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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	Inverted Microscope (Leica, DMi8 automated), Transmission Electron Microscope (HITACHI, HT7800/HT7700), High-resolution laser confocal microscope (Leica, TCSSP8), Flow cytometer (Beckman, CytoFLEX S), Upright microscope (Zeiss, Axio Imager. M2)
Data analysis	Fuji ImageJ_IJ 1.46r, GraphPad Prism 9, FlowJo_v10.8.

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 VSTM2L gene expression in Prostate adenocarcinoma (PRAD) was derived from UALCAN (https://ualcan.path.uab.edu/analysis.html), TCGA PRAD cohort (https://portal.gdc.cancer.gov/), UCSC Xena Browser (https://xena.ucsc.edu/) and GENT2 (http://gent2.appex.kr/gent2/) databases. The survival curves of VSTM2L were derived from cBioPortal (https://www.cbioportal.org/). All data underpinning the conclusions of this research are accessible through a reasonable request

made to the corresponding author.

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	A prostate cancer tissue microarray of Chinese men (Lot No. PRC1601) containing 78 paired tumor and adjacent tissues was obtianed from Guilin Fanpu Biotechnology Co.
Reporting on race, ethnicity, or other socially relevant groupings	The tissues was collected from Chinese men.
Population characteristics	The population characteristics such as age, race or ethnicity were not used to evaluate the differential expression level of VSTM2L in normal and tumor tissues.
Recruitment	participants were not recruited, they are prostate cancer patients who need the examination and treatment.
Ethics oversight	The study using the tissue microarray was approved by the Ethics Committee of Guilin Fanpu Biotechnology Co., Ltd. (Fanpu [2018] No. 23).

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 most experiments, n = 3 was chosen and n = 5 for tumour xenograft assays to ensure an adequate statistical power. All experiments were independently performed at least three times.
Data exclusions	No data was excluded in the study.
Replication	At least triple biological replications are conducted for most experiments to ensure the reproducibility of the data (exception: immunoprecipitation /mass spectrometry and in vivo mouse experiment).
Randomization	All cells and the animals were randomly allocated to experimental groups.
Blinding	Analysis of cell viability, colony forming, trans-well, wound healing and collection or analyzation of data were conducted blindly. FACS, IHC, or photo capture were performed blindly by different individuals. Mass spectrometry analysis were blinded prior to analysis.

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

VSTM2L (25457-1-AP,Protein Tech, U.S.A), VDAC1 (A19707, Abclonal, U.S.A), VDAC1 (ET1601-20, HUABIO, China), GPX4 (sc-166570, Santa Cruz, U.S.A), HK2 (22029-1-AP,Protein Tech, U.S.A), HK2 (66974-1-Ig, Protein Tech, U.S.A), Bax (50599-2-Ig, Protein Tech, U.S.A), Bcl-2 (CPA1095, Cohesion Biosciences, U.K), Cleaved-Caspase 3 (25128-1-AP, Protein Tech, U.S.A), IgG (30000-0-AP, Protein Tech, U.S.A), GFP-Tag (AE012, Abclonal, U.S.A), Flag-Tag (F3165, Merck, Germany), Myc-Tag (16286-1-AP, 60003-2-Ig, Protein Tech, U.S.A), V5-Tag (BE2033, EASYBIO, China), GAPDH (60004-1-Ig, Protein Tech, U.S.A), Alpha Tubulin (11224-1-AP, Protein Tech, U.S.A), Ki 67 (GB151499-100, Servicebio, China), Goat anti-Mouse IgG (H+L) Secondary Antibody, HRP (31430, Thermo, U.S.A), Goat anti-Rabbit IgG (H+L) Secondary Antibody, HRP (31460, Thermo, U.S.A), Goat anti-Mouse Secondary Antibody IgG / FITC (ZF-0312, ZSGB-BIO,China), Goat anti-Rabbit Secondary Antibody IgG / TRITC (ZF-0316, ZSGB-BIO, China), Goat anti-Rabbit Secondary Antibody IgG / FITC (ZF-0311, ZSGB-BIO, China).

Validation

All antibodies used in our study have been validated and detailed information could be found on the website from manufactures as listed below.

VSTM2L (25457-1-AP,Protein Tech, U.S.A), https://www.ptgcn.com/products/VSTM2L-Antibody-25457-1-AP.htm.
Species: Rabbit. Application: WB, IHC, ELISA. Concentration: WB:1:500; IHC:1:100; IF:1:100
Ref: VSTM2L contributes to anoikis resistance and acts as a novel biomarker for metastasis and clinical outcome in ovarian cancer. Biochemical and biophysical research communications.

VDAC1 (A19707, Abclonal, U.S.A), https://abclonal.com.cn/catalog/A19707.
Species: Rabbit. Application: WB, IHC-P, IF/ICC, ELISA. Concentration: WB:1:4000
Ref: SDX on the X chromosome is required for male sex determination. CELL RESEARCH.

VDAC1 (ET1601-20, HUABIO, China),http://www.huabio.cn/products/VDAC1-antibody-ET1601-20.
Species: Rabbit. Application: WB,IF-Cell,IHC-P,FC,IF-Tissue. Concentration: IF:1:100
Ref: Effects and mechanisms of Polygonati Rhizoma polysaccharide on potassium oxonate and hypoxanthine-induced hyperuricemia in mice. Int J Biol Macromol.

HK2 (66974-1-Ig, Protein Tech, U.S.A),https://www.ptgcn.com/products/HK2-Antibody-66974-1-Ig.htm.
Species: Rabbit. Application: WB, IHC, IF/ICC, FC (Intra), ELISA. Concentration: IF:1:100
Ref: High dietary fructose promotes hepatocellular carcinoma progression by enhancing O-GlcNAcylation via microbiota-derived acetate. Cell Metab.

HK2 (22029-1-AP,Protein Tech, U.S.A), https://www.ptgcn.com/products/HK2-Antibody-22029-1-AP.htm.
Species: Rabbit. Application: WB, IHC, IF, IP, CoIP. Concentration: WB:1:5000; IP:3μg.
Ref: NEAT1 is essential for metabolic changes that promote breast cancer growth and metastasis. Cell Metab.

Bax (50599-2-Ig, Protein Tech, U.S.A), https://www.ptgcn.com/products/BAX-Antibody-50599-2-Ig.htm
Species: Rabbit. Application: WB, IHC, IP, CoIP, ChIP, ELISA. Concentration: WB:1:500
Ref: The Cytoplasmic DNA Sensor cGAS Promotes Mitotic Cell Death. Cell.

Bcl-2 (CPA1095, Cohesion Biosciences, U.K), https://www.cohesionbio.com/Primary-Antibody/61499.html.
Species: Rabbit. Application: WB, IH, IF/IC. Concentration: WB:1:500
Ref: GRPR down-regulation inhibits spermatogenesis through Ca2+ mediated by PLCβ/IP3R signaling pathway in long-term formaldehyde-exposed rats. Food Chem Toxicol.

Cleaved-Caspase 3 (25128-1-AP, Protein Tech, U.S.A), https://www.ptgcn.com/products/cleaved-Caspase-3-Antibody-25128-1-AP.htm
Species: Rabbit. Application: WB, IHC, IF, ELISA. Concentration: WB:1:500, IHC: 1:500
Ref: DNAJC12 causes breast cancer chemotherapy resistance by repressing doxorubicin-induced ferroptosis and apoptosis via activation of AKT. Redox Biol.

GPX4 (sc-166570, Santa Cruz, U.S.A), https://www.scbt.com/zh/p/gpx-4-antibody-e-12.
Species: Mouse. Application: WB, IP, IF, IHC(P), ELISA. Concentration: WB:1:1000; IHC:1:200
Ref: Parabacteroides distasonis ameliorates hepatic fibrosis potentially via modulating intestinal bile acid metabolism and hepatocyte pyroptosis in male mice. Nature communications.

IgG (30000-0-AP, Protein Tech, U.S.A), https://www.ptgcn.com/products/IgG-control-Antibody-30000-0-AP.htm.
Species: Rabbit. Application: WB, IP, RIP, IHC, CoIP, ChIP, Cell Treatment. Concentration: IP:3μg
Ref: AQP4 Aggravates Cognitive Impairment in Sepsis-Associated Encephalopathy through Inhibiting Nav 1.6-Mediated Astrocyte Autophagy. Advanced science (Weinheim, Baden-Württemberg, Germany).

GFP-Tag (AE012, Abclonal, U.S.A), https://abclonal.com.cn/catalog/AE012.
Species: Mouse. Application: WB, IP, IF,Co-IP,Pull-down,ChIP,IHC. Concentration: WB:1:500
Ref: Jasmonate Signaling Enhances RNA Silencing and Antiviral Defense in Rice. Cell Host & Microbe.

Flag-Tag (F3165, Merck, Germany), https://www.sigmaaldrich.cn/CN/zh/product/sigma/f3165.

Species: Mouse. Application: WB, IP. Concentration: WB:1:3000;IP:3μg
Ref: AAV-ie enables safe and efficient gene transfer to inner ear cells. Nature communications.

Myc-Tag (16286-1-AP, Protein Tech, U.S.A), https://www.ptgcn.com/products/MYC-tag-Antibody-16286-1-AP.htm.
Species: Rabbit. Application: IF/ICC, IP, WB, ELISA. Concentration: WB:1:500; IP:3μg
Ref: TRIM5α recruits HDAC1 to p50 and Sp1 and promotes H3K9 deacetylation at the HIV-1 LTR. Nature communications.

Myc-Tag (60003-2-Ig, Protein Tech, U.S.A), https://www.ptgcn.com/products/MYC-Antibody-60003-2-Ig.htm.
Species: Mouse. Application: IF/ICC, IP, WB, ELISA, , CoIP, ChIP. Concentration: WB:1:2000; IP:3μg
Ref: Phosphoglycerate dehydrogenase activates PKM2 to phosphorylate histone H3T11 and attenuate cellular senescence. Nature communications.

V5-Tag (BE2033, EASYBIO, China), http://www.bioeasytech.com/product/2411.html?goods_id=4396.
Species: Mouse. Application: WB, IP. Concentration: WB:1:2000; IP:3μg
Ref: N/A

GAPDH (60004-1-Ig, Protein Tech, U.S.A), https://www.ptgcn.com/products/GAPDH-Antibody-60004-1-Ig.htm.
Species: Mouse. Application: FC, IF/ICC, IP, WB, ELISA. Concentration: WB:1:30000
Ref: A signalling pathway for transcriptional regulation of sleep amount in mice. Nature.

Alpha Tubulin (11224-1-AP, Protein Tech, U.S.A), https://www.ptgcn.com/products/TUBA1B-Antibody-11224-1-AP.htm.
Species: Rabbit. Application: WB, IP, IF/ICC, FC, IHC, ELISA. Concentration: WB:1:2000
Ref: Activity-based E3 ligase profiling uncovers an E3 ligase with esterification activity. Nature.

Ki 67 (GB151499-100, Servicebio, China), https://www.servicebio.cn/goodsdetail?id=21813.
Species: Rabbit. Application: IHC, IF. Concentration: IHC:1:700
Ref: N/A

Goat anti-Mouse IgG (H+L) Secondary Antibody, HRP (31430, Thermo, U.S.A), https://www.thermofisher.cn/cn/zh/antibody/product/Goat-anti-Mouse-IgG-H-L-Secondary-Antibody-Polyclonal/31430.
Species: Rabbit. Application: WB, IHC, IP. Concentration: WB:1:5000
Ref: Nucleic acid vaccine candidates encapsulated with mesoporous silica nanoparticles against MERS-CoV. Hum Vaccin Immunother.

Goat anti-Rabbit IgG (H+L) Secondary Antibody, HRP (31460, Thermo, U.S.A), https://www.thermofisher.cn/cn/zh/antibody/product/Goat-anti-Rabbit-IgG-H-L-Secondary-Antibody-Polyclonal/31460.
Species: Rabbit. Application: WB, IHC, IP, ELISA. Concentration: WB:1:5000
Ref: TLR2 promotes traumatic deep venous thrombosis of the lower extremity following femoral fracture by activating the NF κB/COX 2 signaling pathway in rats. Exp Ther Med.

Goat anti-Mouse Secondary Antibody IgG / FITC (ZF-0312, ZSGB-BIO, China), http://www.zsbio.com/product/ZF-0312.
Species: Rabbit. Application: IF. Concentration: IF:1:100
Ref: N/A

Goat anti-Rabbit Secondary Antibody IgG / TRITC (ZF-0316, ZSGB-BIO, China), http://www.zsbio.com/product/ZF-0316.
Species: Rabbit. Application: IF. Concentration: IF:1:100
Ref: N/A

Goat anti-Rabbit Secondary Antibody IgG / FITC (ZF-0311, ZSGB-BIO, China), http://www.zsbio.com/product/ZF-0311.
Species: Rabbit. Application: IF. Concentration: IF:1:100
Ref: N/A

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Human normal prostate epithelial cell line RWPE1 (ATCC, Cat#:CRL-11609), prostate cancer cell lines (DU145 (ATCC, Cat#:HTB-81), PC3 (ATCC, Cat#:CRL-1435), 22Rv1 (ATCC, Cat#:CRL-2505) and LNCaP (ATCC, Cat#:CRL-1740)) and HEK293T cells (ATCC, Cat#:CRL-11268) were purchased from American Type Culture Collection (ATCC).
Authentication	The prostate cancer cell lines were authenticated by the commercial suppliers before purchase using short tandem repeat (STR) profiling.
Mycoplasma contamination	All cell lines were confirmed to be mycoplasma free during our study.
Commonly misidentified lines (See ICLAC register)	HEK293T cells were used for lentiviral production and co-immunoprecipitation assays.

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	4 weeks old male BALB/C-nu/nu mice were obtained from HFK Bioscience CO., LTD (Beijing, PR China). All mice were maintained under a 12-hour light/dark cycle with free access to water and standard mouse chow and housed in a specific-pathogen-free (SPF) facility. All mice were randomized, with each group consisting of five mice, subsequently, one week of adaptive feeding was implemented.
Wild animals	No wild animals involved in this study.
Reporting on sex	Our study mainly focused on prostate cancer in men, so male BALB/C-nu/nu mice were used in this study.
Field-collected samples	No filed samples involved in this study.
Ethics oversight	All animal experiments in this project were approved by the Animal Care and Use Committee of Shaanxi Normal University (Approval No.2024-072).

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

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	Cell Death analysis: Cells were seeded on 24-cell plates for 24 hours before treatment. After relevant stimuli, cells were collected (including floating dead cells) and washed twice with PBS (Solarbio, # P1010), then incubated with 500μL PI staining solution (3μg/ml) in PBS for 30min at 37 . Next, cells were resuspended in 200μL PBS with 2% FBS, and the cell death rate was measured using flow cytometer. Lipid peroxidantion analysis: Cells were seeded onto 24-well plates overnight, and treated with or without RSL3 (TargetMol, # T3646), Ferrostatin-1 (TargetMol, # T6500) or VBIT4 (TargetMol, # T13287) for 24 hours. Cells were then washed twice with PBS and incubated with culture medium (without FBS and PS) containing 5μM BODIPY™ 581/591 C11 at 37 for 30min in dark. Labeled cells were washed twice with PBS to remove the excess dye, and finally resuspended in cold PBS containing 2% FBS for flow cytometer analysis. Mitochondrial ROS analysis: Cells were seeded on 24-well plates overnight, then treated with or without VBIT4 (1μM for 22Rv1, 5μM for DU145) for 24 hours. The cells were washed twice with fresh PBS and stained in serum-free medium containing MitoSOX at 37 for 30 min in dark. The labeled cells were washed and resuspended in PBS, then detected using flow cytometry at PE channel. Mitochondrial membrane potential analysis: Cells were seeded onto 24-cell plates overnight and treated with or without 5μM VBIT4 for 24 hours. After discarding the culture medium, the adherent cells were washed twice with fresh PBS. Subsequently, 300μL of JC-1 (Solarbio, # M8650) working solution was added into the well. The cells were then incubated in the dark at 37 for 20 minutes. The labeled cells were washed twice with the cold washing buffer, then trypsinized and resuspended in PBS with 2% FBS for quantification using a flow cytometer.
Instrument	BECKMAN CytoFLEX S
Software	FlowJo (version 10.8)
Cell population abundance	At least 10000 cells were analyzed for PI, C11-BODIPY and MitoSOX staining. At least 30000 cells were analyzed for JC-1 staining.
Gating strategy	Initial cell population gating (FSC-Area VS SSC-Area or FSC-Height VS SSC-Height) was adopted to define live cells, and then FSC-Area VS Fsc-Height was adopted to make sure only single cell was used for analysis.

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