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	1. Leica Application Suite X 2. Nikon Digital Sight DS-U2 3. Zeiss LSM780 4. eBLOT Touch Imager 5. ImageJ 1.49 6. Stepone software v2.3
Data analysis	1. GraphPad Prism 8.0.1 2. Microsoft Excel v16.65

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

Raw mass spectrometry data for SILAC in this study are available on the ProteomeXchange Consortium (https://proteomecentral.proteomexchange.org/ui?search=PXD039190) under the accession code PXD039190. Processed mass spectrometry data for SILAC are provided in the Source Data folder, including "SILAC exported data for Figure 3a.xlsx" and the "Figure 3" worksheet within the "Source Data.xlsx" file.

Public datasets used in this study include dataset GSE164416 from the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE164416) under the accession code GSE164416, and the data from the STRING without an accession code (https://string-db.org/cgi/network?taskId=bhlFnsy12Vby&sessionId=buNtCnsKYrNR).

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 preference for sex or gender was applied to the study. Data from both males and females are involved.
Reporting on race, ethnicity, or other socially relevant groupings	This study did not consider race, ethnicity, or other socially relevant grouping.
Population characteristics	Patients involved in this study were diagnosed with benign pancreatic neoplasms, and the non-tumor portion of the pancreas, obtained after pancreatectomy, was used in this study. This study included 34 male and 32 female participants, ages 28 to 82. Among them, 39 had type 2 diabetes, while 27 did not.
Recruitment	These archived human pancreatic tissues were obtained from patients previously admitted to National Taiwan University Hospital (NTUH), diagnosed with benign pancreatic neoplasms, and undergoing pancreatectomy. The Department of Pathology at NTUH provided the archived pathological samples, and all patients obtained written informed consent. The Research Ethics Committee of NTUH approved the protocol under IRB# 202306101RINB.
Ethics oversight	This study utilized archived pathological samples from the Department of Pathology at National Taiwan University Hospital (NTUH), with the informed consent for research use previously obtained from all patients and approved by the NTUH Research Ethics Committee. The study was performed following the Declaration of Helsinki. The clinical data, including AC sugar and HbA1C levels, were provided by the Integrative Medical Data Center at NTUH following the approval of the study protocol by the NTUH Research Ethics Committee under IRB# 202306101RINB.

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	Animal experiments were performed with at least three mice for each group. No explicit power calculations were conducted to determine the sample Size. This sample size was determined based on experience, with reference to previously published articles in this field (Quarta et al., Nat Metab. 2022;4:1071-1083; Campbell et al., Nat Med. 2016;22:84-90).
Data exclusions	No data were excluded
Replication	As stated in Sample size, all in vivo and ex vivo data were collected multiple samples (indicated as "n" in the figure legends). All in vitro experiments in this study were replicated independently at least three times to confirm the results.
Randomization	All "in vivo", "ex vivo", and "in vitro" treatment conditions were allocated randomly. For immunohistochemistry and immunofluorescence analysis, the field of view was randomly selected.
Blinding	The investigators were blinded to group allocation during data collection and analysis.

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
[ ]	[x] Antibodies
[ ]	[x] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[ ]	[x] Animals and other organisms
[x]	[ ] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[x]	[ ] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used

I. Primary antibodies
1. Goat polyclonal anti-Spint1 (R&D Cat# AF1141, RRID:AB_2196299)
2. Rabbit polyclonal anti-MafA (Abcam ab26405, RRID:AB_776146)
3. Rabbit polyclonal anti-hepsin (Thermo Fisher Scientific Cat# PA5-30062, RRID:AB_2547536)
4. Rabbit monoclonal anti-Ki67 (GeneTex GTX16667, RRID:AB_422351)
5. Rabbit polyclonal anti-cleaved caspase-3 (Cell Signaling Technology 9661, RRID:AB_2341188)
6. Rabbit monoclonal anti-insulin (Abcam ab181547, RRID:AB_2716761)
7. mouse monoclonal anti-FLAG (Sigma-Aldrich F3165, RRID:AB_259529)
8. Rabbit polyclonal anti-Matriptase (Millipore Cat IM1014, RRID:AB_2255240)
9. mouse monoclonal anti-PDX1 (Abcam ab84987, RRID:AB_1925309)
10. Mouse monoclonal anti- alpha-tubulin (Proteintech 66031-1-Ig, RRID:AB_11042766)
11. Rabbit polyclonal anti- HK6 (Abcam ab37796, RRID:AB_2232078)
12. Rabbit polyclonal anti- neurod1 (Proteintech 12081-1-AP, RRID:AB_2877823)
13. Rabbit polyclonal anti- GAPDH (GeneTex GTX100118, RRID:AB_1080976)
14. mouse monoclonal anti-beta-actin (Proteintech 60008-1-Ig, RRID:AB_2289225)
15. rabbit polyclonal anti-zo-1 (Proteintech 21773-1-AP, RRID:AB_10733242)
16. rabbit polyclonal anti-occludin (Thermo Fisher Scientific 71-1500, RRID:AB_2533977)
17. rabbit polyclonal anti-phospho-creb1-s133 (ABclonal AP0333, RRID:AB_2771008)
18. rabbit polyclonal anti- creb1 (ABclonal A11989, RRID:AB_2758916)
19. mouse monoclonal anti-c-myc (Santa Cruz Biotechnology sc-40, RRID:AB_627268)
20. rabbit monoclonal anti-CD3 (GeneTex Cat# GTX16669, RRID:AB_425123)
21. mouse monoclonal anti-BRDU (Proteintech Cat# 66241-1-Ig, RRID:AB_2881630)
22. rabbit anti-GLP1R (Novus Cat# NBP1-97308, RRID:AB_11139100)
23. Anti-phospho-AKT T308 (Cell Signaling Technology Cat# 13038, RRID:AB_2629447)
24. Anti-phospho-AKT S473 (Cell Signaling Technology Cat# 4060, RRID:AB_2315049)
25. Anti- AKT (Cell Signaling Technology Cat# 9272, RRID:AB_329827)
26. Anti-phospho-ERK (Cell Signaling Technology Cat# 4370, RRID:AB_2315112)
27. Anti-ERK (Cell Signaling Technology Cat# 4695, RRID:AB_390779)
28. Anti-phospho-GSK3 alpha T279 (Abcam Cat# ab239862)
29. Anti-phospho-GSK3 alpha S21 (Abcam Cat# ab2226877)
30. Anti-GSK3 alpha (Abcam Cat# ab62368, RRID:AB_941805)
31. Anti-phospho-P38 (Cell Signaling Technology Cat# 4511, RRID:AB_2139682)
32. Anti-P38 (Cell Signaling Technology Cat# 8690, RRID:AB_10999090)
33. Anti-phospho-INR (Abcam Cat# ab303492, RRID:AB_3083575)
34. Anti-INR (Abcam Cat# a227831)
35. Anti-phospho-EGFR (Cell Signaling Technology Cat# 2234, RRID:AB_331701)
36. Anti-EGFR (Santa Cruz Biotechnology Cat# sc-373746, RRID:AB_10920395)
37. Anti-phospho-IGF1R (Abcam Cat# ab39398, RRID:AB_731544)
38. Anti-IGF1R (Abcam Cat# ab182408, RRID:AB_3106875)
39. Anti-GLP1R (Abcam Cat# ab218532, RRID:AB_2864762)

II. secondary antibodies:
1. Horse anti-rabbit IgG-polyHRP (Vector Laboratories MP-7401, RRID:AB_2336529)
2. Horse anti-goat IgG-polyHRP (Vector Laboratories MP-7405, RRID:AB_2336526)
3. Alexa-Fluor 488 goat polycolonal anti-rabbit (Molecular Probes A-11008, RRID:AB_143165)
4. Alexa-Fluor 568 goat polycolonal anti-mouse (Molecular Probes A-11004, RRID:AB_2534072

	5. Duolink In Situ PLA Probe Anti-Rabbit PLUS (Sigma-Aldrich Cat# DUO92002, RRID:AB_2810940) 6. Duolink In Situ PLA Probe Anti-Mouse MINUS Antibody (Sigma-Aldrich Cat# DUO92004, RRID:AB_2713942)
Validation	All antibodies were validated for the species and application used as stated in the manufacturer's product data sheet.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	1. NIT-1 was purchased from the Bioresource Collection and Research Center (Cat No. 60452). 2. MIN6 was acquired by Dr. Lee-Ming Chuang and Dr. Susumu Seino. 3. 293T was purchased from the American Type Culture Collection (Cat No. CRL-3216). 4. Human primary islet cells were acquired from the ACCEGEN (ACCEGEN, Cat No. ABC-TC4286)
Authentication	All cell lines were authenticated using the short tandem repeat (STR) method.
Mycoplasma contamination	All cell lines tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the list of International Cell Line Authentication Committee.

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	To generate mouse sample, breeders younger than 1 year old were used. 1. Tg(CAG-FLPe)37Ito (Flp) 2. B6.FTB-Tg(Pdx1-cre)6Tuv/J (Pdx1Cre) 2. C57BL/6-Spint1tm1c(EUCOMM)Wtsi (Spint1lacZ/+) 3. Spint1loxP/loxP (Spint1fl/fl) 4. Pdx1-Cre::Spint1fl/fl (Spint1-/-). The experimental mice were maintained in a controlled environment (12-hlight/dark cycle, 21-23°C, 60%-70% humidity) with free access to standard chow pellets and water.
Wild animals	This study did not involve wild animals.
Reporting on sex	Data were collected only from males, while females were used exclusively for breeding purposes.
Field-collected samples	The study did not involved samples collected in the field.
Ethics oversight	All animal experiments were approved by the Institutional Animal Care Use Committee (IACUC) at the National Taiwan University College of Medicine and conducted following the National Institute of Health Guide for the Care and Use of Laboratory Animals and Animal Welfare Act.

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

Plants

Seed stocks	No seed stocks
Novel plant genotypes	No novel plant genotypes
Authentication	No plant authentication