

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

Raw Illumina output was converted to fastq format using Illumina Bcl2fastq

Data analysis

The ChIP-seq (and ATAC-seq) reads were mapped to the hg19 human genome using bwa (version 0.7.17-r1188) with the aln and sampe sub-commands. Samtools (version 1.9) was used to convert sam files to bam format. Enriched ChIP regions were evaluated using MACS2 (version 2.1.4) (49). The Intervene (version 0.6.5) was used to analyze peak intervals, determine overlapped regions, and generate Venn diagrams. The signals associated with genomic regions were visualized using compueMatrix and plotHeatmap tools from deepTools (version 3.3.0). computeMatrix was used to calculate scores for each genomic region and plotHeatmap was used to create a heatmap for scores associated with genomic regions. Motif enrichment analysis was performed using SeqPos with default settings. Binding and Expression Target Analysis (BETA) was performed using the BETA software package (version 1.0.7).

For RNA-seq The human reference genome (hg19) was used to align transcriptome-sequencing reads using STAR (version 2.7.1a). featureCounts (version 2.0.1) from GRCh37 Ensembl reference was used for counting. R package Edger (3.36.0) was then employed to process all gene counts and evaluate the differential expression using the Benjamini-Hochberg false discovery rate (FDR)-adjusted P-value. The expression values were normalized by centering and scaling across samples and displayed using the ComplexHeatmap (version 2.10.0) R package. Gene Set Enrichment Analysis (GSEA) was performed using Software GSEA (version 4.2.2) and R package fgsea (version 1.20.0).

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](#)

All the high-throughput sequencing data have been deposited in GEO under the accession number GSE232555

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	Patients with prostate cancer are of male sex, so no patients of female sex were included.
Reporting on race, ethnicity, or other socially relevant groupings	N/A race, ethnicity and socially relevant groups of the patients who donated tissue were not collected for this study.
Population characteristics	N/A as this study used patient-derived xenografts (PDXs) from patient specimens that were obtained with informed consent
Recruitment	All human tissues were obtained with informed, written consent by an independent clinical coordinator
Ethics oversight	The studies were conducted under Human Research Ethics Committee (Institutional Review Board) approvals at Monash University (7996, 12287) and the Peter MacCallum Cancer Centre (15/98, 97_27).

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	Sample size was determined according to experimental design. No sample size calculation was necessary or performed. All biologic specimens available were used and included in the analysis
Data exclusions	No data were excluded.
Replication	Experiments were generally conducted with at least three independent replicates, and these replicating experiments consistently yielded similar results. For ChIP-seq analyses in cell lines, two to three technical duplicates were performed and then merged for analysis. For ChIP-seq analyses in PDX samples, a minimum of two biological replicates were performed.
Randomization	Samples were randomly allocated
Blinding	The experiments were performed blinded

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	Involvement
<input checked="" type="checkbox"/>	Antibodies
<input checked="" type="checkbox"/>	Eukaryotic cell lines
<input checked="" type="checkbox"/>	Palaeontology and archaeology
<input checked="" type="checkbox"/>	Animals and other organisms
<input checked="" type="checkbox"/>	Clinical data
<input checked="" type="checkbox"/>	Dual use research of concern
<input checked="" type="checkbox"/>	Plants

Methods

n/a	Involvement
<input checked="" type="checkbox"/>	ChIP-seq
<input checked="" type="checkbox"/>	Flow cytometry
<input checked="" type="checkbox"/>	MRI-based neuroimaging

Antibodies

Antibodies used

anti-FOXA1 antibody (Abcam, ab23738, WB:1:2000), anti-FOXA2 antibody (Millipore, 17-10258, WB: 1:1000), anti-FOXA2 antibody (Abcam, ab256493, WB: 1:1000), anti-FOXA2 antibody (Abcam, ab108396), anti-H3K4me2 antibody (Millipore, 07-030, WB:1:1000), anti-H3K27ac antibody (Abcam, ab4729), anti-V5 (Thermo Fisher, R960-25, WB:1:1000), anti-AR (Millipore, 06-680, WB:1:1000), anti-Rabbit IgG (Millipore, 12-370), Mouse IgG (Millipore, 12-371), anti-Methyl-lysine (Abcam, ab23366, WB:1:200), anti-LSD1 (Abcam, ab17721, WB: 1:1000), anti-GAPDH (Abcam, Ab8245, WB:1:5000), anti-FLAG (Sigma, F3040, WB: 1:1000), anti-JUN (CST, 9165S, WB: 1:1000), anti-FOSL1 (CST, 5281S, WB: 1:1000), anti-FOSL2 (CST, 19967S, WB: 1:1000), anti-FOS (CST, 2250S, WB: 1:1000), anti-FOSB (CST, 2251T, WB: 1:1000), anti-Phospho-Aurora A /Aurora B/Aurora C (CST, 2914T, WB:1:1000), anti-rabbit (LI-COR, IRDye 800CW, WB: 1:3000), anti-mouse (LI-COR, IRDye 680RD, WB: 1:3000)

Validation

FOXA1 antibody: reference - PMID: 32868907; <https://www.abcam.com/products/primary-antibodies/foxa1-antibody-ab23738.html>

H3K27ac antibody: reference - PMID: 32868907; <https://www.abcam.com/products/primary-antibodies/histone-h3-acetyl-k27-antibody-chip-grade-ab4729.html>

H3K4me2 antibody: reference - PMID: 32868907; https://www.emdmillipore.com/US/en/product/Anti-dimethyl-Histone-H3-Lys4-Antibody,MM_NF-07-030

FOXA2 antibody: reference - PMID: 32868907; https://www.emdmillipore.com/US/en/product/ChIPAb-FOXA2-ChIP-Validated-Antibody-and-Primer-Set,MM_NF-17-10258?ReferrerURL=https%3A%2F%2Fwww.google.com%2F&bd=1

FOXA2 antibody: reference - PMID: 33009820 <https://www.abcam.com/en-hk/products/primary-antibodies/foxa2-antibody-epr22919-71-chip-grade-ab256493>

FOXA2 antibody: reference - PMID: 28938408; <https://www.abcam.com/products/primary-antibodies/foxa2-antibody-epr4465-chip-grade-ab108396.html>

JUN antibody: reference - PMID: 35617398; <https://www.cellsignal.com/products/primary-antibodies/c-jun-60a8-rabbit-mab/9165>

FOSL1 antibody: reference - PMID: 35617398; <https://www.cellsignal.com/products/primary-antibodies/fra1-d80b4-rabbit-mab/5281>

FOSL2 antibody: reference - PMID: 33219226; <https://www.cellsignal.com/products/primary-antibodies/fra2-d2f1e-rabbit-mab/19967>

FOS antibody: reference - PMID: 37821650; <https://www.cellsignal.com/products/primary-antibodies/c-fos-9f6-rabbit-mab/2250>

FOSB antibody: reference - PMID: 32923607; <https://www.cellsignal.com/products/primary-antibodies/fosb-5g4-rabbit-mab/2251>

AR antibody: reference - PMID: 32868907; https://www.emdmillipore.com/US/en/product/Anti-Androgen-Receptor-Antibody,MM_NF-06-680

anti-Phospho-Aurora A /Aurora B/Aurora C antibody: reference - PMID: 33953309; <https://www.cellsignal.com/products/primary-antibodies/phospho-aurora-a-thr288-aurora-b-thr232-aurora-c-thr198-d13a11-xp-rabbit-mab/2914>

Rabbit IgG Antibody: reference - PMID: 32868907; https://www.emdmillipore.com/US/en/product/Normal-Rabbit-IgG,MM_NF-12-370

Mouse IgG Antibody: reference - PMID: 32868907; https://www.emdmillipore.com/US/en/product/Normal-Mouse-IgG,MM_NF-12-371

Methylated-lysine Antibody: reference - PMID: 32868907; <https://www.abcam.com/en-no/products/primary-antibodies/methylated-lysine-di-methyl-mono-methyl-antibody-ab23366>

LSD1 Antibody: reference - PMID: 31428587; <https://www.abcam.com/products/primary-antibodies/kdm1Lsd1-antibody-nuclear-marker-ab17721.html>

GAPDH Antibody: reference - PMID: 37549269; <https://www.abcam.com/products/primary-antibodies/gapdh-antibody-6c5-loading-control-ab8245.html>

FLAG Antibody: reference - PMID: 37663929; <https://www.sigmaaldrich.com/US/en/product/sigma/f3040>

anti-rabbit: reference - PMID: 32868907; <https://www.licor.com/bio/reagents/irdye-800cw-infrared-dyes>

anti-mouse: reference - PMID: 32868907; <https://www.licor.com/bio/reagents/irdye-680rd-infrared-dyes>

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

PC-3, LNCaP, NCI-H660 and CWR-22Rv1 were purchased from ATCC. SKO and DKO cells were from Dr. Leigh Ellis' lab.

Authentication

Authenticated using short tandem repeat (STR) profiling

Mycoplasma contamination	Mycoplasma contamination was assessed using the MycoAlert kit from Lonza, and no contamination was detected.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used

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	Mouse, ICR SCID, male, 6 weeks; Zebrafish embryos, AB or Tubingen wild-type lines, male/female, 3 days post-fertilization
Wild animals	No wild animals were used in the study
Reporting on sex	The finding only applies to male since prostate cancer is a male-specific disease
Field-collected samples	No field collected samples were used in the study
Ethics oversight	Animal experiments were conducted in accordance with institutional and USA national guidelines and were approved by the Institutional Animal Care and Use Committee (IACUC) of University of Massachusetts Boston. Animal group sizes were estimated based on the power analysis using preliminary data and were approved by IACUC.

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

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.

<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE232555>
<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE114268>
<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE72467>
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Files in database submission

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 201.1_PDX_H3K27ac_Rep1(H9).bigwig
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Genome browser session
(e.g. [UCSC](#))

N/A

Methodology

Replicates

Individual cell line ChIP-seq, technical duplicates were performed and then merged for analysis. Regarding individual PDX samples'

Sequencing depth

ChIP-seq were 51bp paired-end

sample_name	Unique Reads	Duplicate Reads
DKO_NTC_ChIPFOXA2_1_S1_L001_R1_001	7137911	23843626
DKO_NTC_ChIPFOXA2_1_S1_L001_R2_001	7514199	23467338
DKO_NTC_ChIPFOXA2_2_S2_L001_R1_001	6376438	20688062
DKO_NTC_ChIPFOXA2_2_S2_L001_R2_001	6706406	20358094
DKO_ORY10uM_ChIPFOXA2_1_S3_L001_R1_001	11533740	26390444
DKO_ORY10uM_ChIPFOXA2_1_S3_L001_R2_001	12038918	25885266
DKO_ORY10uM_ChIPFOXA2_2_S4_L001_R1_001	11656330	22933132
DKO_ORY10uM_ChIPFOXA2_2_S4_L001_R2_001	12062048	22527414
LN_FOXA2K265R_ChIPFOXA2_1_S1_L001_R1_001	11204891	17305805
LN_FOXA2K265R_ChIPFOXA2_1_S1_L001_R2_001	11569023	16941673
LN_FOXA2K265R_ChIPFOXA2_2_S2_L001_R1_001	10852509	13895563
LN_FOXA2K265R_ChIPFOXA2_2_S2_L001_R2_001	11154851	13593221
ab108396_PC3_Rep1_21-01620_R1	22597891	1857777
ab256493_PC3_Rep1_21-01622_R1	23993484	1690731
H660_ORY_ChIP_FOXA2_1_S23_L001_R1_001	13398797	18914161
H660_ORY_ChIP_FOXA2_1_S23_L001_R2_001	13515239	18914161
H660_ORY_ChIP_FOXA2_2_S24_L001_R1_001	13351508	19103741
H660_ORY_ChIP_FOXA2_2_S24_L001_R2_001	13464894	19103741
H660_Veh_ChIP_FOXA2_1_S21_L001_R1_001	12919541	19072842
H660_Veh_ChIP_FOXA2_1_S21_L001_R2_001	13021927	19072842
H660_Veh_ChIP_FOXA2_2_S22_L001_R1_001	5599247	7265942
H660_Veh_ChIP_FOXA2_2_S22_L001_R2_001	5623740	7265942
H660_Veh_ChIP_H3K4me2_1_S23_L001_R1_001	10520329	11789280
H660_Veh_ChIP_H3K4me2_1_S23_L001_R2_001	10506242	11789280
H660_Veh_ChIP_H3K4me2_2_S24_L001_R1_001	9364057	10472299
H660_Veh_ChIP_H3K4me2_2_S24_L001_R2_001	9351644	10472299
H660_siFOXA2_ChIP-JUN_1_S19_L001_R1_001	13942243	19120687
H660_siFOXA2_ChIP-JUN_1_S19_L001_R2_001	14062194	19120687
H660_siFOXA2_ChIP-JUN_2_S20_L001_R1_001	15644963	22248440
H660_siFOXA2_ChIP-JUN_2_S20_L001_R2_001	15799960	22248440
H660_siNC_ChIP-JUN_1_S17_L001_R1_001	12874805	17330477
H660_siNC_ChIP-JUN_1_S17_L001_R2_001	12961817	17330477
H660_siNC_ChIP-JUN_2_S18_L001_R1_001	14259534	19464930
H660_siNC_ChIP-JUN_2_S18_L001_R2_001	14345142	19464930
H660_siNTC_VEH_ATAC_S1_L001_R1_001	41057790	74506192
H660_siNTC_VEH_ATAC_S1_L001_R2_001	41233498	74506192
LN_FOXA2OE_ChIPFOXA2_1_S1_L001_R1_001	50604697	76129836
LN_FOXA2OE_ChIPFOXA2_1_S1_L001_R2_001	51875569	76129836
LN_FOXA2OE_ChIPFOXA2_2_S2_L001_R1_001	38590985	53069065
LN_FOXA2OE_ChIPFOXA2_2_S2_L001_R2_001	39322064	53069065
LN_FOXA2OE_ChIP_JUN_1_S5_L001_R1_001	8489204	22019857
LN_FOXA2OE_ChIP_JUN_1_S5_L001_R2_001	8688696	22019857
LN_FOXA2OE_ChIP_JUN_2_S6_L001_R1_001	9291303	27006477
LN_FOXA2OE_ChIP_JUN_2_S6_L001_R2_001	9506232	27006477
LN_siFOXA1_ChIP_JUN_1_S15_L001_R1_001	12138693	22516428
LN_siFOXA1_ChIP_JUN_1_S15_L001_R2_001	12327027	22516428
LN_siFOXA1_ChIP_JUN_2_S16_L001_R1_001	13269793	25398565
LN_siFOXA1_ChIP_JUN_2_S16_L001_R2_001	13485426	25398565
LN_siNC_ChIP_JUN_1_S13_L001_R1_001	11139988	18642165
LN_siNC_ChIP_JUN_1_S13_L001_R2_001	11273004	18642165
LN_siNC_ChIP_JUN_2_S14_L001_R1_001	11010900	17245893
LN_siNC_ChIP_JUN_2_S14_L001_R2_001	11116779	17245893
PC3_C12_CHIP-FOXA2_1_S5_L001_R1_001	12448066	16732083
PC3_C12_CHIP-FOXA2_1_S5_L001_R2_001	12526898	16732083
PC3_C12_CHIP-FOXA2_2_S6_L001_R1_001	12955538	17375112
PC3_C12_CHIP-FOXA2_2_S6_L001_R2_001	13029917	17375112
PC3_ORY_CHIP-FOXA2_1_S1_L001_R1_001	15425770	23852117
PC3_ORY_CHIP-FOXA2_1_S1_L001_R2_001	15598523	23852117
PC3_ORY_CHIP-FOXA2_2_S2_L001_R1_001	12558159	18536898
PC3_ORY_CHIP-FOXA2_2_S2_L001_R2_001	12693449	18536898
PC3_VEH_ChIP-FOXA2_1_S3_L001_R1_001	16176211	24798100
PC3_VEH_ChIP-FOXA2_1_S3_L001_R2_001	16352871	24798100
PC3_VEH_ChIP-FOXA2_2_S4_L001_R1_001	13985473	21400151
PC3_VEH_ChIP-FOXA2_2_S4_L001_R2_001	14130647	21400151
PC3_siFOXA2_ChIP_FOSL1_1_S3_L001_R1_001	10675306	23734940

	<p>PC3_siFOXA2_ChIP_FOSL1_1_S3_L001_R2_001 10909423 23734940 PC3_siFOXA2_ChIP_FOSL1_2_S4_L001_R1_001 10810477 22575968 PC3_siFOXA2_ChIP_FOSL1_2_S4_L001_R2_001 11036338 22575968 PC3_siFOXA2_ChIP_JUN_1_S15_L001_R1_001 10960598 14209286 PC3_siFOXA2_ChIP_JUN_1_S15_L001_R2_001 10975196 14209286 PC3_siFOXA2_ChIP_JUN_2_S16_L001_R1_001 8140874 10501364 PC3_siFOXA2_ChIP_JUN_2_S16_L001_R2_001 8155286 10501364 PC3_siNC_ChIP_FOSL1_1_S1_L001_R1_001 14327435 22122565 PC3_siNC_ChIP_FOSL1_1_S1_L001_R2_001 14490936 22122565 PC3_siNC_ChIP_FOSL1_2_S2_L001_R1_001 14910761 22911154 PC3_siNC_ChIP_FOSL1_2_S2_L001_R2_001 15090202 22911154 PC3_siNC_ChIP_JUN_1_S13_L001_R1_001 13307903 18167930 PC3_siNC_ChIP_JUN_1_S13_L001_R2_001 13345814 18167930 PC3_siNC_ChIP_JUN_2_S14_L001_R1_001 13241267 17866678 PC3_siNC_ChIP_JUN_2_S14_L001_R2_001 13288283 17866678 PC3_siNTC_VEH_ATAC_S4_L001_R1_001 72912270 115177815 PC3_siNTC_VEH_ATAC_S4_L001_R2_001 73007758 115177815 PC3_siNC_ChIP_H3K27AC_1_S1_L001_R1_001 24234276 28496885 PC3_siNC_ChIP_H3K27AC_1_S1_L001_R2_001 24215934 28496885 PC3_siNC_ChIP_H3K27AC_2_S2_L001_R1_001 29432323 35308949 PC3_siNC_ChIP_H3K27AC_2_S2_L001_R2_001 29459460 35308949</p>
Antibodies	anti-FOXA2 antibody (Millipore, 17-10258), anti-FOXA2 antibody (Abcam,ab108396), anti-FOXA2 antibody (Abcam,ab256493), anti-H3K4me2 antibody (Millipore, 07-030), anti-H3K27ac antibody (Abcam, ab4729), anti-JUN (CST, 9165S), anti-FOSL1 (CST, 5281S)
Peak calling parameters	macs2 callpeak -g hs --bw 250 --mfold 10 30 -f BAMPE --extsize 100 --seed 1 --fix-bimodal --qvalue 0.05 --SPMR -B
Data quality	<p>ChIP-seq data were demonstrated to be of high quality through various assessments. Fastqc was executed on all samples to confirm the presence of good quality data. Additionally, the number of peaks was considered, with a cutoff of FDR <= 0.05.</p> <p>Sample_name Peak_number DKO_NTC_ChIPFOXA2_peaks 5715 DKO_ORY10uM_ChIPFOXA2_peaks 44943 LN_FOXA2K265R_ChIPJUN_peaks 47505 ab108396_PC3_Rep1_21-01620_R1_peaks 77822 ab256493_PC3_Rep1_21-01622_R1_peaks 62714 H660_ORY_ChIP_FOXA2 11469 H660_Veh_ChIP_FOXA2 11886 H660_siFOXA2_ChIP_JUN 59452 H660_siNC_ChIP_JUN 18401 H660_siNTC_VEH_ATAC_peaks 99959 H660_Veh_ChIP_H3K4me2 70388 LN_FOXA2OE_ChIP_JUN_peaks 23994 LN_FOXA2OE_ChIPFOXA2_peaks 2500 LN_siFOXA1_ChIP_JUN 1964 LN_siNC_ChIP_JUN 2421 PC3_VEH_CHIP-FOXA2_peaks 24038 PC3_C12_CHIP-FOXA2_peaks 8352 PC3_ORY_CHIP-FOXA2_peaks 13732 PC3_siFOXA2_ChIP_FOSL1 1538 PC3_siNC_ChIP_FOSL1 3843 PC3_siFOXA2_ChIP_JUN_peaks 4081 PC3_siNC_ChIP_JUN_peaks 23890 PC3_siNC_ChIP_H3K27AC_peaks 90468 PC3_siNTC_VEH_ATAC_peaks 210960</p>
Software	MACS2 (version 2.1.4)