

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	ABI Step One Real-Time Detection System (Life Technologies) was used to run real-time PCR; Odyssey Infrared Imaging System (LI-COR) was used for collecting data from immunoblot experiment; Microplate reader (BioTek Gen5) was used for assays requiring absorbance and luminescence quantification; OLYMPUS microscope was used for collecting microscopy images ; Aligent Novocyte was used for apoptosis assay; ACQUITY UPLC-Xevo TQ-S was used to collect UPLC-MS/MS data.
Data analysis	Survival curves, calculation of Spearman correlation coefficient, two-paired t test and one-way ANOVA were analyzed using Prism v9.5; the grey values of immunoblots were measured using Image J software v2.1; the scores of IHC staining were evaluated with Image-Pro plus v6.0. Data of flow cytometry assays were collected by Aligent NovoExpress software and analyzed by FCS express V7.22. MassLynx software (version 4.1) was used to analyze UPLC-MS/MS data. The TCGA data analysis was performed using R language and webtool GEPIA.

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 RNA sequencing data generated in this study have been deposited in the GEO database under accession code GSE263889 [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE263889>]. The target region sequencing data of HCC driver genes mutation in this study of peer review file have been deposited in the SRA database under accession code PRJNA1163846 [<https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1163846/>]. The raw data of UPLC-MS/MS in this study have been deposited in Metabolight under accession code MTBLS11903 [<https://www.ebi.ac.uk/metabolights/editor/MTBLS11903>]. All the other data which support the findings of this study are available with in the article, supplementary information and source data. 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	Sample from both female and male were used in this study. For Fig. 2i, we used the samples from 16 female and 175 male. For Fig. 5c, we used the samples from 3 female and 25 male. Sex and gender information was not taken into consideration for the statistical analyses of this study, as it was not the focus of the research.
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	The clinical characteristics of patients in Fig. 2i and Fig. 5c are presented in Supplementary Data 1 and Supplementary Data 2, respectively.
Recruitment	Human tissue specimens were collected from patient with informed consent from Eastern Hepatobiliary Surgery Hospital (Shanghai, China).
Ethics oversight	The study was conducted with approval from the ethics committee of Eastern Hepatobiliary Surgery Hospital (Shanghai, China).

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	No specific calculations or statistical methods were used to predetermine sample size. For most of the in vitro experiments, at least three biological replicates were achieved for statistics. For in vivo experiments, 5-7 mice per experimental group was used.
Data exclusions	No data were excluded from the analyses.
Replication	The in vitro experiments were repeated 2-3 times with similar results. For animal experiments shown in Figure 3c-3j, 6 mice per group were used; for animal experiments shown in Figure 6f-6k, 5 mice per group were used; for animal experiments shown in supplementary Figure 7a-7e, 7f-7k, 7 mice per group were used. All replication attempts were successful.
Randomization	For in vivo experiments, age and sex matched animals were firstly inoculated with tumor cells and then randomly assigned to different experimenting groups, with no significant differences in tumor volume among the groups. For in vitro experiments, cells were equally distributed into culture dishes and followed by different treatments, no randomization was required.
Blinding	Investigator were blinded to RNA sequencing analysis since the samples after treatment were labeled with code names. All other experiments were performed in a non-blinded manner, because the experiments needed multiple treatments, including tumor cells and tumor-bearing mice treated by methionine deprivation, anticancer drug administration and transfection, and the different groups needed to be clearly labeled for the operation, data collection and analysis.

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study).
Research sample	State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.
Sampling strategy	Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.
Data collection	Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection.
Timing	Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort.
Data exclusions	If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.
Non-participation	State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation.
Randomization	If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled.

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.
Research sample	Describe the research sample (e.g. a group of tagged <i>Passer domesticus</i> , all <i>Stenocereus thurberi</i> within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source.
Sampling strategy	Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.
Data collection	Describe the data collection procedure, including who recorded the data and how.
Timing and spatial scale	Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken
Data exclusions	If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.
Reproducibility	Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.
Randomization	Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.
Blinding	Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.

Did the study involve field work? ☐ Yes ☒ No

Field work, collection and transport

Field conditions	<i>Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).</i>
Location	<i>State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).</i>
Access & import/export	<i>Describe the efforts you have made to access habitats and to collect and import/export your samples in a responsible manner and in compliance with local, national and international laws, noting any permits that were obtained (give the name of the issuing authority, the date of issue, and any identifying information).</i>
Disturbance	<i>Describe any disturbance caused by the study and how it was minimized.</i>

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	Western blot antibodies: Mouse anti-YAP (CAT#12395, CST), 1:1,000 dilution Rabbit anti-YAP R124me2a (CAT N/A, Chinapeptides), 1:400 dilution Rabbit anti-Phospho-YAP (Ser127) (CAT#13008, CST), 1:1,000 dilution Rabbit anti-SLC43A2 (CAT#PA5-54451, Thermo Fisher Scientific), 1:1,000 dilution Rabbit anti-PRMT1 (CAT#2449, CST), 1:1,000 dilution Rabbit anti-puromycin (CAT#A21205, ABclonal), 1:3,000 dilution Rabbit anti-phospho-LATS (CAT#AP1517, ABclonal), 1:1,000 dilution Rabbit anti-LATS1 (CAT #3477, CST), 1:1,000 dilution Rabbit anti-LATS2 (CAT#A16249, ABclonal), 1:1,000 dilution Rabbit anti-GAPDH (CAT#97166, CST), 1:5,000 dilution 800CW Goat anti-Rabbit IgG Secondary Antibody (CAT#926-32210, LI-COR Biosciences), 1:3,000 dilution 680CW Goat anti-Mouse IgG Secondary Antibody (CAT#926-68071, LI-COR Biosciences), 1:7,000 dilution IHC antibodies: Mouse anti-ki-67 (CAT#GB121141-100, Servicebio), 1:3,000 dilution Rabbit anti-YAP R124me2a (CAT N/A, Chinapeptides), 1:400 dilution Rabbit anti-SLC43A2 (CAT#PA5-54451, Thermo Fisher Scientific), 1:50 dilution ChIP-qPCR antibodies: Rabbit anti-YAP (CAT#14074, CST), 1:50 dilution Mouse anti-TEAD4 (CAT#AB58310, Abcam), 1:50 dilution Rabbit anti-IgG (CAT#ab172730, Abcam), 1:100 dilution
Validation	Except anti-YAP R124me2a antibody, all other antibodies were well-recognized clones in the field and validated by the manufacturers. These antibodies are further validated and routinely used in our lab. Anti-YAP R124me2a antibody made by Chinapeptides was validation in our previous study (PMID: 38653754).

Eukaryotic cell lines

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

Cell line source(s)	Huh-7 (TCHu182) and SGC7901 (TCHu 46) was purchased from the National Collection of Authenticated Cell Cultures (Shanghai, China). Cell lines HCT 116 (CCL-247), Hepa1-6 (CRL-1830), A549 (CRM-CCL-185) and HEK 293A/293T (CRL-3216)
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were purchased from American Type Culture Collection (ATCC, Manassas, VA). YAP-KO 293A cells were a gift from Prof. Fa-Xing Yu at Children's Hospital of Fudan University.

Authentication

All cell lines were authenticated using the short tandem repeat (STR) analysis.

Mycoplasma contamination

All cell lines were tested negative for mycoplasma contamination.

Commonly misidentified lines (See [ICLAC](#) register)

None commonly misidentified cell lines were used in the experiments.

Palaeontology and Archaeology

Specimen provenance

Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.

Specimen deposition

Indicate where the specimens have been deposited to permit free access by other researchers.

Dating methods

If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight

Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

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

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 6-7-week-old male C57BL/6J mice and 4-5-week-old male Balb/c nude mice, purchased from Shanghai BK/KY Biotechnology Company (Shanghai, China) and quarantined for one week before treatment. All mice were housed under specific pathogen-free conditions and maintained in a humidity controlled environment with a 12 h light/dark cycle at a temperature of 22-25°C.

Wild animals

This study did not involve wild animals.

Reporting on sex

Male mice were used for all experiments.

Field-collected samples

The study did not involve samples collected from field.

Ethics oversight

All mouse experiments were conducted in accordance with the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and were approved by Scientific Investigation Board of Naval Medical University.

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

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration

Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.

Study protocol

Note where the full trial protocol can be accessed OR if not available, explain why.

Data collection

Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.

Outcomes

Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.

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	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.
Novel plant genotypes	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.
Authentication	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.

ChIP-seq

Data deposition

- ☐ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links <i>May remain private before publication.</i>	For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.
Files in database submission	Provide a list of all files available in the database submission.
Genome browser session (e.g. UCSC)	Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates	Describe the experimental replicates, specifying number, type and replicate agreement.
Sequencing depth	Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.
Antibodies	Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

Peak calling parameters	<i>Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.</i>
Data quality	<i>Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.</i>
Software	<i>Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.</i>

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 washed with 1× binding buffer and stained with Annexin V and PI (BioLegend, San Diego, USA) in 1× binding buffer in the dark for 15 min following the manufacturer's protocol.
Instrument	Aligent Novocyte
Software	All samples were acquired on Aligent NovoExpress (Aligent, California, USA) and were analyzed using FCS express (De Novo Software, Pasadena, USA).
Cell population abundance	We obtained a purity of at least 95% of sorted populations determined by flow cytometry
Gating strategy	Forward scatter (FSC) and side scatter (SSC) strategies were used for gating followed by an elimination of the doublets based on the size scatter. The control samples were used to define background
☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.	

Magnetic resonance imaging

Experimental design

Design type	<i>Indicate task or resting state; event-related or block design.</i>
Design specifications	<i>Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.</i>
Behavioral performance measures	<i>State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).</i>

Acquisition

Imaging type(s)	<i>Specify: functional, structural, diffusion, perfusion.</i>
Field strength	<i>Specify in Tesla</i>
Sequence & imaging parameters	<i>Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.</i>
Area of acquisition	<i>State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.</i>
Diffusion MRI	☐ Used ☐ Not used

Preprocessing

Preprocessing software	<i>Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).</i>
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Normalization	<i>If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.</i>
Normalization template	<i>Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.</i>
Noise and artifact removal	<i>Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).</i>
Volume censoring	<i>Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.</i>

Statistical modeling & inference

Model type and settings	<i>Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).</i>
Effect(s) tested	<i>Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.</i>
Specify type of analysis:	☐ Whole brain ☐ ROI-based ☐ Both
Statistic type for inference	<i>Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.</i>
(See Eklund et al. 2016)	
Correction	<i>Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).</i>

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis
Functional and/or effective connectivity	<i>Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).</i>
Graph analysis	<i>Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).</i>
Multivariate modeling and predictive analysis	<i>Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.</i>