

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	No software was used for data collection
Data analysis	R 3.6.3, R studio 1.1.463, MetaboAnalyst v.4.0 & 5.0, Morpheus, Cibersortx, Cytoscape 3.5.1, Metascape v.3.5, GSEA, Image J2 Fiji, SPSS v25&26, GraphPad Prism 9, Matlab R2017a, Harmony version 0.3.0. Custom code: https://github.com/ElementoLab/imc , version 0.1.4 and https://github.com/czambir/PC_pml_code

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](#)

Gene expression data has been deposited to the NIH GEO repository and can be accessed as GSE245535 (Bulk mRNAseq) and GSE267209 (single cell RNAseq). Cytoscape ClueGO with GO Immune system Process was used for gene clustering (<https://apps.cytoscape.org/apps/cluego>) and Metascape (<https://metascape.org/>)

gp/index.html#/main/step1) was used for gene ontology analysis. Gene set enrichment analysis was performed using the Hallmark gene sets from MSigDB (<https://www.gsea-msigdb.org/gsea/msigdb/human/genesets.jsp?collection=H>). The LM22 dataset was used for deconvolution of bulk mRNAseq by Cibersortx (matrix provided in Supplementary_Tables_1.xlsx). Metabolomics source data can be accessed in Supplementary_Tables_1.xlsx. Clinical data in this study can be found in Extended Data Table 1, Supplementary Table S1, Supplementary Table S8 and Supplementary Table S11.

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	The sex of the included patients is reported in Supplementary Table S1 and is in line with the established slightly higher incidence of PaC in males. Sex assignment was based on self-reported questionnaire asking for sex at birth, as documented in the patient medical records. No attempt to select patients on a race, sex and/or gender basis was made.
Reporting on race, ethnicity, or other socially relevant groupings	Gender or race data have not been collected since they were not readily available from the medical records. No attempt to select patients on a race, sex and/or gender basis was made.
Population characteristics	Data regarding sex, age, and co-variables such as BMI, biliary obstruction, tumor stage, histologic subtype, differentiation, lymphovascular/perinural invasion are reported in Supplementary Table 1.
Recruitment	Patients with presumed diagnosis of resectable pancreatic cancer or non-cancerous pancreatic/peripancreatic diseases who were eligible for pancreatotomy at MSKCC and had no contraindication to liver biopsy were approached and recruited to the study after informed consent, under IRB protocol #15-015. All patients presenting in the MSKCC HPB clinic for possible pancreatotomy who met inclusion criteria were screened and considered for recruitment at the discretion of the operative surgeon. All individuals who agreed to participate provided informed consent. The study is compliant with all relevant ethical regulations regarding research involving human subjects. Details are found in the manuscript's Methods section.
Ethics oversight	The collection and analysis of human blood, tumor and liver tissue was approved by the Institutional Review Boards of MSKCC (IRB # 15-015) and Weill Cornell Medicine (IRB # 0604008488). All individuals provided informed consent. The study is compliant with all relevant ethical regulations regarding research involving human subjects.

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	Given that this was a first-in-human study, with complex exploratory outcomes, no precise power calculations were performed. The sample size was approximated by attempting to have 10 patients per group and considering that some patients may not have adequate follow-up or sufficient material for certain experiments. Given the diverse nature of our findings, we are now running a prospective study in a much larger number of patients.
Data exclusions	Patients with diagnoses other than pancreatic ductal adenocarcinoma (mainly patients with colloid carcinoma) were excluded and replaced, as originally planned. Pancreatic cancer (PaC) patients who had inadequate follow-up were only included in the PaC vs Non-PaC comparisons and were excluded from analyses comparing different recurrence groups (as outlined in Figure 1).
Replication	Three liver biopsies were collected to ensure intra-patient reproducibility between samples. Several measures were confirmed by multiple methods (whole tissue RNA sequencing, scRNA sequencing, immunohistochemistry, imaging mass cytometry). Analysis was confirmed by automated quantifications and manual scoring for measures such as IHC.
Randomization	No randomization was needed since there was no intervention. Further, the analyses were performed prior to the occurrence of the final endpoint (timing and site of metastasis).
Blinding	See above. Lead investigators were blinded to outcome at time of data collection. The remaining involved personnel were entirely blinded to the samples they were processing or analyzing even after the outcomes were known. Manual pathological scorings were performed by blinded pathologists.

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	A rabbit monoclonal anti-Ki-67 (clone SP6, abcam cat#16667) was used at 2.5µg/mL concentration and incubated for 6 hours incubation. A rabbit polyclonal anti-IBA-1 (Wako, cat#019-19741) was used in a concentration of 0.1µg/mL for 5 hours incubation. A mouse monoclonal anti-CD45 (clone 2B11, Dako cat#M0701) was used at 2.5µg/mL concentration and incubated for 6 hours incubation. Thereafter, both primary antibodies were followed by 60 minutes of biotinylated goat anti-rabbit IgG (Vector labs, cat.# PK6101) in 5.75 µg /ml concentration. Immunohistochemistry for p53 was performed similarly using the DO-7 mouse monoclonal antibody (Dako, cat# GA616), as described previously for FLEX ready-to-use antibodies (undiluted). CD11B, CD68, CD3, CD8, NE, ctH3 and MPO were stained by IF. The incubations with the primary antibodies were done for 6 hours. A rabbit monoclonal CD11B antibody (clone EPR1344, abcam cat#133357) was used in 1 µg/ml concentration followed by 60 minutes incubation with biotinylated goat anti-rabbit IgG (Vector labs, cat#PK6101) in 5.75µg /ml. A mouse monoclonal CD68 (clone KP1, Dako, cat#M0814) was used in 0.02µg /ml followed by biotinylated anti- mouse secondary (Vector Labs, MOM Kit BMK-2202) in 5.75 µg /ml. A rabbit polyclonal anti-CD3 antibody (Dako, cat#A0452) was used in 2.4 µg /ml concentrations followed by 60 minutes incubation with biotinylated goat anti-rabbit IgG (Vector labs, cat#PK6101) in 5.75 µg /ml. A rabbit polyclonal anti-CD8 antibody (Cell Signaling, cat#98941) was used in 4.8 µg /ml concentrations followed by 60 minutes incubation with biotinylated goat anti-rabbit IgG (Vector labs, cat#PK6101) in 5.75µg /ml. For NET analysis, NE (LS-Bio, LS-B4244), HNE / Neutrophil Elastase Sheep anti-Human Polyclonal Antibody (dilution 1:200), ct-H3 (Abcam, ab5103), Histone H3 (citruiline R2 + R8 + R17) Rabbit antibody - ChIP Grade (dilution 1:250) and MPO (R&D, cat#AF3667): Goat anti-myeloperoxidase (dilution 1:200) was used. For IMC studies Histone H3 Cell Signaling Technology 4499BF D1H2 17 1:400, FOXP3 Invitrogen 14-4777-82 236A/E7 2378013 1:25, CD4 Abcam ab181724 EPR6855 GR3285644-12 1:50, NKG2A Abcam ab273516 EPR23737-127 GR3410074-2 1:25, CD8a Dy162 eBioscience 14-0085-82 C8/144B 2132595 1:100, ARG1 Cell Signalling 89872SF D4E3M 11:50, CD3 Fluidigm 3170019D Polyclonal. C-Terminal 2202221-161:100, TRDC Yb171 Santa Cruz sc-100289 H-41 L13211:50 and KRTS/18 Fluidigm 3174022D (513720071:100 were used.
Validation	All antibodies were validated for the purpose of our studies with positive and negative human control tissues, as well as IgG controls from the same species. In addition, all antibodies used are commercially available and validated according to manufacturer's websites, as stated below. Anti-Ki67 (SP6) is recombinant and abcam validated by knockout (https://www.abcam.com/products/primary-antibodies/ki67-antibody-sp6-ab16667.html). Anti-IBA-1 (https://labchem-wako.fujifilm.com/us/product_data/docs/00055446_doc02.pdf). Anti-CD45 (2B11) has been tested by Dako/Agilent with tonsil B and T cells as positive controls and brain microglia as negative controls (https://www.agilent.com/cs/library/catalogs/public/00230-d58532-02-atlas-of-controls-2nd-edition-agilent.pdf). Anti-p53 (DO7) was validated as shown in Supplementary Data Fig. 1 and according to manufacturer (https://www.agilent.com/en/product/immunohistochemistry/antibodies-controls/primary-antibodies/p53-protein-%28dako-omnis%29-76230). Anti-CD11B (EPR1344) was tested against human tonsil and sleep as stated on the manufacturer's website (https://www.abcam.com/products/primary-antibodies/cd11b-antibody-epr1344-ab133357.html). Anti-CD68 (KP1) was validated against multiple human tissues (https://www.agilent.com/en/product/immunohistochemistry/antibodies-controls/primary-antibodies/cd68-%28concentrate%29-76535). Anti-CD3 was validated by the manufacturer (https://www.agilent.com/en/product/immunohistochemistry/antibodies-controls/primary-antibodies/cd3-%28concentrate%29-76133). Anti-CD8 was validated according to manufacturer (https://www.cellsignal.com/products/primary-antibodies/cd8a-d4w2z-xp-rabbit-mab/98941). Anti-NE was

validated according to manufacturer (<https://www.lsbio.com/pathplus-antibodies/pathplus-hne-antibody-neutrophil-elastase-antibody-elisa-ihc-ls-b4244/118639>). Anti-ct-H3 was validated according to manufacturer (<https://www.abcam.com/products/primary-antibodies/histone-h3-citrulline-r2--r8--r17-antibody-ab5103.html>). Anti-MPO was validated according to manufacturer (https://www.rndsystems.com/products/human-mouse-myeloperoxidase-mpo-antibody_af3667). Anti-histone H3 (D1H2) was validated according to manufacturer (<https://www.cellsignal.com/products/primary-antibodies/histone-h3-d1h2-xp-rabbit-mab/4499>). Anti-FOXP3 was validated according to manufacturer (<https://www.thermofisher.com/antibody/product/FOXP3-Antibody-clone-236A-E7-Monoclonal/14-4777-82>). Anti-CD4 was validated according to manufacturer (<https://www.abcam.com/products/primary-antibodies/cd4-antibody-epr6855-bsa-and-azide-free-ab181724.html>). Anti-NKG2A was validated according to manufacturer (<https://www.abcam.com/products/primary-antibodies/nkg2a-antibody-epr23737-127-bsa-and-azide-free-ab273516.html>). Anti-CD8a (C8/144B) was validated according to manufacturer (<https://www.thermofisher.com/antibody/product/CD8a-Antibody-clone-C8-144B-Monoclonal/14-0085-82>). Anti-arginase-1 was validated according to manufacturer (<https://www.cellsignal.com/products/primary-antibodies/arginase-1-d4e3m-8482-xp-174-rabbit-mab-bsa-and-azide-free/89872>). Anti-CD3 (Fluidigm) was validated according to manufacturer (<https://fluidigm.my.salesforce.com/sfc/p/#700000009DAw/a/4u0000019iHf/m23J6T1Co3D7DkuFRjdXVy7kXUfOMaOh3pr2RZnNql>). Anti-TRDC is validated according to manufacturer (<https://www.scbt.com/p/tcr-delta-antibody-h-41>). Anti-KRT8/18 was validated according to manufacturer (https://fluidigm.my.salesforce.com/sfc/p/#700000009DAw/a/4u0000019iH6/Klv3TAc8ZlVEKmaFXZay5E_i7KKlrKMau0uNZuiXzS8).

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	NCT02393703
Study protocol	A summary of the #15-015 study protocol, which includes additional investigations and endpoints not published here, is available on the ClinicalTrials.gov trial registration website. The full protocol is available on demand by contacting the corresponding authors.
Data collection	Data was collected from the study initiation (4/2015) until closure of followup in 12/2021.
Outcomes	The primary endpoint pertaining to this study was differences in the liver among patients with PaC and Non-PaC. The secondary outcome was hepatic differences between PaC patients with various patterns of recurrence, or no recurrence.

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>