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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	High-throughtput Illumina sequencing. Semi-quantitative and quantitative PCR data were collected on Bio-Rad ChemiDoc System and StepOnePlus (Thermofisher), respectively. Facs data were collected on FACS-Calibur flow cytometer (Becton Dickinson). Luciferase data were collected using Lumat LB 9507 (Eg&G Berthold).
Data analysis	PRISM8 Software was used for statistical analysis and graphics. Densitometric analyses of western blot and agarose gels were performed using ImageJ 1.51g software. FACS data were analysed using FlowJo vX0.7 software. R v3.6.0 was used for statistical computing and graphics. bedtools 2.29.2 was used for conversion of bed files in bam files. NGSplot 2.63 was used for metagene analysis. Biostrings 2.58.0 was used for nucleotide frequency calculation. topGO 2.42.0 was used for Gene Ontology analysis.

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 sequencing data used in this study are deposited and publicly accessible in GEO (GSE198872). Public sequencing data used in this study are: GSE37401 (doi: 10.1016/j.celrep.2012.05.003); GSE85164 (doi: 10.1038/nature21715); GSE46691(doi: 10.1371/journal.pone.0066855); GSE29079 (doi: 10.1186/1471-2407-11-507); and GSE21034 (doi: 10.1016/j.ccr.2010.05.026). Prostate Adenocarcinoma (TGCA, PanCancer Atlas, 494 samples) gene expression data (mRNA) and clinical data (Progression-Free Sruvival) was downloaded from cBioPortal (https://www.cbioportal.org/study/summary?id=prad_tcga_pan_can_atlas_2018).

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

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 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.*
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	No sample size calculations were performed. RNA-seq sample size were chosen based on our previous experience (PMID:30840896; 30865884) and pilot sudies. Sample size for siRNAs experiments were chosen based on our previous studies (PMID: 31066450; 24514149; 23995791). Sample size of each experiment is indicated in Figure legends as well as the type of statistical test used to calculate the significance. In all experiments, three biological replicates were sufficient to reach the significance.
Data exclusions	No data were excluded in this study.
Replication	Experiments were performed on at least three biologically independent replicas. All replications was sucesfully.
Randomization	For correlation analyses using public PC datasets, patients were grouped according to the median of gene expression. Experiments were performed using genetically defined cell lines thus randomization as well as covariates were not applicable.
Blinding	Analysis of RNA-seq data and IHC were performed in blind. The other experiments were not performed in blind, however semiquantitative and quantitative analyses were used to minimize bias.

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

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

The following antibodies were used:
Sam68 (Bethyl cat# A302-110A; WB: 1:2000, IHC: 1:2000, IP: 2µg/ml extract; CLIP: 3µg/ml extract),
XRN2 (Bethyl cat# A301-103A; WB: 1:1000, IHC: 1:400, IP: 2µg/ml extract)
MYC (Cell signaling cat# 9402; WB: 1:1000, ChIP: 5µg/100µg chromatin)
β-actin clone AC-15 (Merck, Sigma-Aldrich cat# A2066; WB: 1:1000),
CPSF160 (Bethyl cat# A301-580A; WB: 1:500),
CPSF100 (Novus cat# NB100-79823; WB: 1:1000),
CPSF73 (Bethyl cat# A301-091A; WB: 1:1000),
CPSF30 (Novus cat# NB100-79826; WB: 1:1000; CLIP: 3µg/ml extract),
WDR33 (Bethyl cat# A301-152A; WB: 1:500),
CFIM68 (Bethyl cat# A301-358A; WB: 1:1000),
CSTF50 (Bethyl cat# A301-250A; WB: 1:1000),
CSTF64 (Bethyl cat# A301-092A; WB: 1:1000; CLIP: 3µg/ml extract),
PCF11 (Bethyl cat# A303-706A; WB: 1:1000),
POLR2A (Rpb1 NTD (D8L4Y) ; Cell signaling cat# 14958; WB: 1:1000),
H3 (abcam cat# ab1791; WB: 1:1000),
MCM10 (Bethyl cat# A300-131A; WB: 1:1000),
ORC2 (Bethyl cat# A302-734A; WB: 1:1000),
Lamin B1 (S20) (Santa Cruz cat #sc-30264; WB: 1:1000),
GFP (B-2) (Santa Cruz cat# sc-9996; WB: 1:1000),
Flag M2 (Merck, Sigma-Aldrich cat# F3165; WB: 1:1000),
BrdU B44 (BD Biosciences cat# 347580; FACS: 1µg per million of cells)
Alexa-488 (Thermo Fisher Scientific cat# A-11001; FACS: 1µg per million of cells).

Validation

All antibodies used are commercially available and validated by the supplier.
Sam68 (Bethyl cat# A302-110A; https://www.thermofisher.com/antibody/product/SAM68-Antibody-Polyclonal/A302-110A),
XRN2 (Bethyl cat# A301-103A; https://www.thermofisher.com/antibody/product/XRN2-Antibody-Polyclonal/A301-103A),
MYC (Cell signaling cat# 9402; https://www.cellsignal.com/products/primary-antibodies/c-myc-antibody/9402),
β-actin clone AC-15 (Merck, Sigma-Aldrich cat# A2066; https://www.sigmaaldrich.com/IT/it/product/sigma/a5441?gclid=EAIaIQobChMI_Pz09oq1-QIVuIxoCR3CpQu4EAAYASAAEgIW3fD_BwE),
CPSF160 (Bethyl cat# A301-580A; https://www.thermofisher.com/antibody/product/CPSF160-Antibody-Polyclonal/A301-580A),
CPSF100 (Novus cat# NB100-79823; https://www.novusbio.com/products/cpsf2-antibody_nb100-79823),
CPSF73 (Bethyl cat# A301-091A; https://www.thermofisher.com/antibody/product/CPSF73-Antibody-Polyclonal/A301-091A),
CPSF30 (Novus cat# NB100-79826; https://www.novusbio.com/products/cpsf4-antibody_nb100-79826),
WDR33 (Bethyl cat# A301-152A; https://www.thermofisher.com/antibody/product/WDR33-Antibody-Polyclonal/A301-152A-M),
CFIM68 (Bethyl cat# A301-358A; https://www.thermofisher.com/antibody/product/CPSF68-Antibody-Polyclonal/A301-358A),
CSTF50 (Bethyl cat# A301-250A; https://www.thermofisher.com/antibody/product/CSTF50-Antibody-Polyclonal/A301-250A),
CSTF64 (Bethyl cat# A301-092A; https://www.thermofisher.com/antibody/product/CSTF64-Antibody-Polyclonal/A301-092A),
PCF11 (Bethyl cat# A303-706A; https://www.thermofisher.com/antibody/product/PCF11-Antibody-Polyclonal/A303-706A),
POLR2A (Rpb1 NTD (D8L4Y); Cell signaling cat# 14958; https://www.cellsignal.com/products/primary-antibodies/rpb1-ntd-d8l4y-rabbit-mab/14958),
H3 (abcam cat# ab1791; https://www.abcam.com/Histone-H3-antibody-Nuclear-Marker-and-ChIP-Grade-ab1791.html?gclsrc=aw.ds%7Caw.ds&gclid=EAIaIQobChMI7Nu_so61-QIVGofVCh2kHAPFEAAYASAAEgLUnvD_BwE),
MCM10 (Bethyl cat# A300-131A; https://www.thermofisher.com/antibody/product/MCM10-Antibody-Polyclonal/A300-131A),
ORC2 (Bethyl cat# A302-734A; https://www.thermofisher.com/antibody/product/ORC2-Antibody-Polyclonal/A302-734A),
Lamin B1 (S20)(Santa Cruz cat #sc-30264; https://www.scbt.com/p/lamin-b1-antibody-s-20?requestFrom=search),
GFP (B-2) (Santa Cruz cat# sc-9996; https://www.scbt.com/p/gfp-antibody-b-2?requestFrom=search),
Flag M2 (Merck, Sigma-Aldrich cat# F3165; https://www.sigmaaldrich.com/IT/it/product/sigma/f3165?gclid=EAIaIQobChMIiJW5uZG1-QIVhYXVCh1V6AIvEAAYASAAEgIUFPD_BwE),
BrdU (BD Biosciences cat# 347580; https://www.bdbiosciences.com/en-it/products/reagents/flow-cytometry-reagents/clinical-discovery-research/single-color-antibodies-ruo-gmp/purified-mouse-anti-brdu.347580)

Alexa-488 (Thermo Fisher Scientific cat# A-11001; https://www.thermofisher.com/antibody/product/Goat-anti-Mouse-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11001).

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	1. LNCaP clone FGC (ATCC) 2. 22Rv1 (CRL-2505, ATCC) 3. 293T (CRL-3216, ATCC)
Authentication	Cell lines were not authenticated.
Mycoplasma contamination	Cell lines were routinely tested for Mycoplasma by PCR. Cell lines were negative for Mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines have been used in this 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 silenced and pulse-labelled with 30 µM BrdU (Sigma-Aldrich) for 1h. Cells were collected, fixed overnight with a solution of 70% ethanol in PBS (vol/vol) (4°C) and, after ice-cold PBS washes, stained with 50 µl of anti-BrdU antibody (0.02µg/µl) diluted in PBS supplemented with 1% BSA and 0.5% Tween-20, for 1h at RT. After washes in PBS, cells were incubated with 50 µl of Alexa-488-conjugated secondary antibody (0.02µg/µl), for 45 min at RT and treated with 10 µg/ml RNAse A (Merck, Sigma-Aldrich) in presence of propidium iodide (20 µg/ml) (Merck, Sigma-Aldrich). For double thymidine block, cells were treated with 2 mM thymidine (Merck, Sigma-Aldrich) and fixed in ice-cold 70% ethanol overnight at 4°C. A total of 20,000 events were counted.
Instrument	FACS-Calibur flow cytometer (Becton Dickinson)
Software	Data were collected with Cell Quest software (Becton Dickinson) and analysed using FlowJo vX0.7 software.
Cell population abundance	No cell populations were sorted
Gating strategy	Cells were gated for single cells by gating for FL2-A/FL2-W signals. Then, single cells were analyzed for one (PI) or two stain experiment (PI and BrdU).

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