nature portfolio

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Last updated by author(s): Apr 22, 2025

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	Data was collected using Excel for MacOS (v16.91 ; Microsoft), FACS Diva (v8.0.1 build 2014 07 03 11 47; BD Biosciences), ImageLab (v6.1.0 build 7 ; Bio-Rad Laboratories), Wave Controller (Agilent Technologies), NIS Element Advanced Research (Nikon), Celigo (Nexcelom), and BZX800 Viewer Capture Still Images (Keyence).
Data analysis	Data were analyzed using Excel for macOS (v16.91; Microsoft), Prism 10 for macOS (v10.4.2; GraphPad), FlowJo (v10.8.1; BD Biosciences), and ImageJ (v2.1.0/1.53c; NIH, USA). Gene expression data were analyzed using R for macOS (v4.1.1 GUI 1.77; R Foundation for Statistical Computing) with Bioconductor libraries (v3.14) DESeq2 (v1.46.0) "marray" and "samr", Sambamba (v1.0.1), SAMtools (v1.21), , and Bowtie2 (v2.5.4). inForm analysis software (Akoya Biosciences) was used for pathology scoring. pClamp software (v8.0 ; Molecular Devices) have been used for electro-physiology analysis. Custom Codes are available in the following links: - https://github.com/GreletLab/DAPI-count - https://github.com/GreletLab/mtDNA-heteroplasmy

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 data supporting the findings of this study are available from the corresponding authors upon reasonable request.
The bioinformatic datasets for the RNA sequencing experiment is available in the NCBI SRA under the accession number "GSE288069":
https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE288069
The RNA microarray dataset is deposited in the NCBI SRA under the accession number "GSE292157":
https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE292157
Plasmids generated for this study are deposited in the Addgene database (greletlab).

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	This is a pilot study examining biological endpoints in men with localized PCa who are scheduled to have radical prostatectomies. Four patients with bilateral localized PCa were recruited to a Phase I/II clinical trial: Neoadjuvant Botox injection prior to radical prostatectomy (NCT01520441), (IRB: H-25362).
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	The trial was designed as a proof of principle that nerves affect the biology of PCa in humans. The inclusion criteria were as follows: male and at least 50 years of age; biopsy-proven, clinically localized PCa; low risk for recurrence defined as a Kattan nomogram score of less than 115, serum PSA<10ng/mL, individual Gleason grade of 7 or lower, or clinical stage T2b or below; must have agreed to radical prostatectomy and signed an informed consent; and the patient must be able to complete the study protocol in the opinion of the investigator.
Recruitment	The inclusion criteria were as follows: male and at least 50 years of age; biopsy-proven, clinically localized PCa; low risk for recurrence defined as a Kattan nomogram score of less than 115, serum PSA<10ng/mL, individual Gleason grade of 7 or lower, or clinical stage T2b or below; must have agreed to radical prostatectomy
Ethics oversight	The study was approver IRB: H-25362. Approvals were obtained from both the Baylor College of Medicine Animal Care and Use and Human Subjects Committee. Informed consent was obtained from all human participants involved in the study.

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 experiments were independently repeated at least three times, each performed in triplicate. The exact number of mice used in each experiment is detailed in the corresponding figure legend. Similarly, the number of patient samples included in the clinical data is specified in the figure legend. While no formal prospective sample size calculation was performed, sample sizes were chosen based on prior experimental experience and reproducibility of outcomes in comparable studies. Previous analyses allowed us to estimate effect sizes using Cohen's d, which informed the selection of sample sizes that provide sufficient statistical power to detect biologically relevant differences using appropriate statistical tests, as specified in each figure legend.
Data exclusions	For the transcriptomic dataset, the samples not meeting quality requirements were not included in the analysis. No inclusion/exclusion criteria were used for other samples or animals.
Replication	Experiments were replicated at least three times and repeated independently. Attempts of replication were successful.
Randomization	Animals were housed in cages of four, and each experimental condition was assigned to one cage. For each experiment, one cage was

Randomization	randomly selected from a pool of pre-assigned condition-specific cages. Although allocation was not randomized at the individual animal level, random selection at the cage level ensured unbiased assignment. All mice were age- and sex-matched, and housed under identical environmental and handling conditions to minimize potential covariates.
Blinding	Blinding was not performed in this study because the experimental procedures, data acquisition, and analysis involved objective measurements that are not influenced by operator bias. All data processing and statistical analyses were conducted using standardized, automated pipelines, minimizing the potential for subjective interpretation.

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	α-Tubulin - Cell Signaling (#2144s, Lot5) Cre Recombinase - Cell Signaling (#15036, Lot2 clone D7L7L) GFP - Santa Cruz Biotechnology (#sc-9996, LotE2521, Clone B-2) HA Tag - Santa Cruz (#sc-7392, LotI0922, clone F-7) mCherry - Cell Signaling (#43590S, Lot2, clone E5D8F) ALDH1L1 (OriGene TA501868, Lot A01, Clone OTI7G8) O4 (R&D Systems MAB1326, Lot: HWW143051 Clone O4) Map2 (Proteintech 17490-I-AP, Lot: 00126726 Tubb3 (Santa Cruz sc80005, Lot: A1821, Clone D-10) Secondary Mouse or Rabbit HRP (ThermoFisher PI31430 or PI31460) Alexa Fluor™ 647 secondary antibody (ThermoFisher A21235, Lot 2836809; A21244 Lot 2674387).
Validation	Antibodies against Cre, mCherry, GFP, and the HA tag were validated in this study using negative (wild-type cells) and/or positive (overexpression) controls. The α-tubulin antibody (Cell Signaling Technology, #2144) used as a loading control was validated by the manufacturer for Western blotting, and its reliability has been extensively confirmed in the literature. For flow cytometry, antibodies targeting TUBB3, Oligo4, MAP2, and ALDH1L1 were validated by the manufacturers. In addition, their specificity was confirmed in this study by demonstrating their ability to detect the corresponding cell types following subventricular zone (SVZ) cell differentiation, as shown in Figure S2I.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	4T1, 50B11, PC-12, HT22, Neuro2A, and NMuMG cells were obtained from the American Type Culture Collection (ATCC). 3T3-L1 cells were purchased from Kerafast, Inc. Mouse embryonic fibroblasts (MEFs) were a gift from R. Stephen Lloyd's laboratory and were generated from C57BL/6 mice. DCIS.COM cells were purchased from Asterand, Inc. Primary SVZ neural stem cells (SVZ-NSCs) were obtained by dissection from fresh brains of BALB/c mice purchased from the Jackson Laboratory.
Authentication	The cell lines used on this study has been authenticated by genomic profiling.
Mycoplasma contamination	The cell lines were routinely checked for mycoplasma contamination by using the Mycostrip Test Kit (Invivogen), and through Hoechst-33342 staining. Plasmocin was used as a prophylactic treatment to prevent mycoplasma contamination. All cells were negative for mycoplasma. Cells were tested by IMPACT testing (Idexx Bioanalystics) prior to animal work .
Commonly misidentified lines (See ICLAC register)	No cell lines used in this study were found in the database of commonly misidentified cell lines that is maintained by ICLAC.

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	6 week-old virgin female SCID-beige mice were used for the intraductal breast cancer model. Mammary fat pad injection of mixed-cell MitoTRACER spheroids was performed on BALB/c female mice (age, 6 wk). Mice were housed under a 12 h:12 h light:dark cycle in a barrier vivarium. Room temperature (22.8 °C ± 1.7 °C) and relative humidity (30 %–70 %) were continuously monitored and maintained.
Wild animals	No wild animals used in the study
Reporting on sex	Female animals were used to align with the origin of the breast cancer cell lines and SVZ NSCs.
Field-collected samples	No field-collected samples used in the study
Ethics oversight	All experiments and procedures were conducted in accordance with the guidelines described in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, Bethesda, MD, USA). Approvals were obtained from both the Baylor College of Medicine Animal Care and Use and Human Subjects Committee and the University of South Alabama Institutional Animal Care and Use Committees.

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	*Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.*
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	*Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

Plants

Seed stocks	No seeds associated to the study.
Novel plant genotypes	No plants associated to the study.
Authentication	No plants associated to the study.

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	Cells were detached using 0.25% trypsin with EDTA, then resuspended in culture media. After centrifugation and supernatant removed, the cell pellet was gently broken up and prevented from clumping by tapping the tube. It was then resuspended in

	PBS containing 2% serum and kept on ice until processing
Instrument	BD FACSAria II Cell Sorter and BD FACSCanto II were used in this study.
Software	BD FACSDiva Software for cell collection and analysis. The .fcs data were analyzed using FlowJo10 software.
Cell population abundance	100,000 to 8,000,000 cells were analyzed. Sorting was performed with 1 cell per well in 96-well plates (single-cell sorting) or a minimum of 5000 cells per well in 6-well plates containing 2 ml of DMEM with 10% FBS.
Gating strategy	Cells were gated based on their mCherry/GFP fluorescence expression. Before this gating process, doublets and debris were removed from the analysis using FSC-A/FSC-H & SSC-H/SSC-A gating. Cells that did not express (WT) or that overexpressed fluorescent proteins served as negative and positive controls, respectively. These controls were used define the boundaries of the gating strategy and accurately distinguish between positive and negative populations. In the nerve-cancer co-culture experiments, monocultures were used as negative controls.

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