nature portfolio

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Last updated by author(s): Aug 7, 2026

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	Experimental data were generated in-house using standard laboratory instrumentations. No in-house code or software used.
Data analysis	cryoSPARC (4.7.1); AlphaFold3; PyMOL (2.5.7); ChimeraX (1.7); ProteinLynx Global Server (3.0.2); HDExaminer (3.4.2); HDXBoxeR; TraceDrawer; Octet Analysis Studio; GraphPad Prism (10.6.1); Fiji/ImageJ (2.14); FlowJo (10). No in-house code or software 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 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

All data supporting the findings of this study, including the raw data underlying the figures, are provided as Source Data files with this 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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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	For all in vitro and cell assays, 3 or more technical replicates were applied. The experiments were all repeated at least 2 times or more. For most of the assays, the data shown were biological replicates. If each biological repeats showed same trend but hard to combine, the representative data was shown instead. For in vivo study, the mice number for each group was minimized based on pilot study. Since the phenotype was quite obvious, only n = 4/5 was used.
Data exclusions	No data was excluded.
Replication	For all in vitro and cell assays, 3 or more technical replicates were applied. The experiments were all repeated at least 2 times or more. For most of the assays, the data shown were biological replicates. If each biological repeats showed same trend but hard to combine, the representative data was shown instead.
Randomization	For in vitro assays, there is no common randomization processes applied. To minimize covariates, methods were used during each repeat, such as using samples from different aliquots, apply different layout of sample distribution, etc. For in vivo study, mice in the same cage were subjected to different experimental groups randomly.
Blinding	During data analysis, experimental conditions were coded using anonymized labels (e.g., A1, A2, A3).

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	Anti-mouse-HRP (CST, #7076); Anti-rabbit-HRP (CST, #7074); Anti-GSDMD (CST, #97558); Anti-GSDME (Abcam, #ab215191); Anti-Pro-

IL-1β (CST, #12242); Anti-IL-1β, p17 (CST, #83186); Anti-Caspase-1 (AdipoGen, #AG-20B-0048); Anti-Caspase-4 (Santa Cruz, #sc-56056), Anti-Caspase-5 (CST, #4429), Anti-Caspase-2 (BD, #611022), Anti-Caspase-3 (CST, #9665), Anti-Caspase-9 (CST, #9502), anti-Ly6G-APC (BD, #560599), anti-CD11b-eFluor450 (eBioscience, #48-0112-80), anti-CD19-BV605 (Biolegend, #115539), anti-F4/80-BV785 (Biolegend, #123141), anti-Ly6C-BV650 (Biolegend, #128049).

Validation: All the antibodies were confirmed based on the manufacturer's website.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	All cells were obtained from ATCC.
Authentication	All cell lines were purchased and used from ATCC.
Mycoplasma contamination	Cell lines were routinely tested for mycoplasma contamination and were negative.
Commonly misidentified lines (See ICLAC register)	There is no commonly misidentified lines.

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	C57BL/6J
Wild animals	N/A
Reporting on sex	Only female mice were used.
Field-collected samples	N/A
Ethics oversight	All animal experiments were approved by the IACUC of Cleveland Clinic (protocol #2481) and were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and institutional guidelines.

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

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	Immune cells from the peritoneal cavity were collected by flushing twice with 7 mL of FACS buffer (PBS with 1% FBS). The cells were pre-incubated with Fc and monocyte blockers, then stained with the primary antibodies for 30 min. After staining, the cells were washed and fixed with 4% PFA.
Instrument	Sony ID7000

Software	FlowJo (10)
Cell population abundance	Because we harvested only suspension cells from the peritoneal cavity, there was no obvious contamination from adherent tissues. The collection was performed carefully, with no major blood vessels disrupted. No obvious red blood cell contamination or pink cell pellet was observed during collection. Therefore, the collected cells are expected to consist predominantly of tissue-resident immune cells, with no significant contamination from circulating blood immune cells.
Gating strategy	All the gating boundaries were confirmed with single stain and FMO controls. Strategy: (1) single cell gating using FSC-A/H. (2) live cell gating by UV/Far-red negative. (3) CD19 negative to remove B cells. (4) neutrophil gating using CD11b & Ly6G. The rest were collected for next step. (5) LPM gating using CD11b & F4/80, and the rest were collected for next step. (6) monocyte and the rest CD11b positive cells gating using CD11b & Ly6C.

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