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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Imaris Software (9.1.2, 64Bit, Bitplane); NeuroLucida (9.14.5 32 Bit, MicroBrightField, Williston, VT); StereoInvestigator (9.14.5 32 Bit, MicroBrightField, Williston, VT); NIH Image J (1.51) Software
Data analysis	Prism Software (7.0c, GraphPad, San Diego, CA) for statistical evaluations. Differential gene expression used the Bioconductor EdgeR package (3.20.1). All described in detail in the methods.

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 upon request. 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

RNAseq data are available at NCBI's Gene Expression Omnibus repository (GSE111529).

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Power calculations were performed using G*Power Software V 3.1.9.242. For quantification of histologically-derived neuroanatomical outcomes such as numbers of axons or percent of area stained, group sizes were used that were calculated to provide at least 80% power when using the following parameters: probability of type I error (alpha) = .05, a conservative effect size of 0.25, 3-10 treatment groups with multiple measurements obtained per replicate.
Data exclusions	Two days after SCI, all mice or rats were evaluated in open field and all animals exhibiting any hindlimb movements were not studied further. Rodents that passed this inclusion criterion were randomized into experimental groups for further treatments and were thereafter evaluated blind to their experimental condition.
Replication	We replicated our findings in both mice and rats, and in two institutions, UCLA and EPFL, with different teams of investigators. All replication attempts were successful. No replication attempts failed.
Randomization	Two days after SCI, all mice or rats were evaluated in open field and all animals exhibiting any hindlimb movements were not studied further. Rodents that passed this inclusion criterion were randomized into experimental groups for further treatments and were thereafter evaluated blind to their experimental condition.
Blinding	Rodents that passed this inclusion criterion were randomized into experimental groups for further treatments and were thereafter evaluated blind to their experimental condition.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☐	☒ Unique materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☐	☒ Research animals
☒	☐ Human research participants

Unique materials

Obtaining unique materials	Our hydrogels are unique materials. We confirm that they are available to other investigators upon request.

Antibodies

Antibodies used	All antibodies used are described in detail, including sources and dilutions in the methods. Primary antibodies were: rabbit anti-GFAP (1:2000; Dako, Santa Clara, CA); rat anti-GFAP (1:1000, Thermofisher, Grand Island, NY); chicken anti-GFAP (1:1000, Novus Biologicals, Littleton, CO); rabbit anti NeuN (1:1000, Abcam, Cambridge, MA); rabbit anti-GDNFR-a (GDNF-receptor alpha) (1:1000, Abcam, Cambridge, MA); sheep anti-BrdU (1:300, Maine Biotechnology Services, Portland, ME); rabbit anti-HSV-TK (1:1,000, 35,39); goat anti-CD13 (1:1000, R&Dsystems, Minneapolis, MN); rabbit anti-Laminin 1 (1:100, Sigma, St.Louis, MO); rabbit anti-Fibronectin (1:500, Millipore, Burlington, MA); rabbit anti-Collagen 1a1 (1:300, Novus Biologicals, Littleton, CO); mouse anti-NeuN (1:2000, Millipore, Burlington, MA); mouse anti-CSPG40 (1:100, Sigma); rabbit anti-Brevican (BCAN) (1:300, Novus Biologicals, Littleton, CO); guinea pig anti-NG2 (CSPG4) (Drs. E.G. Hughes and D.W. Bergles41, Baltimore, MA); rat anti-PECAM-1 (1:200, BD Biosciences, San Jose, CA); guinea pig anti-homer1 (1:600, Synaptic Systems GmbH, Germany); rabbit anti-Synaptophysin (1:600,Dako, Santa Clara, CA); rabbit anti-RFP (1:1000, Rockland,Limerick,PA); chicken anti-RFP (1:500, Novus Biologicals, Littleton, CO); goat anti-GFP (1:1000, Novus Biologicals, Littleton, CO).
Validation	All antibodies have been verified in multiple studies and publications by ourselves and others, including in many cases comparisons with Western blots.

Research animals

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

Animals/animal-derived materials	Animal strains and sexes used, and their care and institutional approvals are described in detail in the methods. All experiments using mice were conducted at UCLA using C57/BL6 female and male mice. RNA sequencing experiments used C57/BL6 mice expressing an mGFAP-RiboTag transgene generated and characterized as described (19). All mice used were young adults between 10 weeks and four months old at the time of spinal cord injury. All surgical procedures in rats were done at EPFL. Experiments were conducted on young adult female Lewis rats between 2 and 4 months of age (180-220g body weight).

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ Magnetic resonance imaging