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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	Whole exome sequencings (WES) and RNA-seq were performed on the Illumina NovaSeq 6000 platform. TMT-based proteomics and phosphoproteomics were performed on a Q-Exactive HF mass spectrometry (Thermo Fisher Scientific) coupled with a nanoflow Easy nLC 1200 UHPLC system (Thermo Fisher Scientific). TMT-based acetylproteomics were performed on a Q-Exactive HF-X mass spectrometry (Thermo Fisher Scientific) coupled with a nanoflow Easy nLC 1200 UHPLC system (Thermo Fisher Scientific). Data-independent acquisition (DIA)-based proteomics were analyzed on a timsTOF Pro mass spectrometry (Bruker) equipped with a nanoElute LC system (Bruker).
Data analysis	The data analysis was performed by programming language R (version 4.0.2) and Python (v3.7.0) in this study. Softwares used for somatic mutation calling and annotation included BWA (v0.7.17), Picard (v2.27.7), Mutect2 (v4.2.6.1), Annovar (v2017 Jul 17). Software used for the analysis of significantly mutated genes included MutSigCV (v1.41). Softwares used for copy number variation analysis included cnvkit (v0.9.7), and GISTIC2. STAR (v2.7.2a), featureCounts, and HPV-EM were used for RNA-seq data analysis and HPV detection. Cell type score inferencing was performed using ESTIMATE (v1.0.13) and Xcell (v1.1.0) R package. Database searching for the mass spectrometry raw data were performed using MaxQuant (v1.6.17) and DIA-NN software (v1.8.0). Statistical analyses and visualization were realized by Python (v3.7.0). Approaches or algorithms used for sample subgrouping included the ConsensusClusterPlus (v1.54.0) R package and HyperChIP. Standard statistical tests were used to analyze the clinical and proteome data, including but not limited to Student's t-test, Fisher's exact test, ANOVA test, and Chi-square test. GSEApy python package was used for pathway enrichment analysis. Kaplan-Meier curves (log-rank test, multivariate log-rank test) were used for survival analysis. Features associated with progression-free time were identified using the univariate Cox proportional hazards regression model. KSEAapp (v0.99.0) R package was used to identify the subgroup-specific kinases. Matplotlib (v3.2.2) and seaborn (v0.11.1) library in Python (v3.7.0) were used for visualization. For validating the findings in this study, each experiment was repeated at least three times independently. In this study, the adjusted P values were calculated using the Benjamini-Hochberg procedure.

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

Data availability
The WES and RNA-seq raw data have been deposited in the Genome Sequence Archive in National Genomics Data Center, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences (Genomics Proteomics Bioinformatics 19, 578-583 (2021); Nucleic Acids Res 50, D27-D38 (2022)) under accession number HRA005516 [https://bigd.big.ac.cn/gsa-human/browse/HRA005516]. The raw WES and RNA-seq data are available for research use only with restricted access, which can be obtained through the Data Access Committees of the GSA-human database. Data access is open to all non-profit researchers in compliance with the guidelines set by GSA-human. Alternatively, the user may also directly contact the corresponding author. Once access has been approved, the data will be available to download for 2 months. The proteomics, phosphoproteomics, and acetylproteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE (Nucleic Acids Res 50, D543-D552 (2022)) partner repository with the dataset identifier PXD055203 [http://www.ebi.ac.uk/pride/archive/projects/PXD055203]. Transcriptomics and survival data of TCGA CC were downloaded from Xena [https://xenabrowser.net/datapages/]. For more information in this study, please contact the corresponding authors. Source data are provided with this paper.

Code availability
The codes are available at https://github.com/guixiuqi/CC_multiomics.
The Data Availability for this study complies with these requirements.

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	The subject of this study is cervical cancer (CC), which is a tumor of the female reproductive system. Due to the nature of CC, all patients included in this study were female.
Reporting on race, ethnicity, or other socially relevant groupings	The patients included in this study were all Chinese from East Asia.
Population characteristics	Out of 139 Chinese CC patients with tumor samples, 112 were diagnosed with squamous cell carcinoma, 19 with adenocarcinoma, 2 with adenosquamous carcinoma, 4 with small cell neuroendocrine carcinoma of the cervix (NECC), and 2 with other mixed histology type. The median age of these patients was 54. In total, 3,65,71 patients were diagnosed as Grade 1,Grade 2 and Grade 3 respectively, while 45, 37 and 57 patients were classified as clinical stages I, II and III-IV respectively. Detailed clinical and pathological characteristics of the patients were summarized in Supplementary Data 1a.
Recruitment	The treatment-naive CC patients were recruited from Cancer Hospital Chinese Academy of Medical Sciences between June 2019 and July 2021. 139 tumors and 33 NATs (30 NATs with paired tumors) were collected, and each sample was homogenized via cryo-pulverization and aliquoted to subsequent genomic, transcriptomic, proteomic, phosphoproteomic, and acetylproteomic analyses.
Ethics oversight	All patients signed separate informed consent forms for sampling, research, and publication. This study was conducted in accordance with the guidelines and regulations set forth by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval No. 22/374-3576).

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	The WES analysis was conducted on the 134 tumor tissues, 123 blood samples. The RNA-seq analysis was conducted on the 135 tumor and 26 normal adjacent tissues. The TMT proteomic profiling was performed on 136 tumor and 33 normal adjacent tissues. The DIA proteomic

profiling was performed on 139 tumor and 33 normal adjacent tissues. The TMT phosphoproteomic profiling was performed on 136 tumor and 33 normal adjacent tissues. The TMT acetylproteomic profiling was performed on 136 tumor and 33 normal adjacent tissues.

Data exclusions

This study strictly followed the Clinical Proteomic Tumor Analysis Consortium (CPTAC) process to collect and process samples. All tissues were stored in liquid nitrogen within 30 min after isolation, and their pathological types were independently confirmed by two pathologists. A cohort of 142 CC patients was recruited from Cancer Hospital Chinese Academy of Medical Sciences from June 2019 to July 2021 and received no prior anticancer treatments. 3 patients had collected paired normal adjacent and tumor tissues, but the protein and RNA of these 3 tumor tissues had degraded after quality control. Finally, 139 tumors and 33 normal adjacent tissues (30 normal adjacent tissues with paired tumors) from treatment-naïve CC patients were collected in this study.

Replication

All experiments were reliably reproduced and indicated in figure legends,each experiment was repeated at least three times independently in order to validating the findings. In addition, to ensure the reliability of mass spectrometry analysis, this study also utilized 293T cell protein for repeated testing.

Randomization

For multi-omic analysis, samples of CC patients were randomly divided into groups to avoid bias for proteogenomic quantification. In addition, the xenograft tumor experiment also randomly grouped nude mice.

Blinding

The investigators who measured mass spectrometry data , RNA-seq data and WES data were blinded to patient's clinical parameters . The investigators who performed IHC and progress-free survival analysis were blinded to patient's progression status and progression time.

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

Western blot analysis:
Rabbit monoclonal anti-PRKCB (Abcam, Cat# ab195039, dilution, 1: 2000),
Rabbit polyclonal anti-B4GALT1 (Abcam, Cat# ab121326, dilution, 1: 3000),
Rabbit polyclonal anti-DHCR24 (Proteintech, Cat# 10471-1-AP, dilution, 1: 3000),
Rabbit polyclonal anti-AGPS (Proteintech, Cat# 21011-1-AP, dilution, 1: 2000),
Rabbit polyclonal anti-ACACA (ABclonal, Cat# A15606, dilution, 1: 1000),
Rabbit monoclonal anti-FOSL2 (Cell Signaling Technology, Cat# 19967, dilution, 1: 2000),
Mouse monoclonal anti-FLAG (Sigma Aldrich, Cat# F3165, dilution, 1: 3000),
Mouse monoclonal anti-Vinculin (Sigma Aldrich, Cat# V4505, dilution, 1: 5000),
Rabbit polyclonal anti-Acetylated-Lysine (Cell Signaling Technology, Cat# 9441, dilution, 1: 2000),
Mouse monoclonal anti-HA (Santa Cruz Biotechnology, Cat# sc-7392, dilution, 1: 5000).

Immunohistochemistry (IHC) analysis:
Rabbit monoclonal anti-PRKCB (Abcam, Cat# ab195039, dilution, 1: 300).

Validation

Anti-PRKCB (Abcam, Cat#ab195039, dilution) validated for IHC (dilution, 1: 300)and western blotting (dilution, 1:2000) by manufacturer [https://www.abcam.cn/products/primary-antibodies/pkc-beta-1-antibody-epr18512-ab195039.html]. Anti-B4GALT1 (Abcam, Cat#ab121326, dilution, 1:3000) validated for western blotting by manufacturer [https://www.abcam.cn/products/primary-antibodies/b4galt1-antibody-ab121326.html]. Anti-DHCR24 (Proteintech, Cat#10471-1-AP, dilution, 1:3000) validated for western blotting by manufacturer [https://www.ptgcn.com/products/DHCR24-Antibody-10471-1-AP.htm].Anti-AGPS (Proteintech, Cat#21011-1-AP, dilution, 1:2000) validated for western blotting by manufacturer [https://www.ptgcn.com/products/Alkyl-DHAP-synthase-AGPS-Antibody-21011-1-AP.htm]. Anti-ACACA (ABclonal, Cat#A15606, dilution, 1:1000) validated for western blotting by manufacturer [https://abclonal.com.cn/catalog/A15606]. Anti-FOSL2 (Cell Signaling Technology, Cat#19967, dilution, 1:1000) validated for western blotting by manufacturer [https://www.cellsignal.com/products/primary-antibodies/fra2-d2f1e-rabbit-mab/19967].Anti-FLAG (Sigma Aldrich, Cat#F3165, dilution, 1:3000) validated for western blotting by manufacturer [https://www.sigmaaldrich.cn/CN/zh/product/sigma/f3165]. Anti-Vinculin (Sigma Aldrich, Cat#V4505, dilution, 1:5000) validated for western blotting by manufacturer [https://www.sigmaaldrich.cn/CN/zh/product/sigma/v4505]. Anti-Acetylated-Lysine (Cell Signaling Technology, Cat#9441, dilution, 1:2000) validated for western blotting by manufacturer [https://www.cellsignal.cn/products/primary-antibodies/acetylated-lysine-antibody/9441]. Anti-HA (Santa Cruz Biotechnology, Cat#sc-7392, dilution, 1:5000) validated for western blotting by manufacturer [https://www.scbt.com/p/ha-probe-antibody-f-7].

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	SiHa (Cell bank of the Chinese Academy of Sciences, Shanghai, China, human-derived, female). HEK293T/17 (Cell bank of the Chinese Academy of Sciences, Shanghai, China, isolated from human embryo kidney tissue).
Authentication	These cell lines were authenticated with short tandem repeat profiling method.
Mycoplasma contamination	These cell lines tested negative for mycoplasma contamination.
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	Five-week-old female BALB/c nude mice (HFK Bioscience) were maintained in pathogen-free conditions. All animals were acclimated for 1 week before experiments. 3*106 experimental and control SiHa cells in 100 µL PBS were subcutaneously inoculated at the flank of randomly grouped nude mice. Tumor size were measured every 3 days with a caliper and tumor volumes were calculated by the formula: volume = (width)2*length*0.52. The maximum tumor burden allowed by the ethics committee did not exceed 1500 mm3.When the tumor burden reached 1500 mm3, the mice were euthanized, and the tumors were dissected for further analysis. After the mice were euthanized, the transplanted tumors were weighed and photographed. All animal procedures were performed according to the guidelines approved by the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College and adhered to the National Institutes of Health Guide for the care and use of laboratory animals.
Wild animals	No wild animals were involved in this study.
Reporting on sex	A total of 46 BALB/c female nude mice were used in this study.
Field-collected samples	No field-collected samples were invoived in this study.
Ethics oversight	All animal procedures were performed according to the guidelines approved by the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College and adhered to the National Institutes of Health Guide for the care and use of laboratory animals.

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.*

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	For cell cycle assays, experimental and control cells were seeded in 6-well plate (2*105 cells per well). The cells were collected by trypsinization and fixed in ice-cold 70% ethanol overnight at 4 °C. The cell cycle detection kit (Nanjing KeyGen Biotech, KGA512) and BD LSR ? flowcytometer (BD Biosciences) were applied to detect cell cycle distribution. The cell cycle result profiles were analyzed using ModFit LT 3.1 (Verity Software House).
Instrument	BD LSR ? flowcytometer (BD Biosciences) was applied in this study.
Software	ModFit LT 3.1.
Cell population abundance	No sort was performed in the study.
Gating strategy	Modfit LT 3.1 was used for data analysis. Forward scatter and side scatter were used to circle the cell population (excluding debris), and the fluorescence channels PE-A (area) /PE-W (width) were used to exclude adherent cells. Finally, the proportion of cells in each stage was fitted.

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