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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	Wallac EnVision Manager 1.12 was used for collecting HTS assay data. Agilent MassHunter Quantitative Analysis software (version B.05.00) was used for quantifying the lipid species measured in the study. SR-Lab version 6500-0091-E was used for auditory tests. BD FACSDiva version 6.1.3 was used for collection flow cytometry data.
Data analysis	Statistical data analysis was performed using R version 3.4.3 and GraphPad Prism version 7. FlowJo version 10.4.2 was used for analyzing flow cytometry data. CIMAGE was used for processing proteomic data.

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

We have provided Supplementary Table 1 for our complete proteomic data, in which UniProt IDs are provided for the proteins detected in the experiments. We have provided Supplementary Table 2 for the abundance of all the lipid species measured in the metabolomics experiments.

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	No statistical analysis was performed to determine sample sizes. The sample sizes in the study were chosen based on prior knowledge on the intrinsic variability of the experiments performed.
Data exclusions	No data were excluded.
Replication	All the experiments except 4-weeks compound treatment study (Fig. 5) were performed at least twice and the trends were reproducible between experiments. 4-weeks compound treatment study was performed once because of the limited access to 8-month-old mice used in the study.
Randomization	The mice used in the study were not randomized. Since we used inbred mice, we expect their genotypes, metabolite levels and immune responses to be nearly identical.
Blinding	Investigators were not blinded to the study except for the auditory tests performed in the study, in which only the IDs of the mice were given to the investigator without treatment information. Additional experimental data are precise measurements of enzyme activity, metabolites, protein, and cytokines and are not subjective measurements of animal behavior.

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	ABHD12(–/–) mice are available upon request.

Antibodies

Antibodies used	Anti-CD8 depletion antibody - Supplier: Leinco / Clone: YTS-169 / Product Number: C2442 / Lot 0118L465 Rat IgG2b isotype control antibody - Supplier: Leinco / Clone: 1-2 / Product Number: I-1034 / Lot 1216L230 For the Anti-CD8 and Rat IgG2b, 0.5 mg of antibody per mouse was used for treatment one day prior to infection and 4 days post-infection. No secondary antibody was used in the study.
Validation	Depletion in C57/BL6 mice was verified via flow cytometry, using a different antibody clone (53.6-7) from BioLegend

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK294T, HEK293F, THP-1, and VeroE6 cells were all from ATCC
Authentication	The cell lines used have been authenticated by ATCC by checking cellular morphology, karyotyping, short tandem repeat profiling, and cytochrome C oxidase assay testing.
Mycoplasma contamination	All the cell line used were tested negative for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.

Animals and other organisms

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

Laboratory animals	8-11 week-old C57BL/6J mice as well as ABHD12(+/+) and ABHD12(–/–) mice were used for compound studies. 8-month-old C57BL/6J mice as well as ABHD12(+/+) and ABHD12(–/–) mice were used for the four-week dosing study and auditory test. Both male and female mice were used in the study.
Wild animals	No wild animals were used in this study.
Field-collected samples	No field-collected samples were used in this study.

Human research participants

Policy information about studies involving human research participants

Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, gender, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*

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 in vivo specific killing assay, spleen or lung samples were harvested and pressed through a 100 micron filter to create single cell suspensions. Red blood cells were lysed with 0.145 M NH4Cl. Samples were resuspended in 2ml FACS buffer. 5 ul 7-AAD (Invitrogen, cat#: 00-6993-50, lot #: 1910547) was added to 400 ul of the spleen sample and all of the lung sample. low cytometry was then performed.
Instrument	BD Biosciences - LSR II
Software	BD FACSDiva version 6.1.3 software was used during collection. Analysis was performed using FlowJo 10.4.2

Cell population abundance	CTV-labeled cells were rare during recovery, so about 10 million events per sample were ran. CTV labeling efficacy was determined prior to injecting the cells, and autofluorescence in the CTV channel is known not to be an issue.
Gating strategy	1) Single cell gate: FSC-H / FSC-W 2) Single cell gate: SSC-H / SSC-W 3) Cell gate: FSC-A / SSC-A 4) Live cell gate: FSC-A / 7-AAD 5) CTV gate: FSC-A / CTV 6) CTV+ Cells were used to make the count / CTV histogram

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