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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒ An indication of 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 statistics 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
☐	☒ Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	qPCR was performed with ABI qPCR 7900HT (Thermo Fisher Scientific) using SDS2.4 software. RNA-seq assays were run on on Illumina HiSeq 2500. RNA-seq data of gene expression in PDAC tumors by TCGA were downloaded from http://www.cbioportal.org on 2018/07/20. Immunoblot images were scanned using Odyssey Imager (Licor). For ELISA assays, signal acquisition and subsequent analysis were carried out by Bio-Plex 200 System (Bio-Rad) for Luminex kits and by Quanterix SX-R for Simoa assays. Histology and IHC images were acquired with a Pannoramic MIDI slide scanner (3DHISTECH), and multiplex immunofluorescence tissue section images were acquired using the VS120-L100 Virtual Slide System (Olympus). For MS assays, TripleTOF 5600 (AB SCIEX) secretome profiling, LTQ-Orbitrap Elite (Thermo) for phosphoproteomic and IP-MS analyses, and Orbitrap Fusion (Thermo) for global profiling of pancreatic tumour samples and PRM-MS assay, were used. Flow cytometry analysis and cell sorting were carried out on a FACSAria III machine.
Data analysis	All data analyses were performed with commonly used software and stated in Figure Legends or Methods parts. Briefly, qPCR was analyzed using SDS2.4 software. For RNA-seq data, raw sequencing data was demultiplexed and converted into FASTQ files using CASAVA (v1.8.2), quality tested using FASTQC (v0.11.2), aligned to the mm10 genome using the STAR aligner (v2.4.0k), and differential gene expression were analyzed using the edgeR package (v3.6.8) and GSEA online tools, and hierarchical clustering was performed using the R (v3.3.2). Immunoblot images were quantified by Odyssey sofware (Licor). Image analysis of immunohistochemistry stained tissue sections with Image J; image analysis of multiplex immunofluorescence stained tissue sections with Imaris with custom MATLAB code. For secretome profiling, raw files were searched against IPI human database (v3.82, 92104 entries) using Mascot (v2.3.02) and processed for spectral counting quantification using Scaffold (v3.4.9). Gene Ontology annotation was performed using DAVID (v6.8). Raw files for phosphoproteomic analysis were processed by MaxQuant (v1.1.1.36) for dimethyl labeling quantification and database searching against IPI human database (v3.79, 91464 entries). IP-MS data was processed by MaxQuant (v1.2.2.5) for label-free quantification and database

searching against the IPI human database (v3.79). For global profiling of pancreatic tumour samples, raw data were searched against the Uniprot human database (70611 entries, downloaded on July 23, 2016) using Sequest HT node integrated within the Proteome Discoverer software (v1.4, Thermo). The PRM raw data were searched against the Uniprot human database by Sequest HT, and then quantified by Skyline (v3.6.0.10493). Flow cytometry data were analyzed with FlowJo software (Tree Star). Statistical analysis were done by Prism 8.0, except ROC curve by pROC package for R.

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/reviewers upon request. 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

In the Methods part, we enclosed a “Data availability” section, stating that “RNA sequencing data have been deposited in the Gene Expression Omnibus under accession numbers GSE99187 and GSE119694. All MS raw data have been deposited to the MassIVE repository (ftp://MSV000081136@massive.ucsd.edu). The custom scripts for quantification of IHC images with Image J and multiplex immunofluorescence images with Imaris will be freely available upon request.”

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	This was a study where the "effect magnitude" was unknown and therefore power was not calculated. Approximated sample sizes (n>10 for in vivo animal study) were estimated based on the general experiences and the variability of pancreatic tumour models used. p values were statistically calculated to determine the significance where applicable.
Data exclusions	All animals and samples generated for the purpose of these studies were included, except the obvious outliers identified by Prism ROUT analysis (Q<0.5), the standard criteria commonly used.
Replication	For all the findings reported in the paper, at least three independent experiments were performed, and all the data were included for analysis and presented, except for qualitative experiments, e.g. immunoblot, the representative results were presented and stated in corresponding figure legends. All experiments were successfully replicated with the properly optimized condition.
Randomization	For all the preclinical studies, including Gem vs saline treatment on KPf/fCL;LIFRf/f mice (Fig. 2), and cerulein-treated KC;LIFRf/f mice (Extended Data Fig. 3h,i), four-arm preclinical trials using KPf/fCL mice (Fig. 3), maintenance KPC model with triple chemotherapy pretreatment (Fig. 4), littermates at the same age were randomly enrolled into the cohorts. In all cases, when the treatment started, the mice were all grossly/visually healthy and body weight was not significant different, so randomly assigned into the cohorts of treatments.
Blinding	All the enrolled mice or subsequent samples were labelled only with mouse ID numbers and did not indicate genotype or type of treatment. Genotype or treatment type were decoded after the data acquisition and quantification analysis were complete.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Antibodies

Antibodies used

These primary antibodies against the indicated proteins were used in this study for immunoblot with indicated dilution: pSTAT3 (Cell Signaling, 9145, clone D3A7, lot 31, 1:1000), pAKT1 (Cell Signaling, 4060, clone D9E, lot 23, 1:2000), and pERK1/2 (Cell Signaling, 4376, clone 20G11, lot 18, 1:1000), STAT3 (Santa Cruz, sc-8019, lot A1816, 1:500), LIFR (Santa Cruz, sc-659, lot 1714, 1:200), and ACTA2 (Santa Cruz, sc-32251, clone 1A4, lot A1218, 1:5000), Krt19 (Epitomics, AC-0073, clone EP72, lot EL050102, 1:2000), -Tubulin (Sigma, clone B-5-1-2, lot 086M4773v, T5186, 1:10,000).
The following primary antibodies were used for IHC and IF with indicated dilution: mouse anti-ACTA2 (Santa Cruz sc-32251, 1:1500), rabbit anti-Cytokeratin 19 (Epitomics AC-0073, 1:200), rabbit anti-phospho-Stat3 (Tyr705) (CST 9145, 1:100), rabbit anti-cleaved Caspase 3 (CST 9661, lot 37, 1:200), rabbit anti-Ki67 (Abcam ab15580, lot GR264768-1, 1:3000), rabbit anti-Zeb1 (Abcam ab87280, lot GR3186880-1, 1:500), and goat anti-Pdx1 (Abcam ab47383, lot GR295217-1, 1:5000).

Validation

Anti-LIF neutralization antibody (Extended Data Fig. 5a-d) and Pdx1 antibody to mark pancreatic cancer cells (Extended Data Fig. 5h) were validated in this study and data were presented. All the other primary antibodies used in this study are commercially available and widely used, and were titrated, optimized and assessed for expected molecular weight (IB) and/or cellular localization (IHC and IF) based on available knowledge and/or published data when available and validation statements on the manufacturer's websites. In all experiments, appropriate positive controls, such EGF stimulation for pERK and pAKT, were used. Negative controls: IHC, matched isotype antibody; IF, omission of primary antibody.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

The human pancreatic cancer cell lines AsPC1 (CRL-1682), BxPC3 (CRL-1687), CFPAC1 (CRL-1918), MIAPaCa2 (CRL-1420), PANC1 (CRL-1469), and BJ fibroblasts (CRL-2522) were acquired from ATCC; KP4 (JCRB0182) from JCRB. HPDE6C7 was provided by Tsao group (U. Toronto). The human pancreatic stellate cell line hPSC, ONO, and YAM1 were provided by Evans group (Salk). MEF cells with Lifr gene knockout were primarily established in the lab.

Authentication

All the cell lines from ATCC were authenticated by STR profiling by ATCC. The rest lines are all primary lines being cultured for limited number of passages.

Mycoplasma contamination

For the established human cell lines received from ATCC and other resources and routinely cultured in the lab, mycoplasma contamination was tested by the MycoAlertTM PLUS Mycoplasma Detection Kit (Lonza), and all are negative. For the primary lines, 10 mg/L ciprofloxacin was added in the culture media to prevent the mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

None.

Animals and other organisms

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

Laboratory animals

KrasLSL-G12D/+;Trp53flox; Rosa26LSL-Luc compound mutant mice (designated as KPf/fL mice) on FVB background were kindly provided by R. Shaw (Salk). Pdx1-Cre mice (stock # 014647) were purchased from The Jackson Laboratory, and backcrossed with KPf/fL mice for at least 6 generations before phenotypic analysis. Frozen sperm of C57BL/6N-Lifrtm1a(EUCOMM)Hmgu/H were purchased from the European Mouse Mutant Archive (EMMA) (order ID: 06941) and rederived by in vitro fertilization in the Salk Transgenic Core Facility to obtain the mutant mice (tm1a) harboring a knockout first allele (reporter-tagged insertion with conditional potential), and then crossed with FLPo mice, Gt(ROSA)26Sortm2(FLP*)Sor/J, to delete the FRT-LacZ-Neo-FRT selection cassette and convert into Lifrflox (tm1c) strain with conditional allele. No phenotypic differences were noticed between Lifr+/+ and Lifrf/+ mice, and therefore data from Lifr+/+ and Lifrf/+ mice were combined and designated as LifrWT mice. No sexual dimorphism was noted in any mouse model, and therefore males and females were equally used for experimental purposes and both sexes are represented in all data sets. Age of mice used for experiments were annotated corresponding in Figure Legends and Methods part.

Wild animals

None.

Field-collected samples

None.

Human research participants

Policy information about studies involving human research participants

Population characteristics	All the covariate-relevant population characteristics of the corresponding archival, deidentified, anonymized human tissue, serum, and FFPE human samples used in this study were provided in Extended Data Fig. 8e,i, and 9d. Briefly, for the 77 PDAC patients from who frozen PDAC tissue samples analyzed by ELISA, the age rang is 40~92 and mean at 65, and we don't have gender information (Extended Data Fig. 8e). For the 18 PDAC patients from who frozen PDAC tissue samples analyzed by PRM-MS assay, the age rang is 44~77 and mean at 64, and we don't have gender information (Extended Data Fig. 9d). For the Extended Data Fig. 8i, we didn't collect the information, e.g. age and gender (Extended Data Fig. 8i).
Recruitment	We just analyzed archival, deidentified, anonymized human tissue, serum, and FFPE specimens. No patients recruitment was involved directly.

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	Mouse pancreatic tumors were washed in RPMI 1640 (Gibco, Life Technologies) and cut into 2-4mm pieces immediately following resection. Dissociation into a single cell suspension was performed using the Miltenyi Biotec Mouse Tumor Dissociation Kit (130-096-730). Briefly, tumor pieces were collected into gentleMACS C tubes containing RPMI 1640 dissociation enzymes, and further homogenized using the gentleMACS Dissociator. Samples were incubated for 40 minutes at 37°C under continuous rotation, then passaged through a 70 µm nylon mesh (Corning). Red blood cells were lysed using RBC Lysis Buffer (eBioscience), and the remaining tumor cells were used for FACS analysis and cell sorting.
Instrument	Analysis and cell sorting were carried out on a FACSAria III machine (Becton Dickinson).
Software	Data were analyzed with FlowJo software (Tree Star).
Cell population abundance	The purity of sorted cell fractions were tested by flow cytometry. A small sample was taken from the sort collection tube and re-ran through the cytometer. Purity was determined to be >95% in all samples.
Gating strategy	For tumor cell experiments, the gating strategy is as follows: (1) gate tumor cells by FSC-A/SSC-A, excluding debris and white blood cells, (2) gate single cells by FSC-A/FSC-W, (3) gate live cells by FSC-A/propidium iodide, only include cells that are propidium iodide-negative. Finally, all compensations were done using samples stained with single fluorophores and gates were determined by no-stain controls. Samples were incubated with mouse Fc block prior to antibody staining in order to reduce nonspecific staining.

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