nature portfolio

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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 (*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	Nikon NIS-Elements version 4.50 and version 5.21, NanoSight NTA 3.2, FluorEssence™ 2.0, R (v3.12 and v3.2.5).
Data analysis	Statistical analyses were performed with GraphPad Prism 8.0. Gray values (Densitometry) for western blotting were analyzed by Image J (Fiji) software version 2.3.0.

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

Source data have been provided in Source Data. For patient cohort expression data, the accession code is in the methods section (GSE14520). The gene expression and clinical data for the LCI dataset including 486 tumors and matched non-tumor liver specimens (non-tumor=239 and tumor=247) are available on Gene Expression Omnibus (GEO) GSE14520 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse14520). All other data supporting the findings of this study are available from the corresponding author on reasonable 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	Samples size for each experiment is indicated in the figures or corresponding figure legends. For animal experiments, at least 5 mice were used in each group in order to obtain statistical significance. Sample size was determined based on previous experience and relevant literatures. For all experiments, we followed the acceptable practice in the field and maximize the sample size within the reasonable size range.
Data exclusions	One set of data from more than 4 different sets for Fig. 7a was excluded from final statistical analysis as technical errors in immunoblotting of the same protein sample resulted in ambiguous readouts in two repeats.
Replication	Experiments were repeated at least 3 times independently to ensure reproducibility.
Randomization	The allocation of cells/mice to different treatments was completely random.
Blinding	For mouse studies, the experiments were performed in a double blinded fashion. Individuals performing the assays were not aware of the treatment groups until the data analyses were completed.

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

Sox9 (CST, #82630), WB (1:1000), IHC (1:100)
c-Myc (CST, #5605), WB (1:1000)
Hes1 (CST, #11988), WB (1:1000), Bioss, #bs-2972R, IHC (1:100)
HRS (CST, #15087), WB (1:1000)
Phospho-Akt (Ser473) (CST, #4046), WB (1:1000)
Akt Phospho-Substrate (RXXS*/T*) (CST, #9614), WB (1:1000)
Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (CST #4370), WB (1:1000)
GAPDH (CST, #2218), WB (1:1000)
Jagged1 (CST, #70109), WB (1:1000), IF (1:200)
CD63 (abcam, #ab8219), IF (1:500); #ab134045; #ab217345, WB (1:1000)
Rab8 (BD, #610844), WB (1:1000)
LAMP1 (DSHB, clone 1D4B), IF (1:500)
Flag (Sigma, #F3165, #F1804), WB (1:1000), IF (1:500)
Rabin8 (Proteintech, #12321-1-AP), WB (1:1000)
HA (Roche, clone 12CA5), WB (1:1000)
Ki67 (CST, #12202), IHC (1:100)
PCNA (CST, #2586), IHC (1:100)
Cleaved Caspase-3 (CST, #9664), IHC (1:100)
TSG101 (Santa Cruz C-2, sc-7964), WB (1:1000)
Syntenin-1 (Abcam ab19903), WB (1:1000)

Grp94 ((D6X2Q) XP® #20292), WB (1:1000)
Alix (Santa-Cruz (1A12): sc-53540), WB (1:1000)
Rab27a (Sicgen, #AB0023), Rab27a (CST (D7Z9Q, 69295), WB (1:1000)
pan-Akt (CST, #4685), WB (1:1000)

Validation

Validated for antibodies against human and mouse proteins for western blotting: HRS (CST, #15087), Sox9 (CST, #82630), c-Myc (CST, #5605), Hes1 (CST, #11988; Bioss, #bs-2972R), Jagged1 (CST, #70109), CD63 (abcam, #ab8219; #ab134045; #ab217345), Rab8 (BD, #610844), Rabin8 (Proteintech, #12321-1-AP),Rab27 (Sicgen, #AB0023), Rab27a (CST (D7Z9Q), LAMP1 (DSHB, clone 1D4B), Flag (Sigma, #F3165), HA (Roche, clone 12CA5), Rabin8 (Proteintech, #12321-1-AP), GAPDH (CST, #2218), Grp94 ((D6X2Q) XP® #20292), Alix (Santa-Cruz (1A12): sc-53540), Syntenin-1 (Abcam ab19903), TSG101 (Santa Cruz C-2): sc-7964).
Validated for mouse tissue immunohistochemistry: Ki67 (CST, #12202), PCNA (CST, #2586), Cleaved Caspase-3 (CST, #9664), Sox9 (CST, #82630)
Validated for human: pan-Akt (CST, #4685), Phospho-Akt (Ser473) (CST, #4046), Akt Phospho-Substrate (RXXS*/T*) (CST, #9614), Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (CST #4370), GFP antibody (homemade).
Validated for immunofluorescence microscopy: Jagged1 (CST, #70109), CD63 (abcam, #ab8219), LAMP1 (DSHB, clone 1D4B), Flag (Sigma, #F3165)

Detailed validation statement for antibody is provided on the manufacturer's websites. Antibodies in the list above were further validated by using positive and negative controls, molecular weight markers in our studies with specific applications implicated, or subcellular localization.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Huh7 (Cat: CCLV-1079, RRID: CVCL_0336, ATCC), Panc1 (Cat: CRL-1469, ATCC), MCF-7 (Cat: HTB-22, ATCC), Hepa1-6 (Cat: CRL-1830, ATCC), MCF10A (Cat: CRL-10317, ATCC), MCF10AT and MCF10CA1d cells (derived from MCF10A in Dr. Fred Miller's Lab, Karmanos Cancer Institute, Wayne State University). Cryo-preserved primary human hepatocytes (Cat: 454541 BD Gentest Bioscience).
Authentication	All of the cell lines used were authenticated by STR profiling.
Mycoplasma contamination	Mycoplasma testing was regularly conducted to ensure that all cells used were free from contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used for this study.

Animals and other organisms

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

Laboratory animals	7-week-old male C57L/J mice were housed under standard specific-pathogen-free (SPF) conditions.
Wild animals	Study did not involve wild animals.
Field-collected samples	No samples were collected in Field.
Ethics oversight	All animal experiments were performed in accordance with protocols approved by the Institutional Animal Care and Use Committee of University of Pennsylvania.

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