nature portfolio

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Last updated by author(s): Nov 22, 2022

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	XF-96 analyzer (Seahorse Bioscience) was used to perform energetics studies. Agilent 6410B (Agilent Technologies) interfaced with a 1200 Series HPLC quaternary pump (Agilent Technologies) with MassHunter Quantitative B.07.01.sp was used to acquire and quantify targeted mass spectrometry metabolite data. Dionex U3000 RSLC in front of a Orbitrap Eclipse (Thermo) or Easy-nLC 1200 system in front of a Q-Exactive HF or Orbitrap Fusion (Thermo) were used to acquire proteomics data. A 7890A GC system (Agilent Technologies) combined with a 5975C Inert MS system (Agilent Technologies) were used to measure global metabolite levels.
Data analysis	GraphPad Prism 9 was used to perform statistical analysis and plot results. Extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) were analyzed by Wave (Agilent Technologies, Inc.). Proteomics data processing was carried out in Skyline 21.1, using either the sum of MS1 isotopic peak areas or the sum of fragment ion areas for each peptide PRM. Proteomics data were searched with Proteome Discoverer 2.4 using the Sequest. node. PyMOL 2.5 was used to build structural models.

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

Data will be available upon acceptance.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design whether sex and/or gender was determined based on self-reporting or assigned and methods used. Provide in the source data disaggregated sex and gender data where this information has been collected, and consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, 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.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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	3-9 mice per group were used for animal studies. No prior sample size calculation was performed. Group sizes for animal studied were established considering previous experience with yields of cell numbers and biological matrices.
Data exclusions	No data exclusions were made.
Replication	Results of experiments are based on representative results of at least 3 independent bone marrow derived macrophage cultures (for in vitro experiments)/cohorts of mice (for in vivo experiments) following the same protocol. All findings were replicated successfully.
Randomization	Animals were randomized by age for bone marrow extractions. For in vivo studies, mice were also randomized by bodyweight and sex prior to challenge with LPS.
Blinding	No blinding was performed.

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

Methods

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

Antibodies

Antibodies used	anti-Mouse antibodies for immuno blot: from R&D systems: Human/Mouse/Rat PDHX Affinity Purified Polyclonal Ab (RRID:AB_1964669). from Millipore: Rabbit Anti-Lipoic Acid Polyclonal Antibody, Unconjugated (RRID:AB_212120) from Santa Cruz Biotechnology: Mouse monoclonal anti-TOM20 (RRID: AB_2207538) also used for immunoprecipitation: Anti-Pyruvate Dehydrogenase E2 (Abcam) (RRID:AB_2827534), Recombinant Anti-Lipoamide Dehydrogenase (Abcam)(RRID:AB_2732908)
Validation	Antibody validation was according to manufacturer's website

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 and NOS2 deficient mice (B6.129P2-Nos2tm1Lau/J purchased from the Jackson Laboratory) were maintained and bred in the Frederick National Laboratory Core Breeding Facility, aged 8-10 weeks at start of experiments.
Wild animals	Wild animals were not used
Reporting on sex	Sex based analyses were not performed.
Field-collected samples	Field collected animals were not used
Ethics oversight	Mice were used in accordance with an approved protocol by the NCI Frederick Institutional Animal Care and Use Committee

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