nature portfolio

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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	1: Western blot: ChemiDoc MP imaging System (Bio-Rad) or film scanned with an Epson Perfection V700 Photo scanner. 2: Real-Time PCR: LightCycler 480 instrument (Roche). 3: Histology stained images: Aperio ScanScope XT and Aperio-Turbo Slide Scanner with Leica Biosystems Aperio ImageScope and ImageScope eSlide viewer. 4: Cell migration assay: EVOS™ FL Imaging System (Thermo Fisher Scientific, Cat#AMF4300). 5. Oxygen consumption rates: Extracellular Flux Analyzer XF24 (Seahorse Biosciences). 6. RNA-seq: Illumina platform (NovaSeq 6000) sequenced as 150bp paired-end reads by Novogene Inc. 7: Metabolite profiling: LC-MS/MS using a triple quadrupole mass spectrometer (QQQ 6470) equipped with a 1290 ultra high-pressure liquid chromatography system (Agilent Technologies, Santa Clara, California, USA) and GC-MS using an Agilent 5975C GC/MS equipped with a DB-5MS+DG (30 m x 250 µm x 0.25 µm) capillary column or a Select FAMES (100 m x 250 µm x 0.25 µm) capillary column (Agilent J&W, Santa Clara, CA, USA). 8. ChIP-seq: Illumina platform (NovaSeq 6000) sequenced as 150bp paired-end reads by Novogene Inc.
Data analysis	1: Immunoblots presentation and quantification: Adobe photoshop 2021, Adobe illustrator 2021, and ImageJ (version 1.5.3). 2. RNA-seq analysis: The Hisat2 software (version 2.0.5), Feature Counts software (version 1.5.0-p3) , and DESeq2 R package (version 1.20.0). 3: Transcriptome functional analysis: Enrichr, GSEA (version 4.3.2), and WebGestalt. 4. Gene expression analysis of clinical samples: cbioportal.org and GEPIA. 5: Histology staining images: Aperio ImageScope (version 12.4.3.5008; Leica Biosystems), and ImageScope eSlide viewer (Leica Biosystems). 6. Metabolomics analysis: MassHunter Quant (Agilent Technologies), MetaboAnalyst (version 5.0). 7. ChIP-seq analysis: Trimmomatic (version 0.36), BWA-MEM (version 0.7.12), Picard tools (version 2.0.1), MACS2 software suite (version

2.1.1.20160309), HOMER software suite (version 4.11.1), and deepTools (version 3.5.0).
8: Statistics and graphing: GraphPad Prism 9 or 10 and Microsoft Excel.

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

RNA-seq data of xenograft tumors derived from PTEN+ERRglow, PTEN+ERRg+, PTEN-ERRglow, and PTEN-ERRg+ DU145 cell lines as well as ERRg ChIP-seq data from PTEN-ERRg+ and PTEN-ERRglow DU145 cells reported in this study will be deposited in the NCBI Gene Expression Omnibus (GEO) upon acceptance of the paper.
Publicly available expression datasets used in this study obtained from cbioportal.com are: 1) Prostate Adenocarcinoma (MSK, Cancer Cell 2010); 2) Prostate Adenocarcinoma (Broad/Cornell, Nat Genet 2012); 3) Prostate Adenocarcinoma (TCGA, PanCancer Atlas 2013) (Cancer Genome Atlas Research Network, 2013); 4) Prostate Adenocarcinoma (TCGA, Cell 2015); 5) Prostate Adenocarcinoma (SMMU, Eur Urol 2017); and 6) Prostate Adenocarcinoma (DKFZ, Cancer Cell 2018); and expression data obtained from GEO are: 1) human prostate adenocarcinoma and NEPC (GSE21032); 2) human primary and metastatic PCa (GSE21034); 3) human PCa pre- and post-ADT (GSE183100); and 3) mouse PCa models (GSE90891).
Source data underlying the graphs are presented in the Extended data Table 6. Uncropped immunoblots are shown in Extended data Figure 6. Any additional information required to reanalyze the data reported in this paper is available from the lead contact 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	We did not compute statistical analyses to predetermine sample sizes before performing experiments. For in vivo studies, sample size was chosen based on animal availability. Sample size was determined to be adequate based on the consistency of measurable differences and significance level required to attain statistical significance of $p<0.05$ between groups. Sample sizes for in vitro experiments (at least three independent experimental replicates unless otherwise indicated) were chosen based on the standard practice of the field. Sample sizes are indicated for each experiment in the manuscript.
Data exclusions	No data was excluded.
Replication	Experimental design was based on the use of at least 3 biological replicates as described in the figure legends and methods section generating consistent data as indicated by the significance of the results unless otherwise indicated.
Randomization	For in vivo study, mice analyzed were age matched, littermates and weight matched whenever possible, and they were then randomly allocated to each experimental group. For in vitro experiments, groups were allocated based on the genetic background of cells and different pharmacological treatments, thus no randomization was required. Randomization is not applicable for analyzing public dataset as groups have already been determined.

Blinding	Investigators were not blinded to experimental conditions for planning of experiments due to the complexity of the experiments, e.g. western blots require samples to be loaded in appropriate orders and mice in different genotypes were measured in the rotation manner to avoid the effects caused by difference in time.

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	anti-CHGA (Cell Signaling Technology, Cat#85798) anti-ENO2 (Cell Signaling Technology, Cat#24330, RRID:AB_2868543) anti-phospho EZH2 T311 (ABclonal, Cat#AP1269) anti-EZH2 (Abcam, Cat#ab191080) anti-SYP (Abcam, Cat#ab52636, RRID:AB_882786) anti-PTEN (Cell Signaling Technology, Cat#9559, RRID:AB_390810) anti-ERRg (Dr. Anastasia Kralli, Johns Hopkins University, USA) anti-phospho AKT T308 (Cell Signaling Technology, Cat#9275, RRID:AB_329828) anti-AKT (Cell Signaling Technology, Cat# 9272, RRID: AB_329827) anti-phospho RET Y905 (Cell Signaling Technology, Cat#3221, RRID:AB_2179887) anti-RET (Abcam, Cat#ab134100) anti-alpha-TUBULIN (Cedarlane, Cat# CLT-9002, RRID:AB_10060319) anti-RPLP0 (Proteintech, Cat#11290-2-AP, RRID:AB_2254064) anti-rabbit (GE Healthcare, Cat#NA934, RRID:AB_772206) anti-mouse (GE Healthcare, Cat#NA931, RRID:AB_772210) Ki67 (Abcam, Cat#ab16667, RRID:AB_302459) SYP (Abcam, Cat#ab52636, RRID:AB_882786) EZH2 (Abcam, Cat# ab191080)
Validation	https://www.cellsignal.com/product/productDetail.jsp?productId=85798 https://www.cellsignal.com/product/productDetail.jsp?productId=24330 https://abclonal.com/catalog-antibodies/PhosphoEZH2KMT6T311RabbitpAb/AP1269 https://www.abcam.com/products/primary-antibodies/kmt6--ezh2-antibody-epr93072-n-terminal-ab191080.html https://www.abcam.com/en-jo/products/primary-antibodies/synaptophysin-antibody-ep1098y-ab52636 https://www.cellsignal.com/product/productDetail.jsp?productId=9559 https://www.cellsignal.com/product/productDetail.jsp?productId=9275 https://www.cellsignal.com/product/productDetail.jsp?productId=9272 https://www.cellsignal.com/product/productDetail.jsp?productId=3221 https://www.abcam.com/products/primary-antibodies/ret-antibody-epr2871-ab134100.html https://www.cedarlanelabs.com/Products/Detail/CLT9002?lob=AllProducts https://www.ptglab.com/products/RPLP0-Antibody-11290-2-AP.html https://www.sigmaaldrich.com/CA/en/product/sigma/gena9341ml https://www.sigmaaldrich.com/CA/en/product/sigma/gena9311ml https://www.abcam.com/products/primary-antibodies/ki67-antibody-sp6-ab16667.html https://www.abcam.com/products/primary-antibodies/synaptophysin-antibody-ep1098y-ab52636.html https://www.abcam.com/products/primary-antibodies/kmt6--ezh2-antibody-epr93072-n-terminal-ab191080.html

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	LNCaP (Cat#CRL-1740), 22Rv1 (Cat#CRL-2505), DU145 (Cat#HTB-81), PC3 (Cat#CRL-1435), NCI-H660 (Cat#CRL-5813), and HEK293T (Cat#CRL-3216) were originally obtained from ATCC.
Authentication	Authentication of LNCaP, 22Rv1, DU145, PC3, NCI-H660 were based on the expression of PTEN. HEK293T cells were not specifically authenticated beyond being obtained from the ATCC.
Mycoplasma contamination	Cells were routinely screened for possible mycoplasma contamination using a mycoplasma PCR detection kit (cat. no. G238; Applied Biological Materials) and showed no signs of infection.
Commonly misidentified lines (See ICLAC register)	No cell lines used are listed in the database of commonly misidentified cell lines.

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	Unless otherwise noted, mouse experiments involved age-matched male housed 2-5 per cage. Mice were maintained in a constant environment (humidity: 30%-70%; temperature: 18°C-24°C; 12 h light/dark cycle: 7AM-7PM light/7PM-7AM dark) with ad libitum access to standard normal diet (ND, cat. no. 2920x; Envigo; Teklad Rodent diet; 3.1 kal/g, 24 kcal% protein, 16 kcal% fat, 60 kcal% carbohydrate) and water in a McGill University animal facility. All transgenic mice were males aged as noted and maintained in a C57BL/6 background. Ptenf/+:PBCre4+ (Pten pc+/-) mice were generated by breeding Ptenf/f:PBCre4- females with PBCre4+ males. Ptenf/+-:Esrrgf/f:PBCre4+ (Pten pc+/-:Esrrg pc-/-) mice were obtained from crossing Ptenf/f:Esrrgf/f:PBCre4- females with Esrrgf/f :PBCre4+ males. Pten loxed mice and PBCre4 mice were kindly provided by Dr. Maxime Bouchard and Esrrg loxed mice on a C57BL/6 genetic background were were kindly provided by Dr. Anastasia Kralli.
Wild animals	No wild animals were used in the study.
Reporting on sex	All mouse experimental data were derived from male mice.
Field-collected samples	No field collected samples were used in the study.
Ethics oversight	All experiments performed with mice were conducted in accord with accepted procedures by the McGill Facility Animal Care Committee and complied with the Canadian Council on Animal Care.

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

Plants

Seed stocks	No plants were used in the study.
Novel plant genotypes	No plants were used in the study.
Authentication	No plants were used in the study.

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	Reviewer GEO access link: https://can01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2Fgeo%2Fquery%2Facc.cgi%3Facc%3DGSE249864&data=05%7C02%7Ccathy.dufour%40mcgill.ca%7Cc82810b69c194944042a08dbfa623933%7Ccd31967152e74a68afa9fcf8f89f09ea%7C0%7C0%7C638379071990875535%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=D3SiTyCvAxSn19M63p4NJoxTtzpdrgUcbjJXrTxhq1E%3D&reserved=0 Enter token szcbqgwchvkvhkf into the box

Files in database submission	Raw files: fastq; processed files: bigwig, bedgraphs, annotated peaks
Genome browser session (e.g. UCSC)	*Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates	Single replicates
Sequencing depth	Samples were sequenced as paired-end 150bp reads at a depth of 20 million reads/sample (6G).
Antibodies	anti-ERRg (Dr. Anastasia Kralli, Johns Hopkins University, USA)
Peak calling parameters	ChIP-seq reads were first trimmed for adapter sequences and low-quality score bases using Trimmomatic v0.36. The resulting reads were mapped to the human reference genome (hg38) using BWA-MEM v0.7.12 in paired-end mode at default parameters. Only reads that had a unique alignment (mapping quality > 20) were retained and PCR duplicates were removed using Picard tools v2.0.1 (https://broadinstitute.github.io/picard/). Peaks in PTEN-ERRg+ DU145 cells were called using MACS2 software suite v2.1.1.20160309 at an FDR alpha < 0.05 using sequenced libraries of ChIP'd DNA from PTEN-ERRglow DU145 cells as control.
Data quality	At an FDR < 0.05, 2775 ERRg peaks were detected in PTEN-ERRg+ vs PTEN-ERRglow DU145 cells. Of 2775 peaks found, 961 (35%) were found enriched at least 5-fold by MACS2.
Software	Peak annotation was performed using the annotatePeaks.pl command from HOMER software suite v4.11.163. For heatmap generation, computeMatrix followed by plotHeatmap from deepTools v3.5.0 was used to formulate the figure based on normalized (RPKM) bigwig track information and peak locations. De novo motif enrichment analysis of peaks was performed by HOMER using the findMotifsGenome.pl with default parameters. ChIP-seq tracks were visualized using the UCSC genome browser.