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 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 wherever 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

- BIOQUANT Life Sciences software (v. 1.8.5), Bioquant Image Analysis Corporation, BD FACSDiva software (v. 1.6.3), BD Biosciences, GeneTool software (v. 2.0), BioTools Inc., Niranjan software (v. 1.9.4), Biq Analysis.

- ZEN Blue Edition software (v. 2.3), Carl Zeiss.

Data analysis

- FlowJo software (v. 10.8), Tree Star Inc., GraphPad Prism 9 software (v. 9.4.1), GraphPad Software Inc.

*For manuscripts utilizing custom algorithms or software that are not standard or published, details must be included in the Methods section (and not just in the text within the manuscript body), to allow reproduction of the research. Further information and templates can be found at the author guidelines (https://www.nature.com/documents/authors/author_guidelines.pdf).* For manuscripts utilizing custom algorithms or software that are published, details of publication must be given.

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 data that support the findings of this study are available from the corresponding author upon request.
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 | Statistical evaluations were performed using the Student’s t-test or one- or two-way ANOVA or repeated-measures ANOVA, as indicated in the figure legends. Post-ANOVA comparisons were made using the Bonferroni correction. For behavioral analyses, the number of mice per group was >8, which represents a >98% probability of detecting a significant change if alpha is set at 0.05 and standard deviations (SDs) are 20% of average. Histological and immunohistochemical comparisons were performed using unpaired Student’s t-test (2 groups) or a one-way (>2 groups) ANOVA, followed by post hoc correction. At least 4 mice per condition were used. This represents a >98% probability of detecting a significant change if alpha is set at 0.05 and SDs are 8% of average. Statistical powers were calculated using the maximum SD observed in our previous studies. For the in vitro experiments, the values of 6 wells were averaged for each tested condition. |
| Data exclusions | No data were excluded from the analyses. |
| Replication | Data were pooled from two independent experiments for the following figures: Fig. 1A-D, Fig. 6B-C, Fig. 7C-D, Fig. 7I-J, Fig. 8C-D, Fig. 8I-J, and Fig. 10F-L. The results of these experiments were reproducible. Each symbol represents one mouse/well and the total sample size (n) is indicated in the legends. |
| Randomization | Negative control groups (e.g. genotype, vehicle treatment) were included in all experiments. Male and female mice were randomly assigned (in equal numbers) to control and treatment groups. |
| Blinding | All quantifications were done blind with respect to the identity of the animals. Behavioral testing was carried out by a blinded investigator. |

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 | Methods |
|---------------------------------|---------|
| n/a | n/a |
| Antibodies | ChIP-seq |
| Eukaryotic cell lines | Flow cytometry |
| Palaeontology and archaeology | MRI-based neuroimaging |
| Animals and other organisms | |
| Human research participants | |
| Clinical data | |
| Dual use research of concern | |

Antibodies

Neutrophils were depleted through repeated injections of rat anti-mouse Ly6G antibody (50 µg, clone 1A8, BioXCell, BE0075-1) and mouse anti-rat IgG2a (50 µg, clone MAR 18.5, BioXCell, BE0122), while rat IgG2a isotype (50 µg, clone 2A3, BioXCell, BE0089) served as a control.

Primary antibodies used for immunofluorescence come from the following sources (clone and catalog numbers in parentheses) and were used at the indicated dilutions: rat anti-BrdU (1:1000, clone BU175 [ICR1], Abcam, ab6326), rat anti-C3 (1:100, clone 1H9, Abcam, ab18682), mouse anti-CC1 (1:1000, clone CC1, Abcam, ab16794), rat anti-CD11b (1:250, clone SC6, AbD Serotec, MCA711), rabbit anti-c-fos (1:500, clone 9F6, Cell signaling, #2250), mouse anti-GalC (1:800, clone mGalC, Millipore, MAB342), goat anti-lba1 (1:3500, Novus Biologicals, NB100-1028), goat anti-IL-1β (1:100 dilution, R&D Systems, AF-400-NA), rabbit anti-Ki67 (1:200, Abcam, ab15580), rabbit anti-laminin (1:1000, Dako, Z0097), rat anti-Ly6G (1:2000, clone 1A8, BD Biosciences, #551459), mouse anti-NeuN (1:250, clone A60, Millipore, MAB377), rabbit anti-Ng2 (1:100, Millipore, Ab5320), rat anti-Ng2 (1:200, clone 546930, R&D Systems, MAB6689), mouse anti-O4 (1:400, clone 04, R&D Systems, MAB1326), goat anti-Olig2 (1:400, R&D Systems, AF2418), rabbit anti-P2ry12 (1:500, AnaSpec, AS-55043A), goat anti-Sox9 (1:250, R&D Systems, AF3075), and rabbit anti-Sox9 (1:1000, Millipore, AB5535).

OPCs and pro-OLs were isolated by immunopanning using a rat anti-PDGFβRα/CD140a (1:300, clone APA5, BD Biosciences, #558774) and a mouse anti-O4 (1:300, clone 04, R&D Systems, MAB1326).
Validation

The antibodies used in this study were chosen based on their extensive use in the literature (supported by the references available on the supplier's website) and a significant amount of experiments in our hands (see the references provided in the Methods section).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)
Oligodendrocyte precursor cells (OPCs) were isolated from the neonatal (P7-P9) mouse brain. Endothelial cells were isolated from the brain capillaries of mice aged 6-8 weeks. Mouse primary astrocytes were isolated from the cortex of P0-P2 C57BL/6 mice.

Authentication
Morphology and immunophenotypic characterization were performed to assess the purity of the cultures.

Mycoplasma contamination
The cell lines were not tested for mycoplasma contamination.

Commonly misidentified lines (See ICLAC register)
N/A

Animals and other organisms

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

Laboratory animals
Male and/or female C57BL/6 mice were purchased from Charles River Laboratories or The Jackson Laboratory (JAX) at 8-10 weeks of age. Cx3cr1CreER mice were obtained from the European Mouse Mutant Archive, with prior authorization from Dr. Steffen Jung (Rehovot, Israel). Breeder for Rosa26-tdTomato (R26-Tdt, also known as A19, stock #007905), PdgfraCreER (stock #018280), GfapCre (stock #024098), and Il1r1fl/fl (stock #028398) mice were all purchased from JAX. Male and/or female C57BL/6 mice were purchased from Charles River Laboratories or The Jackson Laboratory (JAX) at 8-10 weeks of age.

Wild animals
No wild animals were used in the study.

Field-collected samples
No field collected samples were used in the study.

Ethics oversight
All animal procedures were approved by the Comité de protection des animaux de l’Université Laval (protocols #CHU-20-675 and #CHU-21-860) and conducted in compliance with relevant ethical regulations and guidelines of the Canadian Council on Animal Care.

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

Flow Cytometry

Plots

Confirm that:
1. The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
2. 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).
3. All plots are contour plots with outliers or pseudocolor plots.
4. A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation
AUTOMATED BLOOD CELL COUNT, FLOW CYTOMETRY AND CELL SORTING. Blood was collected via cardiac puncture using a...
22-gauge heparinized syringe. Blood samples were immediately transferred into EDTA-coated microtubes (Sarstedt) and subjected to 15 minutes at 4°C to prevent nonspecific binding. Multicolor labeling was then performed using the LIVE/DEAD™ Fixable Yellow Dead Cell Stain Kit (Thermo Fisher Scientific) and the following fluorescently-conjugated primary antibodies (all from BD Biosciences): PerCP-conjugated anti-CD45 (1:50 dilution), Alexa 700-conjugated anti-CD11b (1:50), and BD Horizon™ V450 conjugated anti-Ly6G (1:83). Data were acquired on a BD LSR II flow cytometer using the BD FACSDiva software, and further analyzed using FlowJo software.

For the purification of microglia required for DNA and mRNA analyses via quantitative real-time PCR (qPCR) and RT-PCR (qRT-PCR), respectively, microglia were isolated from the adult spinal cord as described above and then sorted using a BD FACSAria II. The following primary antibodies were used (all from BD Biosciences): PerCP-conjugated anti-CD45 (1:50 dilution), Alexa 700-conjugated anti-CD11b (1:50), FITC-conjugated anti-Ly6G (1:83), and PE-Cy7 conjugated anti-Ly6C (1:50). Microglia were identified as CD45intCD11b+Ly6C-Ly6G− cells.