

## 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

- |                                     |                                     |  |
|-------------------------------------|-------------------------------------|--|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | A description of all covariates tested   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | 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

Leica Application Suite Software  
Zeiss ZEN 3.0  
Bio-Rad Image Lab 6.1.0  
Leica DM-6000  
Zeiss Axio Imager 2  
STED microscope (Abberior Expert Line)  
Exploris480 Orbitrap mass spectrometer (ThermoFisher)  
EliSpot reader Version 7.0 (AlphaDiagnostics)  
vSpot Spectrum  
Alphafold Multimer AF2 multimer v3  
Zeiss LSM 980 microscope equipped with Airyscan 2  
ZEN Blue software

#### Data analysis

Leica Application Suite Lite  
GraphPad Prism 10.2.3  
ImageJ 1.54f  
FIJI  
Foci analyzer ImageJ macro (<https://github.com/Biolmaging-NKI/Foci-analyzer>; mean foci intensity analysis for microscopy)  
TIDE (<https://tide.nki.nl>)  
Spectronaut v18.1.230626 (Biognosys)  
Perseus v1.1.6.15

ColabFold  
Chimera X  
Adobe Illustrator 2020  
Adobe Illustrator 2025

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 mass spectrometry proteomics data generated in this study have been deposited to the ProteomeXchange Consortium via the PRIDE [1] partner repository with the dataset identifier under the accession code PXD059881 (<https://www.ebi.ac.uk/pride/archive/projects/PXD059881>). All raw STED images can be found on DataVerseNL (<https://doi.org/10.34894/O3KAFO>). The interactive Wiener Filter used for deconvolution of STED images using Jupyter Notebook has been deposited to Zenodo. This code can be found at <https://doi.org/10.5281/zenodo.15075205>.

## 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

n/a

Reporting on race, ethnicity, or other socially relevant groupings

n/a

Population characteristics

n/a

Recruitment

n/a

Ethics oversight

n/a

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](https://www.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 sizes were determined based on previous work and experience of our research groups or based on literature. No statistical methods to determine sample size were employed.

Data exclusions

No data was excluded

Replication

To verify the reproducibility of our results, multiple measures were taken. For all experiments sample sizes and number of repeats are indicated.

Depletion or knockout of CIP2A is for each cell line verified with either immunofluorescence and western blot, or immunofluorescence, western blot and genomic sequencing.

Randomization

Randomization was not applicable. Cells were split across multiple culture vesicles to compare different experimental settings such as drug treatments simultaneously.

Blinding

Investigators were not blinded during our experimental analyses.

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

## Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

## Antibodies

### Antibodies used

Target (cat. nr., company, clone, lot)

Primary antibodies:

yH2AX (05-636, Millipore, JBW301, 3924583)  
 yH2AX (#9718, Cell Signaling, 20E3, 21)  
 CIP2A (sc-80659, Santa Cruz, 2G10-3B5, E1523)  
 CIP2A (PA5-83469, Invitrogen, N/A, 000008181)  
 TOPBP1 (Bethyl, A300-111A-M, N/A, 2)  
 ERCC1 (sc-17809, Santa Cruz, D-10, C0922)  
 XPF (ab76948, Abcam, N/A, GR172751-11)  
 MUS81 (ab14387, Abcam, N/A, GR3237490-5)  
 BTBD12 (H000844644-BP01P, Abnova, N/A, NC281)  
 V5 (13202S, Cell Signalling, D3H8Q, 7)  
 V5 (R960-25, Invitrogen, SV5-Pk1, 2735895)  
 PICH (H00054821-B01P, Abnova, N/A, N9011)  
 RAD52 (ab124971, Abcam, EPR3464(2), 1028958-4)

Actin (#69100, MpBiomedicals, C4, 0101008716)  
 GAPDH (ab14387, Abcam, EPR6256, 1027850-12)  
 MDC1 (ab11171, Abcam, N/A, GR252252)  
 Vinculin (ab129002, Abcam, EPR8185, 1010179-69)  
 BRCA2 (OP95, Calbiochem, N/A, N/A)  
 HSP90alpha/beta (sc13119, Santa Cruz, F-8, K1424)  
 HRP-conjugated-Beta Actin (HRP-60008, Proteintech, N/A, 21004768)  
 Alpha-tubulin (2125, Cell signaling, 11H10, GR323417-5)  
 BRCA1 (OP92-100ug, Sigma, N/A, 3890557)

Secondary antibodies:

Goat Anti-Rabbit Immunoglobulins/HRP (P0448, Dako, N/A, 41723082)  
 Rabbit Anti-Mouse Immunoglobulins/HRP (P0260, Dako, N/A, 41646605)  
 Goat-anti-mouse Alexa-Fluor 647 (A32728, ThermoFisher, N/A, YJ376701)  
 Donkey anti-rabbit Alexa-Fluor 488 (A21206, ThermoFisher, N/A, GR3365969-5)  
 Goat-anti-rabbit Alexa-Fluor 488 (A11008, ThermoFisher, N/A, 2765658)  
 Goat-anti-mouse Alexa-Fluor 488 (A11029, Thermofisher, N/A, 2486523)  
 Donkey anti-rabbit Alexa-Fluor 647 (A31573, ThermoFisher, N/A, 2752586)  
 Donkey anti-mouse Alexa-Fluor 647 (A31571, ThermoFisher, N/A, 2720365)  
 Donkey anti-rabbit Alexa-Fluor 488 (A32790, Invitrogen, N/A, YF374677)  
 Donkey anti-mouse Alexa-Fluor 555 (A31570, Invitrogen, 2716871)

580 goat anti-mouse (ST580-1001, Abberior STAR, N/A, N/A)  
 580 goat anti-rabbit (ST580-1002, Abberior STAR, N/A, N/A)  
 635 goat anti-mouse (ST635-1001, Abberior STAR, N/A, N/A)  
 635 goat anti-rabbit (ST635-1002, Abberior STAR, N/A, N/A)

### Validation

CIP2A antibodies was KO-validated, shRNA-validated and siRNA-validated on western blot in the manuscript on Suppl. Fig 1B, 3A, 3G, 7A, 7D, 7E, 7F, 10D, 10G, 10H, 10I.

BRCA1 antibody was KO-validated on western blot in the manuscript on Suppl. Fig 10H, and depletion upon BARD1 degradation in Suppl. Fig. 10C. BRCA2 antibody was KO-validated and shRNA-validated on western blot in the manuscript Suppl. Fig 10G, 10I.

SLX4 antibody was siRNA-validated on western blot in the manuscript Suppl. Fig 4B and Suppl. Fig 10H, 10I.  
MUS81 antibody was siRNA-validated on western blot in the manuscript Suppl. Fig 4C.  
XPF antibody was siRNA-validated on western blot in the manuscript Suppl. Fig 4E.

All antibodies were validated by the supplier.

## Eukaryotic cell lines

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

Cell line source(s)	RPE1, DLD1, HEK293T, HCT116, MDA-MB231, BT549, HCC38
Authentication	STR profiling was used to validate cell lines.
Mycoplasma contamination	Cells were routinely tested for mycoplasma infection and always tested negative.
Commonly misidentified lines (See <a href="#">ICLAC</a> register)	N/A

## Plants

Seed stocks	<i>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.</i>
Novel plant genotypes	<i>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.</i>
Authentication	<i>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, mosaicism, off-target gene editing) were examined.</i>