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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 *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	Electrophysiology data were collected with a MultiClamp 700B amplifier (Molecular Devices) and digitized at 10 kHz with an Axon Digidata 1550B (Molecular Devices). Data were recorded and analyzed using pClamp 11 software suite (Molecular Devices). Confocal images were acquired on either a Zeiss LSM700, Zeiss Airyscan1 LSM800, or Zeiss Airyscan2 LSM980 using Zen 2011 v8.1. Bioluminescence imaging was performed using an IVIS imaging system (Xenogen). Flow cytometry data were acquired using CytExpert software.
Data analysis	Statistical tests were conducted using GraphPad Prism v9.1.0 software. For analysis of previously published scRNAseq data, R studio 1.4.1106-5 was used, and the Seurat package was used for violin plot construction. Confocal images were analyzed and quantified using ImageJ v.2.1.0/1.53c. 3D image reconstructions were processed using IMARIS v10.0.0. Flow cytometry data were analyzed with FlowJo.

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 research materials are available upon request. All data reported in this paper will be shared by the corresponding authors upon request. Any additional information required to reanalyze the data reported in this paper is available from the corresponding authors upon request.

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	The sample size for all the studies is typically four or greater measurements. No statistical methods were used to predetermine sample sizes. Sample sizes were chosen based on those commonly used in comparable studies and were equal to or larger than those reported in such studies.
Data exclusions	No data were excluded.
Replication	All attempts at replication were successful for more than three times in indepedent trials.
Randomization	Samples (cells, slides, animals) were randomized accordingly during experiments.
Blinding	Investigators were blinded during analysis of the data.

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

For western blot experiments, primary antibodies against the NLGN3 ectodomain (Abcam #90080), N-terminal regions of CSPG4 (Cell Signaling Technology #52635), and C-terminal regions of CSPG4 (Abcam ab139406) were used. HRP-conjugated secondary antibody (CST #7074) was used for detection. For phospho-AKT flow cytometry analysis, phospho-AKT Ser473 rabbit mAb (CST #4075) was used. For FACS isolation of CSPG4 KO cells, Alexa Fluor 647-labeled anti-CSPG4 antibody (BD Biosciences #562414) was used. For immunohistochemistry experiments, rabbit anti-Ki67 antibody (1:500, Abcam ab15580) was used, followed by Alexa 594 donkey anti-rabbit IgG (1:500, Jackson ImmunoResearch). For 3D reconstruction, rabbit PIEZO1 antibody (1:500, ProteinTech 15939-1-AP) and chicken anti-GFP antibody (Abcam ab13970) were used, followed by anti-chicken 488 (Jackson ImmunoResearch 703-545-155) and anti-rabbit 594 secondary antibodies (Jackson ImmunoResearch 111-585-144). For OPC differentiation assays, anti-MBP (Abcam ab7349), anti-CSPG4 (gift from Dr. Jacqueline Trotter), and anti-OLIG2 (R&D AF2418) antibodies were used, followed by fluorescent secondary antibodies from Jackson ImmunoResearch.

Validation

All antibodies used were validated by the manufacturers, as noted by the catalogues numbers above, and the validation statements are mentioned in the manufacturer's websites.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

expi293 cell lines (A14635) from Thermo Fisher was used for protein preparation. Patient-derived glioma cell cultures were generated in the Monje lab or obtained from collaborators using IRB-approved protocols and with informed consent. .

Authentication

STR fingerprinting and mycoplasma tersting is routinely performed on all pateint-derived glioma cell cultures.

Mycoplasma contamination

Glioma cells were routinely tested for mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

Cells are not listed in the database.

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

For all xenograft studies, NSG mice (NOD-SCID-IL2R gamma chain-deficient, The Jackson Laboratory) were used. Male and female mice were used equally.

Wild animals

N/A

Reporting on sex

male and female mice were used equally

Field-collected samples

N/A

Ethics oversight

All animal experiments were conducted in accordance with protocols approved by the Stanford University Institutional Animal Care and Use Committee (IACUC) and performed in accordance with institutional guidelines. Animals were housed according to standard guidelines with unlimited access to water and food, under a 12 hour light : 12 hour dark cycle. For brain tumor xenograft experiments, the IACUC has a limit on indications of morbidity (as opposed to tumor volume). Under no circumstances did any of the experiments exceed the limits indicated and mice were immediately euthanized if they exhibited signs of neurological morbidity or if they lost 15% or more of their initial body weight.

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	For the experiment medium was removed and cells were detached with 100 µL TrypLE (Gibco, 12605010) for 5 min at 37 °C. Cells were transferred to 96-well U-bottom plates containing 15 µL freshly opened 16% paraformaldehyde (final ~2.1% PFA) and fixed for 10 min at room temperature on a shaker, protected from light. Cells were centrifuged at 1,600 × g for 3 min, resuspended in 200 µL ice-cold 100% methanol with gentle mixing, and permeabilized overnight at −20 °C. Cells were then centrifuged at 1,600 × g for 4 min and washed twice with 200 µL FACS wash buffer (1% (w/v) BSA, 0.05% (w/v) sodium azide in PBS). Cells were stained with 50 µL of AlexaFluor 647-conjugated phospho-Akt (Ser473) (D9E) XP rabbit mAb (Cell Signaling Technology, #5315, 1:50 dilution) in wash buffer for 1 h at room temperature, protected from light. After two washes in 200 µL wash buffer, cells were resuspended in 100 µL wash buffer and analyzed immediately.
Instrument	Flow cytometry data were acquired on a Beckman Coulter CytoFLEX.
Software	Flow cytometry data were acquired using CytExpert software and analyzed using FlowJo (v10).
Cell population abundance	For each sample, ≥10,000 cell events were acquired within the gate. Median fluorescence intensity (MFI) of pAKT(S473)-AF647 was quantified within the live singlet population and is reported in the corresponding figure panels.
Gating strategy	Intact cells were selected on FSC-A vs SSC-A based on size and granularity, excluding debris and cell fragments then singlets were selected on FSC-H vs FSC-A (and SSC-H vs SSC-A) to exclude doublets and aggregates. Afterwards, MFI of pAKT(S473)-AF647 was quantified within the singlet gate.

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