed and fixed with 0.4% paraformaldehyde in PBS.
Instrument	SONY SH800
Software	Flowjo v10. Software
Cell population abundance	N.A.
Gating strategy	The examined cell were collected from Flu infected mice or from MOCK infected mice. Cells were gated based on their FSC/SSC (cells with FSC larger than 250K or SSC larger than 250K were expelled) and their viability (FSC-H/FSC-A). Gating boundaries were chosen based on control (unstained cells) and by comparing to cells extracted from control mice (mock infected with PBS)

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