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	No code was used for data collection.
Data analysis	The analysis code for data processing is available in the supplementary material and at Mendeley Data (https://data.mendeley.com/datasets/bs54ny7ns2/1). Fluorescence polarization data was analyzed with Prism 10 (GraphPad). Flow cytometry data was analyzed with FlowJo (BD Biosciences). Western blot signal intensities were quantified in Image Lab (Bio-Rad). cryo-EM data were pre-processed in cryoSPARC live and cryoSPARC v4.4.1 (Punjani et al., 2017), and then transferred to RELION 5.0 beta63 for further processing, 3D reconstruction, and final refinement. All refinements were done using BLUSH regularization implemented in RELION 5.0 beta63. Molecular models and cryo-EM maps were visualized in UCSF Chimera65, UCSF Chimera X72, and PyMOL (the PyMOL molecular graphics system, Schrödinger, LLC) for analysis, interpretation and figure preparation.

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 and analysis code for data processing are available in the supplementary material and at Mendeley Data (https://data.mendeley.com/datasets/bs54ny7ns2/1). Raw counts from the deep sequencing of peptide-encoding oligonucleotide sequences are available in Table S1 (peptide tiling SIMBA experiment) and Table S3 (mutational scanning SIMBA experiments). The atomic models and cryo-EM maps of the and CDK2 - cyclin A2 - GMNC, CDK2 - cyclin A2 - SAMHD1 and CDK2 - cyclin A2 - SCAPER complexes have been deposited to the EM Data Resource with accession codes EMD-52201, EMD-52204, and EMD-52208 and the PDB with accession codes 9HIU, 9HIW, and 9HJ1, respectively. Further information and requests for resources and reagents should be directed to and will be fulfilled by Peter Pryciak (peter.pryciak@umassmed.edu) and Norman Davey (norman.davey@icr.ac.uk).

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	Not applicable.
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable.
Population characteristics	Not applicable.
Recruitment	Not applicable.
Ethics oversight	Not applicable.

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 statistical method was used to predetermine sample size. Sample size was determined according to standard practices and was sufficient for statistical analysis. SIMBA experiments, fluorescence polarisation, and western blotting were carried out in 2-3 replicates.
Data exclusions	In SIMBA competitive growth experiments, oligonucleotides with <40 reads at t0 were dropped from further analysis in order to reduce noise from low representation. No other data was excluded.
Replication	All experiments were carried out in 2-3 replicates. In case of quantitative data, the presented data includes all replicate experiments. In case of western blots, a representative example is shown. The findings were reproduced in all replicates.
Randomization	Randomization was not applicable in this study.
Blinding	Blinding is not necessary in SIMBA experiments, because we are comparing binding of peptides in a pooled library in one vessel. To ensure consistency, all samples in an experiment were processed in parallel with identical 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: The following primary antibodies were used: sc-20044 (Santa Cruz Biotechnologies) at 1:500 for Cyclin D1, sc-247 (Santa Cruz Biotechnologies) at 1:500 for cyclin E, sc-271682 (Santa Cruz Biotechnologies) at 1:500 for cyclin A, sc-245 (Santa Cruz Biotechnologies) at 1:500 for cyclin B, anti-GAPDH (D16H11) XP® Rabbit mAb #5174 (Cell Signaling Technologies) at 1:1000 for GAPDH, a-FLAG tag (D6W5B) Rabbit mAb (Cell Signaling Technologies) at 1:1000. HRP-conjugated anti-mouse IgG (#7076, Cell Signaling Technologies) at 1:2000 and HRP-conjugated anti-rabbit IgG (#7074, Cell Signaling Technologies) at 1:10000 were used as secondary antibodies.

Validation: All these antibodies were commercially obtained and validated by vendors and multiple published studies, see manufacture's website for references and manufacturer's validation experiments.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): RPE1-hTERT cell line was obtained from Jonathon Pines, The Institute of Cancer Research. RPE1-hTERT is of female origin. HEK293T/17 cells were obtained from ATCC (CRL-11268).

Authentication: The cell line was authenticated by morphological analysis. No STR profiling was performed.

Mycoplasma contamination: The cell lines were tested negative for Mycoplasma.

Commonly misidentified lines (See ICLAC register): No commonly misidentified cell lines were used in the study.

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
✘	☐	Public health
✘	☐	National security
✘	☐	Crops and/or livestock
✘	☐	Ecosystems
✘	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
✘	☐	Demonstrate how to render a vaccine ineffective
✘	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
✘	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
✘	☐	Increase transmissibility of a pathogen
✘	☐	Alter the host range of a pathogen
✘	☐	Enable evasion of diagnostic/detection modalities
✘	☐	Enable the weaponization of a biological agent or toxin
✘	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.

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 fixed with 70% ethanol at 4°C for at least one hour. The ethanol-fixed cells were washed twice with PBS and resuspended in 300 µl solution containing 5 µg/ml propidium iodide and 25 µg/ml RNase A in PBS. The mixture was incubated at 37°C in the dark for 30 minutes and analyzed by flow cytometry using BD LSR Fortessa.

Instrument	BD LSR Fortessa
Software	The data was collected using BD FacsDiva software and analyzed using FlowJo.
Cell population abundance	Data from 10 000 cells was collected. All cells were analyzed.
Gating strategy	The cells were gated by FSC/SSC for live cells and by FSC area/height for single cells.

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