

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 (<i>n</i>) 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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☒	☐ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ 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 <i>d</i> , Pearson's <i>r</i>), 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	Immunoblots: GelCap v5.6 (Tanon) Luciferase measurements: ICE v1.0.9.0 (Berthold) qPCR: LightCycler® 480 SW v1.5.1 (Roche) Colony formation assay: Incucyte 2023A Rev2 (Sartorius) Slide scanning: NDP.view2 (Hamamatsu)
Data analysis	The landscape of gene mutation The STAR-counts data and mutation maf data of tumours were downloaded from the TCGA database (https://portal.gdc.cancer.gov). The data in TPM format was subsequently extracted from the STAR-counts data and normalized using log2(TPM+1). The samples that had RNAseq data, maf mutation data, and clinical information were then retained. The maftools package in R software was utilized to download and visualize the somatic mutations of patients. Statistical analysis was conducted using R software, version v4.0.3. Molecular dynamics simulation The molecular dynamics simulations of all studied protein/DNA complexes were performed with the AMBER 22 molecular simulation package. The crystal structure of tumour-suppressor protein p53/DNA complex (PDB code: 2AC0) was used for the calculation. The starting structures of all molecular systems were solvated in TIP3P water using an octahedral box, which extended 8 Å away from any solute atom. To neutralize the negative charges of simulated molecules, Na⁺ counter-ions were placed next to each negative group. MD simulations were carried out by using the PMEMD module of AMBER 22. The calculation began with 500 steps of steepest descent followed by 500 steps of conjugate gradient minimization with a large constraint of 500 kcal mol⁻¹ Å⁻² on the atoms of the protein and DNA. Then 1000 steps of steepest descent followed by 4000 steps of conjugate gradient minimization with no restraint on the complex atoms were performed. Subsequently, after 200

ps of MD, during which the temperature was slowly raised from 0 to 300 K with weak (5 kcal mol⁻¹Å⁻²) restraint on the protein/DNA, the final unrestrained production simulations of 200.0 ns were carried out at constant pressure (1 atm) and temperature (300 K). In the entire simulation, SHAKE was applied to all hydrogen atoms. Periodic boundary conditions with minimum image conventions were applied to calculate the non-bonded interactions. A cutoff of 10 Å was used for the Lennard–Jones interactions. The final respective conformations of all the protein/DNA complexes used for discussion were produced from the last 50.0 ns of MD.

Whole-transcriptome analysis

Total RNA was extracted from tumour xenograft of different mice (three replicates for each group) using TRIzol reagent. RNA libraries were constructed using the VAHTS Universal V6 RNA-seq Library Prep Kit for Illumina (Vazyme, NR604-02) according to the manufacturer's instructions. The concentration of the extracted RNA was detected using the Nanodrop2000 (Thermo Fisher, Nanodrop2000), and its integrity was tested using the Agilent 2100 (Vazyme, G2939BA). The quality and quantity of the constructed libraries were assessed using the BioAnalyzer 2100 system (Agilent Technologies). Subsequently, the libraries were sequenced on an Illumina NovaSeq X Plus platform with 150-bp paired-end reads. The sequencing data were quality-controlled using the Q30 metric. After adapter trimming at the 3' end and removing low-quality reads with the fastp (<https://github.com/OpenGene/fastp>, fastp-V0.20.1), high-quality clean reads were aligned to the reference genome using the HISAT2 (<https://daehwankimlab.github.io/hisat2/>, hisat2-2.0.4). Guided by the gffcompare, the ballgown software package was used to obtain gene-level FPKM (Fragments Per Kilobase of transcript per Million mapped reads) values as the expression profiles of mRNA. The total number of expressed genes and the log2FPKM values of mRNA in different tumour xenograft groups were plotted and compared. Significant differences between samples were analyzed using DEseq2, and genes with a multiplicity of difference FoldChange>2 times and P-value<0.01 were defined as differential genes and subsequently analyzed.

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 tumour suppressor gene mutation data were downloaded from the TCGA database (<https://portal.gdc.cancer.gov/>), IntOGen database (<https://www.intogen.org/>) and COSMIC database (<https://cancer.sanger.ac.uk/cosmic>). The RNA-seq raw data used in this study have been deposited in the Genome Sequence Archive (GSA) of the National Genomics Data Center under accession number CRA037180 (<https://ngdc.cncb.ac.cn/gsa/browse/CRA037180>). The mass spectrometry data have been deposited to the ProteomeXchange Consortium via the iProX partner repository with the dataset identifier PXD083048 (<https://proteomecentral.proteomexchange.org/cgi/GetDataset?ID=PX083048>). Super tRNA-tumour suppressor gene-manuals are available as supplementary material. The remaining data are available within the Article, Supplementary Information or Source Data file. Source data are provided with this paper.

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	We determined the sample sizes based on preliminary studies in our laboratories or in similarly published research. The samples were enough to be detected and we observed statistical significant difference in replicated independent experiments. For animal experiments, we used
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	8-12 female mice for each group and followed the 3 R's of animal research
Data exclusions	No data were excluded.
Replication	Experiments were reproduced in multiple independent biological replicates (at least three times) with similar and consistent results.
Randomization	All samples were independently measured in a controlled manner, namely the control and the experimental conditions were performed in parallel.
Blinding	Blinding is not relevant for the study, the experiments were performed by different co-authors.

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	anti-p53 antibody (DO1) (Santa Cruz Biotechnology, Dallas, TX, USA; catalog number: sc-126, Dilution. 1:200) anti-P21 antibody (Proteintech, China; catalog number: 10355-1-AP, Dilution. 1:2000) anti-GAPDH antibody (Proteintect, China; catalog number: 60004-1-Ig, Dilution. 1:100000) HRP-conjugated Goat Anti-Mouse IgG(H+L) (Proteintect, China; catalog number: SA00001-1, Dilution. 1:2000) HRP-conjugated Goat Anti-Rabbit IgG(H+L) (Proteintect, China; catalog number: SA00001-2, Dilution. 1:2000) Anti-Ki67 Mouse mAb(Servicebio, China; catalog number: GB121141, Dilution for IHC. 1:200) Anti-PCNA Mouse mAb (Servicebio, China; catalog number: GB12010, Dilution for IHC. 1:200) Anti-Caspase-3 Rabbit pAb (Servicebio, China; catalog number: GB11532, Dilution for IHC. 1:200)
Validation	These antibodies have either been validated in the published literature or have been validated in our laboratory by Western blotting using overexpression vectors. Validation statements are displayed on the manufacturers' websites. anti-p53 antibody (DO1) https://www.scbt.com/p/p53-antibody-do-1 anti-P21 antibody https://www.ptgcn.com/Products/P21-Antibody-10355-1-AP.htm anti-GAPDH antibody https://www.ptgcn.com/products/GAPDH-Antibody-60004-1-Ig.htm HRP-conjugated Goat Anti-Mouse IgG(H+L) https://www.ptgcn.com/Products/HRP-conjugated-Goat-Anti-Mouse-IgG-H-L-SA00001-1.htm HRP-conjugated Goat Anti-Rabbit IgG(H+L) https://www.ptgcn.com/products/HRP-conjugated-Goat-Anti-Rabbit-IgG-H-L-SA00001-2.htm Anti-Ki67 Mouse mAb https://www.service-bio.com/goodsdetail?id=6801 Anti-PCNA Mouse mAb https://www.service-bio.com/goodsdetail?id=5609 Anti-Caspase-3 Rabbit pAb https://www.service-bio.com/goodsdetail?id=1271

Eukaryotic cell lines

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

Cell line source(s)	Human HEK293 cells (ATCC CRL-11268), Human Calu-6 cells (ATCC HTB-56), Human Caco-2 cells (ATCC HTB-37), Mouse 4T1 cells (ATCC CRL-2539) was purchased from Procell LifeScience&Technology Co.,Ltd. (Wuhan, China).
Authentication	All cells were authenticated by the suppliers.
Mycoplasma contamination	Authentication and tests for mycoplasma were performed with the MycAway™ one-step mycoplasma detection kit (Yeasen). No mycoplasma contamination was found.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

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	The BALB/c nude mice or BALB/c mice (female, 6-8 weeks old) were purchased from the Department of Laboratory Animal Science, Peking University Health Science Center. Female BALB/c nude mice or BALB/c mice were housed in an SPF facility in a 12-h light-dark cycle and allowed free access to water and food.
Wild animals	The study did not involve wild animals.
Reporting on sex	Female mice were used, which has been specified in method.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	The animal experiment was proven by the Institutional Animal Care and Use Committee of Peking University Health Science Center (DLASBD0468), and all animals received humane care according to the standards outlined in the 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	<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>