nature research

Corresponding author(s): Katrin Andreasson

Last updated by author(s): Nov 22, 2020

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.

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	Transmission electron microscopy (TEM) images were collected by Gatan Microscopy Suite (GMS) v3
Data analysis	Data was analyzed using GraphPad Prism software (La Jolla, CA); Flow data was analyzed by FlowJo v10 (Ashland, Oregon); TEM images were analzed using ImageJ software v1.6.0_65.

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. 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

The data that support the findings of this study are available for the corresponding author upon request. Untargeted metabolomics data is available by request to corresponding author. GEO Accession numbers for nanostring transcriptomics will be provided in the manuscript upon publication. For reviewers, the GEO Accession number is: GSE155992; private token for reviewer access: oranowgadhcbfsz.

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	Sample size was chosen based on power analysis conducted by the "pwr" package from R with effect size of 0.1, alpha < 0.05, and power = 0.8.
Data exclusions	No data was excluded
Replication	Each experiment was repeated three times with a minimum of n = 5 biological replicates, unless otherwise stated. All attempts at replication were successful.
Randomization	Mice were randomized to behavioral groups
Blinding	Investigators were blinded to electron microscopy data when analyzing quantity and quality of the mitochondria between young and aged CD11bCre;Ep2loxl/lox. Investigators were also blinded when analyzing Novel Object Location as well as Barnes Maze behavioral results of young and aged CD11bCre;Ep2loxl/lox mice as well as EP2 antagonist treated young and aged mice.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used

Western Antibodies:
Antibody Source Catalog No. Dilution
Anti-Synapsin Millipore Sigma AB1543P 1:1000
Anti-SNAP25 Abcam ab41455 1 µg/ml
Anti-PSD95 Abcam ab2723 1 µg/ml
Anti-CamKIIa (pan) Cell Signaling Technology 3362S 1:1000
Anti-EP1 Cayman Chemical 101740 1:200
Anti-EP2 Abcam Ab167171 1:1000
Anti-EP3 Cayman Chemical 101760 1:200
Anti-EP4 Santa Cruz Sc-55596 1:100
Anti-p(Ser473)AKT Cell Signaling Technology 4060S 1:1000
Anti-AKT (pan) Cell Signaling Technology 2920S 1:1000
Anti-p(Ser9)GSK3ß Cell Signaling Technology 9336 1:500
Anti-GSK3ß Abcam ab93926 1:500
Anti-p(Ser641,645,649)GYS1 Millipore Sigma 07-817 1:500
Anti-GYS1 [Human] ThermoFisher Scientific MA5-15802 1:500
Anti-GYS1 [Mouse] ThermoFisher Scientific MA5-15022 1:1000
Anti-TOM20 Santa Cruz sc-17764 1:500
Anti-VDAC Abcam ab14734 1:500
Anti-TIM17 Santa Cruz sc-271152 1:500
Anti-OPA1 BD Biosciences 612607 1:1000
Anti-MFN2 Abnova 11325-6A8 1:1000

Anti-p(Ser616)DRP1 Cell Signaling Technology 4494S 1:250
Anti-FIS1 Proteintech 10956-1-AP 1:1000
Anti-COX2 Cayman Chemical 160126 1:1000
Anti-PGES Abcam Ab62050 1:500
Anti-ß-Tubulin EMD Millipore 05-661 1:5000
Anti-ß-Actin Millipore Sigma A5441 1:10000

Flow Antibodies:
Formatted: Marker, Channel, Catalog #, Dilution, Clone, Supplier
CD14 [Human], APC-Cy7, 557831, 1:50, MφP9, BD Biosciences
CD64 [Human], FITC, 560970, 1:50, 10.1, BD Biosciences
CD86 [Human], APC, 555660, 1:50, FUN-1, BD Biosciences
CD206, PE, 566281, 1:50, 19.2, BD Biosciences
CD68, PE-Cy7, 565595, 1:200, Y1/82A, BD Biosciences
CD23, BV421, 338521, 1:50, EBVCS-5, BD Biosciences
CD163, 563889, 555660, 1:50, GHI/61, BD Biosciences
EGR-2, APC, 1706691-82, 1:50, ERONGR2, Invitrogen
CD301, PE, 145703, 1:50, LOM-14, BioLegend
CD80 [Mouse], BV421, 562611, 1:50, 16-10A1, BD Biosciences
CD86 [Mouse], BV605, 563055, 1:50, GL1, BD Biosciences
CD71 [Mouse], FITC, 561936, 1:50, C2, BD Biosciences
I-A/I-E (MHC Class II), PerCPCy5.5, 562363, 1:50, M5/114.15.2, BD Biosciences
CD14 [Mouse], PE-Cy7, 553740, 1:50, rmC5-3 BD Biosciences

Validation

For immunoblotting, antibodies to components of the EP2 signaling pathway were validated using positive controls wherein cDNAs for all enzymes/receptors were transfected in HEK cells, and lysates served as positive controls.

Animals and other organisms

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

Laboratory animals

This study was conducted in accordance with NIH guidelines, and protocols were approved by the Institutional Animal Care and Use Committee at Stanford University. All mice were housed in an environment controlled, pathogen-free barrier facility on a 12 h light/dark cycle, temperature, and humidity, with food and water available ad libitum.

Wild animals

This study did not involve the use of wild animals

Field-collected samples

This study did not involve the use of Field-collected samples

Ethics oversight

All animal protocols were approved and overseen by the Institutional Animal Care and Use Committee at Stanford University

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

huMDMs were plated in 10 cm plates at 10 x 106 cells / well and were harvested using 0.25% trypsin-EDTA (Cat. No. 25200056, ThermoFisher Scientific, Pittsburgh, PA) at 37°C. Cells were then washed with FACS buffer (PBS with 2% FCS, 2mM EDTA, and 25mM HEPES), followed by incubation with blocking buffer (5% mouse serum in FACS buffer) for 15 minutes at 4°C. Cells were then stained with the desired antibody combinations for 30 minutes at 4°C. Dead cells were excluded with the addition 0.5 µg/mL propidium iodide. Anti-human and mouse antibodies used for flow cytometry of huMDMs and mouse macrophages, respectively, are listed in Supplementary Table 2 (Supplementary Materials, Table 2).

Instrument

BD FACSAria II (BD Biosciences)

Software

Raw FCS files were analyzed with FlowJo software (Treestar, Ashland, OR).

Cell population abundance

CD14+ cells consisted of nearly 95% of the population of cells collected per sample.

Gating strategy

The following controls were used: unstained cells, single-stained cells and dead cells. The cells were gated using forward and side scatter, as well as live/dead staining using DAPI (ThermoFisher Scientific).

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