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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 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	Odyssey infra red imaging system LI-COR biosciences Leica TCS SP8 microscope ABI ViiA™ 7 Real Time PCR sysytem TD-20e Luminometer (Turner) Incucyte 96 well kinetics cell migration and invasion assay software module
Data analysis	GraphPad Prism version 6 FloJo 10.4.2 software ImageJ v.1.52j ViiA7 RUO software (Life Technologies) Image StudioTM Lite Software (Li-Cor)

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 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

The RNA-seq data used in this study are from publically available datasets TCGA-Breast Invasive Carcinoma and TCGA-Mesothelioma accessible from the TCGA database (https://portal.gdc.cancer.gov/) . The remaining data are available within the Article, Supplementary Information and Source data file with this paper.

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	Sample sizes for cell culture experiments were selected to be at least n=2 based on standards in the literature. Sample sizes for in vivo tumor studies were determined based on pilot studies in mice, which established tumor incidence, and variability in data between the individual mice.
Data exclusions	No data was excluded from the analysis.
Replication	All experiments were performed at least 2-3 times. Detailed information on replicates is available in the methods and figure legends.
Randomization	For in vivo study, animals were randomly assigned to tumor cell injection or treatment groups. Randomization is not relevant for in vitro cell line experiments.
Blinding	No blinding test was used in this study since the same investigator designed and performed experiments.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	YAP, Santa Cruz (sc-101199, Lot# F2916)1:1000 for WB and 1:800 for IF CTGF, Santa Cruz (sc-25440, Lot# G1814) 1:1000 MYC, Santa Cruz (sc-40, Lot# A2315)1:1000 MLC2, Santa Cruz (sc-517205 Lot# K1016)1:1000 RhoA, Santa Cruz (sc-418 Lot# F0717))1:1000 pan-Rac, Santa Cruz (sc-514583, Lot # I0117)1:1000 Cdc42,Santa Cruz (sc-8401, Lot #E3017)1:1000 ROCK1, Santa Cruz (sc-17794, Lot# B2113)1:1000

ROCK2,Santa Cruz (sc-5561, Lot# D2015)1:1000
p-YAP, Cell Signaling, (13008S Lot: 5)1:1000
p-Cofilin, Cell Signaling, (3313S Lot: 7)1:1000
p-MLC2, Cell Signaling, (3674S Lot: 5)1:1000
Cofilin, Cell Signaling, (5175S Lot:5)1:1000
pPAK1, Cell Signaling, (2606S Lot: 6)1:1000
pPAK4/5, Cell Signaling, (3241S Lot:5)1:1000
GAPDH, Santa Cruz (sc-47724, Lot#J1119) 1:1000
PAK2, Cell Signaling, (2608S Lot:5)1:1000
PAK4, Cell Signaling (62690 Lot:5)1:1000
Caspase3, Cell Signaling, (9662)1:200
Ki67, Cell Signaling, (12202)1:200
TEAD4, AbCam (ab58308 Lot: GR49788-1)1:1000
mouse anti-α-tubulin, Sigma (05-829)1:10000
normal rabbit IgG, Santa Cruz (sc-2027, Lot #C0411)
normal mouse IgG, Santa Cruz (sc-2025, Lot #B0619)
mouse anti-β-actin, Sigma (A5316) 1:10000
Dako EnVision+System-HRP Labelled Polymer anti rabbit, Dako (K4003, Lot#11158845)

Validation

All antibodies are commercially available and are stated to be tested by the manufacturer for species reactivity to human and mouse. Information in CST, AbCam, Santa Cruz and Dako certificate of analyses. Cell signaling uses hallmark strategies binary model, ranged expression, orthogonal data, multiple antibodies, heterologous expression, and complementary assays. Abcam and Santa Cruz antibodies are knock-out validated or validated in cells with established levels of protein expression. Sigma uses cell treatment antibody validation methods where antibodies directed against pan proteins are tested in multiple cell lines that express varying levels of protein across different species. Dako concentrate antibody antibodies are validated through cross-lot testing and on end user operating procedures. The statements and validation data for each primary antibody for the species and application are also available on the manufacturer's website. In addition antibodies were monitored in house to detect protein of the reported size by western blot in over expression and/or knock down experiments.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	All cell lines (MCF10A, MDA MB 231, MDA MB 468, HEK293T, H2052, U373MG, U251 MG, SF295, HCC193, PC-9. HCC1395, HCC1954, U138MG, SK-MEL-2, SK-LMS-1, HCC1937, HCC1806, H1299, LN229, M059J, M059K BT-549, H2373, MSTO-211H, Snu387, SK-BR-3) were procured from ATCC
Authentication	All cell lines used in the study were profiled for STR conducted by Genewiz, USA or in house DNA sequencing facility and cross-checked for authentication with the published STR profile provided by ATCC
Mycoplasma contamination	All cell lines used in the study were routinely tested for mycoplasma infection and were found to be free of contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study

Animals and other organisms

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

Laboratory animals	6-week-old immunocompromised female SCID mice purchased from Charles River Laboratories, USA. They were maintained in 12 hr light/dark cycles (7AM to 7PM) at 68F to 70F with 30 to 70% humidity condition.
Wild animals	Study did not involve wild animals
Field-collected samples	Study did not involve samples collected from the field
Ethics oversight	All mouse experiments were approved by the Icahn School of Medicine at Mount Sinai Animal Care and Use Committee (Protocol no. LA12-00037).

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

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	30,000 cells (control empty vector and shP53 cells) were processed for FACS 24 hrs after plating. Cell pellets were washed with phosphate buffered saline and fixed/permeabilized with 70% ice-cold ethanol. Pellets were washed and resuspended in 50 µg/ml ribonuclease A and 62.5µg/ml propidium iodide.
Instrument	BD FACSCanto™ II Cell Analyzer
Software	FloJo 10.4.2 software
Cell population abundance	Cell sorting not employed
Gating strategy	Using the FSC/SSC gating, debris was removed by gating on the main cell population. Positivity threshold for each cell line was defined on the basis of control (empty vector) sample. Identical positivity threshold was applied to all samples within cell line.

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