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	Plasma Proteomics: Vanquish Neo UPLC system. ELISA: TECAN infinite F plex. ultrasound images: MicroscanTM transducer MS-550D. quantitative PCR: ABI7500 or QuantStudio 6 Flex (Applied Biosystems) system. fluorescent images:Leica SP8 confocal microscope or NanoZoomer S60(Hamamatsu Photonics) slide scanner. Flow cytometry: FACSymphony™ A5 (BD Biosciences) analyzer. immunohistochemistry images: NanoZoomer S60(Hamamatsu Photonics) slide scanner. RNA-seq: Illumina NovaSeq platform. Western blotting: Amersham ImageQuant 800 imaging system.
Data analysis	GraphPad Prism 8, FlowJo 10.6.1, QuPath 0.4.2, Imaris 9.5.1, ImageJ 1.5, GSEA v.4.0.3, Seurat v.3.2.2 , R (v.4.0.3), Trimmomatic v.0.36, STAR aligner v.2.5.2b, Vevo Lab v.3.2.0, JASPAR 2022, edgeR package.

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

RNA-seq data for KPFV; Spp1wt/wt, KPFV; Spp1 Δ/Δ and KPFV; Cd61wt/wt, KPFV; Cd61 Δ/Δ organiod have been deposited in the Gene Expression Omnibus under the accession codes GSE269971 and GSE269972, respectively. The mass spectrometry proteomics data are available via ProteomeXchange with identifier PXD053603. For human PDAC scRNA-seq data, fastq files of 24 PDAC and 11 normal pancreas samples were downloaded from the Chinese National Genomics Data Center (Genome Sequence Archive: CRA001160). GSE71729, ICGCarray, ICGCseq, TCGA, GSE62452 and GSE79668 pancreatic adenocarcinoma dataset.The Cell-based computational model code were submitted in Code Ocean (10-498690-0).

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	No sex/gender specific analysis was performed since there is no known association with prognosis.
Reporting on race, ethnicity, or other socially relevant groupings	No race, ethnicity, or other socially relevant groupings specific analysis was performed since there is no known association with prognosis.
Population characteristics	Peripheral venous blood was collected from 26 patients with pancreatic cancer at the Seventh Affiliated Hospital of Sun Yat-sen University. Including 14 stage Ⅰ & Ⅱ and 12 stage Ⅲ&Ⅳ patients. The median age in patients was 69.5 years. Among them, 6 were female and 20 were male.
Recruitment	All patients diagnosed with pancreatic cancer with the Seventh Affiliated Hospital of Sun Yat-sen University between January 2018 and January 2024. Patients were retrospectively selected based on the different stages of tumor.
Ethics oversight	Informed consent was obtained from all participants, and approvals were secured from the ethics board of the Seventh Affiliated Hospital of Sun Yat-sen University for the use of these specimens in research. All clinical samples were collected with informed consent, and all experiments adhered to the regulations and approvals of the internal review and ethics board at the Seventh Affiliated Hospital of Sun Yat-sen University. The Institutional Review Board approval number is KY-2024-249-01 and SYSU-IACUC-2025-B0073.

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

Life sciences study design

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

Sample size	No statistical methods were used to predetermine sample size. All in vitro studies included at least three independent experiments, which was determined based on prior experience, our and others' published literature on the same research area. For in vivo studies, sample sizes were determined by our preliminary experiments with optimisation.
Data exclusions	No data were excluded from analysis.
Replication	All experiments were repeated multiple times and/or on multiple biological replicates with similar results as indicated in the figure legends.
Randomization	For studies involving autochthonous mouse tumour models, the mice were not randomised, and selected according to their correct genotype. For the in vivo subcutaneous and orthotopic transplantation experiments, mice were randomised. For the therapeutic experiment, tumour bearing mice were randomised for vehicle and Spp1 antibody treatment.
Blinding	Blinding was not performed. The data are based on instrumentation and software-based quantitative analysis of phenotypes, and are not subjective.

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

The following antibodies were used in this study: CK19 (TROMA III) (DSHB, rat, 4/5/18-198ug/mL); Cytokeratin 19(Dako, mouse, M0888, RCK108); Vimentin (CST, rabbit, 5741s, D21H3, Lot# 8 and 6); Vimentin (Abcam, rabbit, ab16700, SP20, 1012972-99); GFP/YFP (Abcam, Goat, ab6673, GR287379-16); GFP/YFP (Abcam, Chicken, ab13970, GR3361051-2); NF-kappaB p65(CST, Rabbit, 8242T,D14E12,16); Osteopontin/OPN (R&D Systems, Goat, AF808, BDO0821121); Osteopontin/OPN (R&D Systems, Goat, AF1433, IWX2122101); Osteopontin (SPP1) (Bio X Cell, Rat, BE0382,MPIIIB10, 832222J3,929223N1,929224A2); ß-Actin (Abcam, Mouse, ab49900, AC-15,GR3283184-6); Histone H3(CST, Rabbit, 4620, D2B12); CD61 (APC)(ThermoFisher, Rat, 17-0611-82, 2C9.G3, 2460154); Integrin beta 3/CD61(NOVUSBIO, Rabbit, NBP2-67416, H661304011); aSMA(Dako, mouse, M0851, 1A4); CD45 (BV421) (BioLegend, Rat, 103126, 30-F11, B336453); CD31(BV421)(BioLegend, Rat, 102422, 390,B202554); TCRβ (APC) (BioLegend, Armenian Hamster, 109212, H57-597,B273860); CD4 (FITC) (BioLegend, Rat, 100405, GK1.5,B434018); TCRβ (BV650) (BioLegend, Armenian Hamster, 109251, H57-597,B407302); CD8 (APC) (BioLegend, Rat, 100711, 53-6.7,B435786); CD45 (APC) (BioLegend, Rat, 103112, 30-F11,B393765); NK1.1 (BV605) (BioLegend, Mouse, 108739, PK136,B429389); CD11b (BV650) (BioLegend, Rat, 101239, M1-70,B402100); F4/80 (PE) (BioLegend, Mouse, 157304, QA17A29,B366645); CD11c (APC) (BioLegend, Armenian Hamster, 117309, N418,B396301); MHC II (PerCP-Cy5.5) (BioLegend, Rat, 107625, M5/114.15.2,B433648); Ly6G (BV605) (BioLegend, Rat, 127639, 1A8,B444903); B220 (PE/Cy5) (BioLegend, Rat, 103209, RA3-6B2,B434512); Goat IgG (H+L) (HRP)(Jackson ImmunoResearch, Donkey, 705-035-147, 118345); Goat IgG (H+L) (Alexa 488)(ThermoFisher, Donkey,A32814, YA363610); Rabbit IgG (H+L) (Alexa 546) (ThermoFisher, Donkey, A10042, 2743014); Rat IgG (H+L) (Alexa 647)(ThermoFisher, Donkey, A48272, YL384215); Chicken IgG (H+L) (Alexa 647)(ThermoFisher, Donkey, A78952, 2515348); Mouse IgG (H+L) (Alexa 488)(ThermoFisher, Donkey, A21202, 2266877).

Validation

All the reagents had been previously optimized and validated by the companies.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

Human HEK293T was obtained from The Institute of Cancer Research, London.

Authentication

HEK293T cell line was authenticated using Short Tandem Repeat (STR) DNA profiling by the Cell Service of The Institute of Cancer Research, London.

Mycoplasma contamination

HEK293T cell line was tested negative for mycoplasma.

Commonly misidentified lines
(See ICLAC register)

Name any commonly misidentified cell lines used in the study and provide a rationale for their use.

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 following mouse lines were used in this study: KrasLSL-G12D (Jackson, 2001), Trp53flox (Marino, 2000), Pdx1-Cre (Hingorani, 2003), Pdx1-Flp, KRasFSF-G12D, Trp53frt, Rosa26FSF-CreER (Schönhuber, 2014), Rosa26LSL-YFP (Srinivas, 2001), Rosa26mT/mG (Muzumda, 2007), Grem1flox (Gazzerro, 2007), Trp53R172H(Olive, 2004) and Spp1flox (Cat. NO. NM-CKO-210205, Shanghai Model Organisms Center, Inc.). These lines were inter-crossed to generate the desired genotypes on a C57BL/6 background. Mouse genotypes were determined using real-time PCR with specific probes designed for each gene (Transnetyx). Mice with correct complex genotypes were used for autochthonous tumour development and metastasis analysis, typically with the age between 8-30 weeks. The immunocompromised Nu/Nu mice have also been previously described, and adults (aged 8–12 weeks) obtained from Charles River Laboratories were used for transplantation.

Wild animals	The study did not involve wild animals.
Reporting on sex	The mice in our study were not gender-specific. For Genetically Engineered Mouse Models were intercrossed to generate the desired genotypes of both sexes on a C57BL/6 background in Charles River Laboratories. The immunocompromised Nu/Nu mice were adults (aged 8–12 weeks) obtained from Charles River Laboratories were used for transplantation.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal experiments were approved by the Institute of Cancer Research, London's Animal Welfare and Ethical Review Body and conformed to UK Home Office regulations under the Animals (Scientific Procedures) Act 1986 including Amendment Regulations 2012, or by the Institutional Animal Care and Use Committee (IACUC), Sun Yat Sen 531 University. Approval No. SYSU IACUC 2025 B0073.

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

Plants

Seed stocks	N.A.
Novel plant genotypes	N.A.
Authentication	N.A.

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	Organoids or tissues were dissociated into single cells as mentioned above. Single cells were suspended in FACS buffer (PBS containing 2% FCS). The cells were incubated with fluorophore-conjugated isotype control or experimental antibodies in FACS buffer on ice in the dark for 30 minutes. Cells were washed three times with PBS, filtered through a 40µm nylon mesh (Corning), and then incubated in FACS buffer containing 3µM DAPI or Propidium Iodide (PI). Single-color and fluorescence minus one staining controls were used as necessary.
Instrument	The cells were analyzed using the FACSymphony™ A5 (BD Biosciences) analyzer.
Software	FlowJo 10 software
Cell population abundance	The sorted target populations within post-sort fractions were highly pure, with the purity more than 95%. The purity was determined by reanalysing the sorted fraction using the same parameters and gates.
Gating strategy	The cell suspension were first gated by DAPI/FSC or PI/FSC to exclude dead cells and live single cells were gated by FSC-H/FSC-A and SSC-H/SSC-A. The boundary between "positive" and "negative" was determined by the fluorescence-minus-one control or the isotype control.

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