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	Data were collected by using Microsoft Excel 2016 64-bit (Microsoft), IMAGEJ version win64 (NIH:https://imagej.nih.gov/ij/), Zeiss Microscope with Canon EOS 450D camera, ImageScope Slide Viewing APERIO Software 12.1, GraphPad Prism Version 7.00 (GraphPad), StepOne software v2.2 (Life Technologies), FUSION SOLO S FX6 Edge 18.14-SN (Vilber Smart Imaging), Monolith NT.115 (NanoTemper Technologies BmbH).
Data analysis	To analyse ATAC sequencing data the following tools were used: - FastQC (v.0.11.9), TrimGalore, Bowtie2, SAMtools, BEDtools, Genrich, featureCounts. - DESeq (v1.36.0) and ChIPseeker in R environment (v.4.2) To analyse RNA sequencing data the following tools were used: - FastQC (v.0.11.9), STAR (v.2.6.1c) - DESeq2 (v1.36.0), cameraPR, enrichR (v.3.1)

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

Raw data of RNA-seq experiment of RWPE-1 and VCaP cell lines are stored in ArrayExpress database with the following accession numbers: E-MTAB-12029 and E-MTAB-12031 (https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-12029?query=E-MTAB-12029%20; https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-12031?query=E-MTAB-12031%20). Raw data ATAC-seq data are stored with the accession number E-MTAB-12025 (https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-12025?query=E-MTAB-12025). Raw data of RNA-seq experiment of VCaP cells treated with MAT2A inhibitors are stored with the following accession number E-MTAB-12536 (https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-12036?query=E-MTAB-12029%20. Raw data of ChIP-seq are stored with the accession number E-MTAB-12990 (https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-12990?query=E-MTAB-12990%20). The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium 89 via the PRIDE 90,91 partner repository with the dataset identifier PXD042895 (http://www.ebi.ac.uk/pride/archive/projects/PXD042895). Source data are provided with this paper (see Source data file). The remaining data are available within the Article, Supplementary Information or Source Data file. The publicly available RNA-seq data used in this study are available in GEO (Gene Expression Omnibus), SRA (Short Read Archive), and EMBL-EBI databases under accession codes and respective hyperlinks: GSE12079592 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE120795), GSE12074193(https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE120741), GSE11843594 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE118435),GSE12607895 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE126078),PRJNA47744996 https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA477449,PRJEB2109297 https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJEB21092, and E-MTAB-965698 (https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-9656). The publicly available ERG ChIP-seq data are available in NCBI GEO repository under accession number GSE28951. https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE28951 .

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	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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	For in vitro studies: sample sizes were determined based on pilot studies and previous similar studies from this group. For in vivo studies: animal experiments were conducted with 4 -7 mice per groups. These sample sizes in previous and similar studies have given statistically significant results based on the variance of xenograft growth in control mice. For ethical reasons, the minimum number of animals necessary to achieve the scientific objectives was used.
Data exclusions	No data excluded
Replication	All experiments were performed with sufficient biological and technical replicates with cells and animals per group in order to demonstrate statistical significance.
Randomization	For in vivo experiments, animals were randmonly subdivided into respective groups for experiments. For in vitro and other experiments, no randomization was necessary.
Blinding	For experiments blinding was not necessary during the experimentation and data collection. As the results were quantitative and did not require critical interpretations or subjective judgment. Also these groups were well defined and studied using standard protocols.

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

Rabbit polyclonal anti-MAT2A (cat. NB110-94158, Novus Biological, lot. F-4, 1:500)
Rabbit polyclonal anti-ERG (cat. ab-92513, Abcam, lot. 1033223-26, clone. EPR3864 1:3000)
Rabbit polyclonal anti-AR (cat. 06-680, Merk Millipore, lot. 2387519, 1:1000)
Rabbit monoclonal anti-EZH2 (CST, cat. 5246, clone. D2C9, 1:1000)
Mouse monoclonal anti-EZH2 (cat. 612667, BD Biosciences, lot.9122760, 1:1000)
Mouse monoclonal anti-mERG (custom-made; 10.1038/s41467-021-24380-6, 1:1000)
Rabbit polyclonal anti-Chromogranin A (cat. ab-15160, Abcam, 1: 1000)
Rabbit Monoclonal anti-synaptophysin (MA5-14532, ThermoFisher Scientific, clone. SP11, 1:1000)
Rabbit polyclonal anti-H3K4me2 (cat. 9725S, Cell Signaling, lot. 13, 1:1000)
Rabbit polyclonalanti-H3K4me3 (cat. 9751S, Cell Signaling, lot. 15, 1:1000)
Rabbit polyclonalanti-H3K27me3 (cat. 9733S, Cell Signaling, lot.19, 1:1000)
Rabbit polyclonal anti-H3K9me2 (cat. 4658S, Cell Signaling, lot.10, 1:1000)
Rabbit polyclonal anti-H3K9me3 (cat. 13969S, Cell Signaling, lot. 5, 1:1000)
Rabbit polyclonal anti-H3K36me3 (cat. 4909S, Cell Signaling, lot. 6, 1:1000)
Rabbit polyclonal anti-H3 (cat. 4499S, Cell Signaling, lot. 7, 1:1000)
Rabbit Monoclonal anti Ki67 (Lab Vision: RM-9106-R7, clone. SP6)
Anti-GAPDH (cat. sc-47724, Santa Cruz Biotechnology, clone 0411 sc-47724, lot. C3117, 1:10000)
Anti-HSP90 (cat. 13171-1-AP, ProteinTech, clone: F-8 sc-13119, lot. C1011, 1:10000)
Anti-alpha-Tubulin (cat. CP06, Calbiochem, DM1A D00175772, 1:10000)
Normal mouse IgG (cat. 12-371, Millipore, lot. 32087775)

Validation

Rabbit polyclonal anti-MAT2A (cat. NB110-94158, Novus Biological, lot. F-4, 1:500)
Validation: https://www.novusbio.com/products/mat2a-antibody_nb110-94158

Rabbit polyclonal anti-ERG (cat. ab-92513, Abcam, lot. 1033223-26, clone. EPR3864 1:3000)

Validation: https://www.abcam.com/erg-antibody-epr3864-ab92513.html

Mouse monoclonal anti-EZH2 (cat. 612667, BD Biosciences, lot.9122760, 1:1000)
Validation: https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/purified-mouseanti-ezh2-11ezh2/p/612667

Rabbit monoclonal anti-EZH2 (CST, cat. 5246, clone D2C9, 1:1000)
https://www.cellsignal.com/products/primary-antibodies/ezh2-d2c9-xp-rabbit-mab/5246?_requestid=2081038

Rabbit polyclonal anti-Chromogranin A (Abcam, cat. ab15160)
https://www.abcam.com/products/primary-antibodies/chromogranin-a-antibody-ab15160.html

Rabbit polyclonal anti-AR (cat. 06-680, Merk Millipore, lot. 2387519, 1:1000)
Validation: https://www.merckmillipore.com/CH/de/product/Anti-Androgen-Receptor-Antibody,MM_NF-06-680

Rabbit Monoclonal anti-synaptophysin (MA5-14532, ThermoFisher Scientific, clone. SP11, 1:1000)
https://www.thermofisher.com/antibody/product/Synaptophysin-Antibody-clone-SP11-Monoclonal/MA5-14532

Rabbit Monoclonal anti Ki67 (Lab Vision: RM-9106-R7, CLONE. SP6)
Validation: https://assets.thermofisher.com/TFS-Assets/APD/Specification-Sheets/D12537~.pdf

Normal mouse IgG (cat. 12-371, Millipore, lot. 32087775)
Validation: https://www.merckmillipore.com/CH/de/product/Normal-Mouse-IgG,MM_NF-12-371

anti-GAPDH (Santa Cruz: sc-47724)
Validation: https://www.scbt.com/p/gapdh-antibody-0411

anti-alpha-tubulin (Calbiochem: Cp06)
Validation: https://www.merckmillipore.com/CH/de/product/Anti-Tubulin-Mouse-mAb-DM1A,EMD_BIO-CP06

Rabbit polyclonal anti-H3K4me2 (cat. 9725S, Cell Signaling)
Validation: https://www.cellsignal.com/products/primary-antibodies/di-methyl-histone-h3-lys4-c64g9-rabbit-mab/9725

Rabbit polyclonalanti-H3K4me3 (cat. 9751S, Cell Signaling)
Validation: https://www.cellsignal.com/products/primary-antibodies/tri-methyl-histone-h3-lys27-c36b11-rabbit-mab/9733

Rabbit polyclonalanti-H3K27me3 (cat. 9733S, Cell Signaling)
Validation: https://www.cellsignal.com/products/primary-antibodies/tri-methyl-histone-h3-lys4-c42d8-rabbit-mab/9751?site-search-type=Products&N=4294956287&Ntt=h3k4me3&fromPage=plp

Rabbit polyclonal anti-H3K9me2 (cat. 4658S, Cell Signaling)
Validation: https://www.cellsignal.com/products/primary-antibodies/di-methyl-histone-h3-lys9-d85b4-xp-rabbit-mab/4658?site-search-type=Products&N=4294956287&Ntt=h3k9me2&fromPage=plp

Rabbit polyclonal anti-H3K9me3 (cat. 13969S, Cell Signaling)
Validation: https://www.cellsignal.com/products/primary-antibodies/tri-methyl-histone-h3-lys9-d4w1u-rabbit-mab/13969?site-search-type=Products&N=4294956287&Ntt=h3k9me3&fromPage=plp

Rabbit polyclonal anti-H3K36me3 (cat. 4909S, Cell Signaling)
Validation: https://www.cellsignal.com/products/primary-antibodies/tri-methyl-histone-h3-lys36-d5a7-xp-rabbit-mab/4909?site-search-type=Products&N=4294956287&Ntt=h3k36me3&fromPage=plp

Rabbit polyclonal anti-H3 (cat. 4499S, Cell Signaling)
Validation: https://www.cellsignal.com/products/primary-antibodies/histone-h3-d1h2-xp-rabbit-mab/4499?site-search-type=Products&N=4294956287&Ntt=4499s%2C&fromPage=plp&_requestid=1393616

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	RWPE-1 (ATCC: CRL-11609). VCaP (ATCC: CRL-2876). EPG2 cell line was established in our laboratory. LNCaP (ATCC: CRL-1740). LNCaP abl (Cellosaurus: CVCL-4793). 22Rv1 (ATCC: CRL-2505). UGSM-2 (Cellosaurus: CVCL_LF83). NCI-H660 (ATCC: CRL-5813).

Authentication	RWPE-1, VCaP , LNCaP, 22Rv1 and NCI-H660 cells were purchased from ATCC. ATCC uses PCR based approaches, karyotyping, and morphology to confirm the identity of human cell lines. LNCAPabl and UGSM-2 were purchased from Cellosaurus and authentication performed by STR.
Mycoplasma contamination	Cells were regularly checked for mycoplasm contamination using MycoAlert Mycoplasma detection kit [Lonza]. Results were always negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in present 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	Male of NOD.Cg-PrkdcSCID Il2rgtm1Wjl/SzJ (NSG) and NOD-Rag2-IL2rgTm1/Rj (NRG) mice (8-10 weeks old, Jackson Laboratories) were used for xenografts establishment. The PbCre4; Pten flox/+ R26LSL;ERG male mice (24–26 weeks old) were used in the experiments (Line generously provided by Dr. Charles L. Sawyers). Cages were well ventilated, softly lit and subject to a light/dark cycle. The relative humidity kept at 45 to 65%. Mouse rooms and cages kept at a temperature range of 20-24°C. Animals handling was carried out according to the protocol approved by the Swiss Cantonal Veterinary Authority (TI 04/2020).
Wild animals	No wild animals were used.
Reporting on sex	All experiments were performed on male mice.
Field-collected samples	No field-collected samples were used.
Ethics oversight	Animals handling was carried out according to the protocols approved by the Swiss Cantonal Veterinary Authority (TI29/19, TI44/23, and TI04/20).

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

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

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.*	Raw data of Chip-seq experiment are stored in ArrayExpress database with the following accession numbers: E-MTAB-12990. For each sample fastq and bam files were provided.
Files in database submission	VCaP_Ctrl_H3K4me2_REP1 VCaP_Ctrl_H3K4me2_REP2 VCaP_Ctrl_H3K4me2_REP3 VCaP_Ctrl_Input_REP1 VCaP_Ctrl_Input_REP2 VCaP_Ctrl_Input_REP3 VCaP_shMAT2A_H3K4me2_REP1 VCaP_shMAT2A_H3K4me2_REP2 VCaP_shMAT2A_H3K4me2_REP3 VCaP_shMAT2A_Input_REP1 VCaP_shMAT2A_Input_REP2 VCaP_shMAT2A_Input_REP3

Genome browser session (e.g. UCSC)	Link genome index: http://igenomes.illumina.com.s3-website-us-east-1.amazonaws.com/Homo_sapiens/UCSC/hg38/Homo_sapiens_UCSC_hg38.tar.gz

Methodology

Replicates	For ChIP-seq: 3 replicates per conditions (shCTRL Input, shCTRL H3K4me2, Sh1 Input, Sh1 H3K4me2)
Sequencing depth	read length = 120, single-end FASTQ Sample; total number of reads VCaP_Ctrl_H3K4me2_REP1; 55255931 VCaP_Ctrl_H3K4me2_REP2; 38765433 VCaP_Ctrl_H3K4me2_REP3; 36535639 VCaP_Ctrl_Input_REP1; 41097303 VCaP_Ctrl_Input_REP2; 41364778 VCaP_Ctrl_Input_REP3; 46555172 VCaP_shMAT2A_H3K4me2_REP1; 53749724 VCaP_shMAT2A_H3K4me2_REP2; 54166222 VCaP_shMAT2A_H3K4me2_REP3; 44243774 VCaP_shMAT2A_Input_REP1; 37214832 VCaP_shMAT2A_Input_REP2; 37750150 VCaP_shMAT2A_Input_REP3; 45739839
Antibodies	H3K4me2 (cat. 9725S, Cell Signaling) Validation: ttps://www.cellsignal.com/products/primary-antibodies/di-methyl-histone-h3-lys4-c64g9-rabbit-mab/9725
Peak calling parameters	macs3 callpeak -t SAMPLE.rmDup.bam -c input.rmDup.bam -g hs -n SAMPLE.bam
Data quality	The data quality was ensured with FastQC
Software	For the Chip Seq analysis, the following tools were exploited: Bowtie2, Trim Galore, Picard, MACS3, DiffBind, ChIPseeker