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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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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

To collect data, we used NIS Elements 5.30.05, Living Image 4.5.2, ANY-maze 7.65, Noldus Catwalk XT 10.2, LI-COR Acquisition Software 2.4, Amersham ImageQuant TL 11, and Axis Navigator 3.12.7. All are freely or commercially available, no custom software or code was used.

Data analysis

Data analysis was carried out using GraphPad Prism 10.3.1, NIS Elements 5.30.05, Living Image 4.5.2, ANY-maze 7.65, ImageQuant TL 11, and R packages FastQC 0.12.0, STAR 2.7.11b, DESeq2 1.52, NIH ImageJ 1.54h, and Axion Neural Metrics tool 4.1.5. All are freely or commercially available, no custom software or code 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 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](#)

The lipidomic, RNA-seq and proteome profiler datasets that support the findings of this study are included in this published article (and its source data files). The RNA sequencing data are available in the GEO database under accession number GSE338763.

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	Not applicable.
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable.
Population characteristics	Not applicable.
Recruitment	Not applicable.
Ethics oversight	Not applicable.

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](https://www.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	Sample sizes were chosen based on prior experiments using the same outcome measures. These historical datasets included sufficient replicates to achieve statistical power greater than or equal to 0.8.
Data exclusions	Data were not excluded for any reason once a test subject entered into an experiment. Mouse subjects were excluded from analysis if they underwent MC38 injection and failed to develop a detectable tumor (<5% of cases). Tissues from rhesus macaques were excluded prior to analysis for a number of potentially-confounding health conditions.
Replication	All data in this manuscript are derived from multiple biological replicates, generated as part of at least two experimentally distinct cohorts of animals/cell cultures. All attempts at replication were successful and are included in the manuscript and its supplementary files.
Randomization	Where possible, assignment of animals to experimental groups was random. For example, injection of vehicle or tumor cells was randomized across individual subjects, after controlling for group assignment based on sex. Drug treatment provided in drinking water could not be randomized at the individual level because mice were group-housed. Rather, entire cages (5 mice each) received either regular drinking water or carprofen-dosed water.
Blinding	Investigators were blinded to group allocation and tissue/cell type during testing, data acquisition and analysis.

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	Primary Antibodies:
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PGP9.5/Uchl1 Rabbit 1:250 Abcam ab108986 Clone EPR4118
 CD68 Rat 1:500 Bio-Rad/AbD Serotec MCA1957GA Clone FA-11 Lot 58250
 S100B Rabbit 1:100 Abcam AB227914 Clone CL2720
 CD206 Rabbit 1:500 Cell Signaling 24595 Clone E6T5J Lot 5.
 Iba1 (used on mouse tissues) Rabbit 1:500 Fujifilm Wako 019-19741 Polyclonal
 Mouse IgG, F(ab')₂ fragment Goat 1:100 Jackson ImmunoResearch 115-005-072 Polyclonal Lot 143001.
 NF200 Rabbit 1:100 Millipore Sigma N4142 Polyclonal Lot 508946
 Iba1 (used on rhesus tissues) Rabbit 1:300 Abcam ab178680 Clone EPR6136(2)
 RyR Mouse 1:1000 Santa Cruz Biotechnology sc-376507 Clone F-1
 FKBP12/Calstabin-1 Mouse 1:1000 Santa Cruz Biotechnology sc-133067 Clone H-5
 DNP (Dinitrophenol) Mouse 1:1000 Millipore MAB2223 Clone 9H8.1

Secondary Antibodies:

Rabbit IgG-Alexa 488 Goat 1:500 Thermo Fisher A-11008
 Rabbit IgG-Alexa 594 Goat 1:500 Thermo Fisher A-11012
 Rabbit IgG-Alexa 647 Goat 1:500 Thermo Fisher A-21245
 Goat IgG-Alexa 488 Donkey 1:500 Thermo Fisher A-11055
 Rabbit IgG-Alexa 555 Donkey 1:500 Thermo Fisher A-31572
 Mouse IgG IRDye680LT Goat 1:10,000 Li-Cor 926-68020

Validation

PGP9.5: Specificity confirmed by manufacturer in Western Blot testing in PGP9.5 knockout cells (ab263773). <https://www.abcam.com/en-us/products/primary-antibodies/pgp95-antibody-epr4118-neuronal-marker-ab108986>. Negative control staining shown in Supplementary Fig. 1b.

CD68: Specific labeling shown by manufacturer in Western Blot. <https://www.bio-rad-antibodies.com/monoclonal/mouse-cd68-antibody-fa-11-mca1957.html?f=purified>. Negative control staining shown in Supplementary Fig. 14a.

S100b: Specific labeling shown by manufacturer in Western Blot. <https://www.abcam.com/en-us/products/primary-antibodies/s100-beta-antibody-astrocyte-marker-ab227914>. Negative control staining shown in Supplementary Fig. 11e.

CD206: Negative control staining in immunofluorescence and Western Blot shown on manufacturer's website. <https://www.cellsignal.com/products/primary-antibodies/cd206-mrc1-e6t5j-rabbit-monoclonal-antibody/24595>

Iba1: Chemogenetic depletion of macrophages reduces Iba1 immunoreactivity (PMCID: PMC6112686)

Mouse IgG F(ab')₂ fragment: Negative control staining shown in Supplementary Fig. 13a. Mature B-cell knockout mouse validation shows no labeling in Fig. 5j-k.

NF200: Negative control staining shown in Supplementary Fig. 13a.

Iba1 (used on rhesus tissues): Product website shows absence of staining in secondary antibody only and isotype controls, and a specific band in Western Blot. <https://www.abcam.com/en-us/products/primary-antibodies/iba1-antibody-epr61362-microglia-marker-ab178680>

RyR: Validated by the manufacturer using rat heart tissue extract as a positive control. Others have cross-validated specificity using a GFP-tagged RyR and GFP antibody, producing similar specific banding patterns. <https://doi.org/10.1038/s41467-023-40268-z>

Calstabin: Produces a single band of the expected molecular weight in Western Blot. <https://www.scbt.com/p/fkbp12-antibody-h-5>

DNP: Manufacturer validated in Western Blot: The Oxyblot protein standards (S7151) were used to test this antibody. These standards are phosphorylase B, BSA, OVA, Carbonic Anhydrase, and trypsin inhibitor which all contain 1-3 DNP residues per protein. <https://www.sigmaaldrich.com/US/en/product/mm/mab2223>

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s) MC38-Luc-RFP; RRID: CVCL_B7NQ, Alstem Cell Advancements

Authentication The cell lines used were purchased directly from reputable vendors. No additional authentication was carried out.

Mycoplasma contamination Cell lines tested negative for mycoplasma.

Commonly misidentified lines (See [ICLAC](#) register) None found.

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

Mice: C57BL/6J (Strain #: 000664), C57BL/6-Tg(Csf1r-EGFP-NGFR/FKBP1A/TNFRSF6)2Bck/J (Macrophage Fas-Induced Apoptosis (MaFIA); strain #: 005070), and B6.129S2-Ighmtm1Cgn/J (muMt; strain #: 002288) were all sourced from Jackson Laboratories. No breeding was carried out in-house. All mice entered into experiments between 8 and 12 weeks of age.

Mice were housed on a 12:12 light:dark cycle switching at 06:00 and 18:00. ambient temperature was maintained between 18-23 degrees Celsius and 40-60% relative humidity.

Wild animals

Not applicable.

Reporting on sex

Findings apply to both sexes, both sexes were used in approximately equal numbers for behavioral, histological and ex vivo functional analyses. These numbers are reported in the Source Data file associated with this paper. Behavioral tests showed no significant sex differences when comparisons were made between sexes.

Field-collected samples

Field-collected samples were not used in this study.

Ethics oversight

All experiments and procedures involving the use of live animals were approved by MD Anderson Cancer Center Animal Care and Use Committee (Houston, TX, USA), in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals.

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

Plants

Seed stocks

Seed stocks were not used in this study.

Novel plant genotypes

Novel plant genotypes were not used in this study.

Authentication

Seed stocks or novel plant genotypes were not used in this study.