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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	Solidworks 2012 SP05, ChemDraw professional 16.0.
Data analysis	ImageJ with 64-bit Java 1.8.0_112, Microsoft Excel 2016; Graphpad Prism 7.0; RStudio 1.0153

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

All data supporting the findings of this study are available from the corresponding authors upon request.

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 sample size (n) of each experiment is provided in the corresponding figure captions in the main manuscript and supplementary information files. Sample sizes were chosen to ensure they are sufficient for statistical comparison between different groups.
Data exclusions	No data was excluded from the analyses.
Replication	All in vitro experiments were replicated independently for at least 3 times. In vivo sample size (n) in each group is detailed in the figure legends or methods section. All attempts at replication were successful.
Randomization	In the reported in vivo experiments, mice were randomly grouped before treatment. As the work does not involve participant groups, randomization was not used for this study.
Blinding	All data collection and all related analyses were predetermined. The work does not involve participant groups. Therefore, blinding was not used to the study.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	The following antibodies were used in this study. They are list as antigen first, followed by supplier, catalog number, lot/clone number and dilution as application. 1) Anti-POLR2A, Santa Cruz, sc-47701, D2617, CTD4H8, 1:10000 for western blot/1:200 for immunofluorescence staining. 2) Anti-p53, Santa Cruz, sc-126, F0909/DO-1, 1:5000 3) Anti-β-actin, Abgent, AM1829B, SG100806AD/137CT26.1.1, 1:5000 4) HRP-anti-rabbit IgG, Santa Cruz, sc-2030, G2617, 1:5000 5) HRP-anti-mouse IgG, Santa Cruz, sc-516102, G2617, 1:5000 6) Alexa Fluor 488 anti-mouse IgG, Life Technologies, A11001, 1219843, 1:250.
Validation	All antibodies were verified by the supplier and each lot has been quality tested.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	MDA-MB-231, MDA-MB-453, and HCC1937 cell lines used in this work were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). HER18 cells (stably overexpress HER2, parent line MCF-7) were a gift from Dr. Mong-Hong Lee (MD Anderson Cancer Center).
Authentication	Cell identity was confirmed by validating the STR DNA fingerprinting using the AmpFLSTR Identifiler Kit (Applied Biosystems #4322288) according to the manufacturer's instructions.
Mycoplasma contamination	The cell lines were tested with Universal Mycoplasma Detection Kit (ATCC #30-1012K) and confirmed free of mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Female NU/NU nude mice (6 weeks old) were purchased from Charles River (Wilmington, MA,USA) for the for the TNBC tumour models or The Jackson Laboratory (Bar Harbor, ME, USA) for the HER2+ tumour model. Female C57BL/6J mice (6 weeks old) were purchased from The Jackson Laboratory (Bar Harbor, ME, USA).
Wild animals	The study did not involve wild animal.
Field-collected samples	The study did not involve samples collected from field.
Ethics oversight	All animal studies were conducted by following protocols approved by the Institutional Animal Care and Use Committee (IACUC) at either The Ohio State University and Indiana University School of Medicine. The animal protocols are compliant with all relevant ethical regulations.

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