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Reporting Summary

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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

The cancer genome atlas (TCGA)
cBioPortal for Cancer Genomics
TIMER2.0 for analysis of tumor-infiltrating immune cells

Data analysis

nf-core rnaseq pipeline (version 3.6)
Trimgalore (version 0.6.7)
STAR RNA-Seq aligner (version 2.6.1d)
Salmon (version 1.5.2)
DeSeq
https://www.gsea-msigdb.org/gsea/index.jsp
https://maayanlab.cloud/Enrichr/
Singleron Celescope tool (https://github.com/singleron-RD/CeleScope)
R version 4.1.1 (2021-08-10)

package	*	version	date (UTC)	lib	source
abind		1.4-5	2016-07-21	[1]	CRAN (R 4.1.0)
Biobase	*	2.52.0	2021-05-19	[1]	Bioconductor
BiocGenerics	*	0.38.0	2021-05-19	[1]	Bioconductor
BiocParallel		1.26.2	2021-08-22	[1]	Bioconductor
bitops		1.0-7	2021-04-24	[1]	CRAN (R 4.1.0)

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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

Proteomics data were deposited to PRIDE database under PXD044287 accession number. GEO entries (GSE240383) for RNA-seq and scRNA-seq are now available.

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	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design; whether sex and/or gender was determined based on self-reporting or assigned and methods used.* *Provide in the source data disaggregated sex and gender data, where this information has been collected, and if consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected.* *Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Reporting on race, ethnicity, or other socially relevant groupings	*Please specify the socially constructed or socially relevant categorization variable(s) used in your manuscript and explain why they were used. Please note that such variables should not be used as proxies for other socially constructed/relevant variables (for example, race or ethnicity should not be used as a proxy for socioeconomic status).* *Provide clear definitions of the relevant terms used, how they were provided (by the participants/respondents, the researchers, or third parties), and the method(s) used to classify people into the different categories (e.g. self-report, census or administrative data, social media data, etc.)* *Please provide details about how you controlled for confounding variables in your analyses.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	Prostate cancer samples were obtained from 1) Vancouver Prostate Centre and analysed at Vancouver Prostate Centre, and 2) Oslo University Hospital, and analyzed by Oslo University Hospital.
Ethics oversight	All patient specimens were obtained with written informed consent and the approval of the local institutional review board.

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	It is standard for the mouse studies of type we undertook to have 3-10 mice per group, which we have done.
Data exclusions	Some mice were excluded due to unexpected necrosis, unexplained frailty, or lack of tumor growth.
Replication	All in vitro experiments were replicated 2-3 times. All mouse experiments included analysis on at least 6-16 tumor samples.
Randomization	Mice were injected with cancer cell and randomized for any treatment.
Blinding	Blinding was not relevant in this study.

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-IRE1α (Cell signaling, 3294S, lot:10, 1:1000 western; 1:50 IHC) anti-β-Actin (Cell signaling, 3700, lot:2, 1:20000) anti-CD68 (Cell Marque, 168M-95, Clone Kp-1; 1:200) anti-PD-1 (ichorbio, ICH1132UL, lot: 0522L310) anti-IgG2a (ichorbio, ICH2244UL, lot: 0123L370) anti-PTEN (Cell Signaling, #9559S, 1:1000) anti-AR (Santa Cruz, sc-816, clone N-20, 1:50)
Validation	All the antibodies were validated by manufacturer, and the information about the validation can be found on the manufacturer's website through the links below: https://www.cellsignal.com/ https://www.cellmarque.com/ https://ichor.bio/ https://www.scbt.com/

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Myc-CaP (ATCC, CRL-3255); Myc-CaP-PTEN KO (generated in this study); RM-1 (ATCC, CRL-3310)
Authentication	No authentication was performed.
Mycoplasma contamination	Lack of Mycoplasma contamination was regularly confirmed
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

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	Four week-old male Nude (BALB/c Nu/Nu), FVB/NRj, or C57BL/6 mice were used in the study. All animal studies were performed according to the experimental protocol (mouse strain, animal sex, age, number of animals allowed, and housing).
Wild animals	No wild animals were used in the study.
Reporting on sex	Experiments were performed in male mice since we study prostate cancer.
Field-collected samples	The study did not involve field-collected samples.
Ethics oversight	All animal studies were performed according to the experimental protocols (mouse strain, animal sex, age, number of animals allowed, and housing) that were approved by the University of Oslo Institutional Animal Care and Use Ethical Committee and Norwegian Food Safety Authority under FOTS ID #27414.

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 ICMJEguidelines for publication of clinical research and a completedCONSORT 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.*

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	Apaptosis analysis was performed following the standard flow cytometry apoptosis protocol. Briefly, cells were trypsinized and washed with cell staining buffer (Biolegend). 100 µl of cells in Annexin V binding buffer (Biolegend) were stained with 3 µl of 7-AAD viability staining solution (Biolegend) and Annexin V (Biolegend) for 15 minutes at room temperature. Cells were then resuspended in Annexin V binding buffer and analysed via flow cytometry. Cell cycle analysis was performed following the standard cell cycle flow cytometry protocol. Briefly, cells were resuspended by adding -20˚ C pre-cooled methanol drop by drop with gently vortexing. Cells were fixed overnight at -20˚C in methanol. Fixed cells were then washed with PBS and resuspended in staining buffer (PBS containing 1.5 µg/ml Hoechst 33258 and 100 µg/ml RNase A). Cells were then subjected to flow cytometry. For cell sorting, Myc-CaP cells were transfected with PX458 plasmid expressing Cas9, GFP, and sgRNA against IRE1α. After 72 hours, cells were resuspended in cell sorting buffer (PBS containing 2% FBS and 2mM EDTA), positive cells were FACS sorted via BD FACSAria III Cell Sorter into 96-well plates as 1 cell/well. They were then allowed to form colonies and analyzed.
Instrument	BD LSR II Flow Cytometer, BD FACSAria III Cell Sorter
Software	Kaluza Analysis Software (Beckman Coulter Life Sciences), BD FACSuite

Cell population abundance	Cell population abundance was determined based on green fluorescent protein (GFP) as a marker after transfecting Myc-CaP cells with the PX458 plasmid.
Gating strategy	All flow events were gated with SSC-A/FSC-A. Then, single cells evenrs were gated with SSC-A/SSC-W.

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