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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	For metabolomics: Thermo Scientific Xcalibur v. 4.3 (Thermo Fisher Scientific). For RNA-seq: NovaSeq Control Software 1.6.
Data analysis	For metabolomics: Raw data were processed using Progenesis QI version 1.0 (NonLinear Dynamics) for feature alignment, nontargeted signal detection, and signal integration. Targeted processing of a subset of known metabolites was conducted using TraceFinder version 5.0 (Thermo Fisher Scientific). For RT-qPCR: Primer3 v. 0.4.0 For RNA-seq: BWA version 0.7.15-r1142-dirty. R version 3.5; edgeR v3.15; GenomeView v2600; PhyloPhlAn v3.0.51; USEARCH v8.1 For FACS data: FlowJo 10.8.0; R version 4.1 For bacteriological data and mouse data processing as well as statistical analysis, GraphPad Prism version 9.0 was used.

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

RNA-sequencing data is available on the Sequence Read Archive (SRA) under BioProject ID PRJNA838968. Source data are provided with this paper. Human microbiome data was accessed through data deposited on the SRA under BioProject ID PRJNA436359.

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 statistical tests were used to determine sample size. Power analysis was not formally conducted, however sample sizes were chosen based on previous experience and published literature. For in vitro and in vivo experiments, a minimum of 2 were independently performed to ensure data reproducibility.
Data exclusions	We did not exclude any data.
Replication	Each experiment was replicated at least two times in two different moments. Reproducibility was observed in all the experiments.
Randomization	In all in vitro experiments, experimental treatment group allocation was random. Allocation of mice was random in all in vivo experiments.
Blinding	The investigators were not blinded to allocation during the experiments and outcome assessment. Data collection and analysis were not blinded due to the nature of the experimental designs in this study, but unbiased quantifications were applied to obtain the results.

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	CD45 BUV805 (30-F11) BD Biosciences cat:748370 RRID: AB_2872789; Ly6G BV605 (1A8) BioLegend cat: 127639 RRID: AB_2565880; and Ly6C efluor450 (HK1.4) Invitrogen cat: 48-5932-82 RRID: AB_10805519 All antibodies were used at a 1/400 dilution.
Validation	CD45 BUV805 (30-F11) (BD Bioscience): Immunol Rev. 1979; 47:63-90. Ly6G BV605 (1A8): Fleming TJ, et al. 1993. J. Immunol. 151:2399. Ly6C efluor450 (HK1.4): 1. Jutila MA, et al. 1988. Eur. J. Immunol. 18:1819. 2. Cerwenka A, et al. 1998. J. Immunol. 161:97.

Animals and other organisms

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

Laboratory animals	C57BL/6N female or male ASF mice aged 6-10 weeks and maintained in the germ-free facility at the Broad Institute in gnotobiotic conditions. These mice were bred in-house but orginally purchased from Taconic. We also utilized male wild-type C57BL/6J mice (strain # 000664) and iNOS knockout mice in the same background (strain #002609; B6.129P2-Nos2tm1Lau/J), both from Jackson Laboratories, aged 8-10 weeks.
Wild animals	No wild animals were used in this study.
Field-collected samples	No field-collected samples were used in this study.

Ethics oversight	All mouse experiments were performed according to protocols approved by the Institutional Animal Care and Use Committees (IACUC) of the Broad Institute and complied with all relevant ethical regulations.

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	Epithelial cells were first stripped via mechanical disruption in RPMI (Gibco) containing 2 mM EDTA (Corning) and 1% fetal bovine serum (Gibco) for 45 min. Lamina propria lymphocytes were then obtained via subsequent mechanical disruption of remaining tissue in RPMI (Gibco) containing 0.5 mg/mL Collagenase VIII (Sigma) and 20% fetal bovine serum (Gibco) for 1 hr. The following conjugated antibodies were used to identify cellular markers: CD45 BUV805 (30-F11), Ly6G BV605 (1A8), and Ly6C efluor450 (HK1.4).
Instrument	Cytek Biosciences: Cytek Aurora
Software	FlowJo 10.8.0
Cell population abundance	No sorting was conducted for the experiments in the manuscript
Gating strategy	The primary gate used was to gate on cells expressing CD45 that were negative for a viability dye (Zombie-UV BioLegned 423107). Cells were then gated for FSC-A versus viability to help exclude debris which tend to sit close to 0 on FSC-A/ Next cells were gated to exclude doublets by gating FSC-A vs. FSC-H and excluding cells that do not fall on the diagonal. Finally, cells were gated for the markers of interest in Ly6G vs. Ly6C.

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