## SUPPLEMENTAL INFORMATION

### SUPPLEMENTAL EXPERIMENTAL PROCEDURES.

**Cell Lines.** Pancreatic cancer cell lines, HPAFII, KP4, MiaPaCa, SW1990, YAPC, 8988T, PSN1, 89a, Panc03.27, Panc-1, BxPc3, HPAC, Panc8.13, ASPC-1, Su86.86 and HPNE were obtained from American Type Culture Collection (ATCC; Rockville, MD), and grown in their required growth medium per the ATCC description. The DanG pancreatic cancer cells were obtained from DSMZ, SUIT-2 were obtained from JCRB cell bank and COLO357 was a gift from Paul Chiao (MD Anderson). All were grown in RPMI 1640 supplemented with 10% fetal bovine serum and 1% penicillin (100 U/ml)/streptomycin (100 Ug/ml) (Invitrogen Gibco). Human pancreatic ductal epithelial cells (HPDE) (Furukawa et al., 1996) were obtained from Ming Tsao (University of Toronto) and grown in keratinocyte serum-free (KSF) medium with 0.2 ng/ml EGF and 30 μg/ml bovine pituitary extract (Invitrogen Gibco, Carlsbad, CA) at 37 °C under 5% CO2. To establish mouse pancreatic cancer cell lines, freshly isolated tumor specimens from *Sirt6*$^{f/f}$;*Kras*$^{G12D}$;*p53*$^{f/+}$;*p48-Cre* (SIRT6 KO) and *Sirt6*$^{+/+}$;*Kras*$^{G12D}$;*p53*$^{f/+}$;*p48-Cre* (SIRT6 WT) mice were minced with sterile razor blades, digested with trypsin for 30 mins at 37°C, and then resuspended in RPMI 1640 and supplemented with 10% fetal bovine serum and 1% penicillin (100 U/ml)/streptomycin (100 Ug/ml) (Invitrogen Gibco) and seeded on plates coated with rat tail collagen (BD Biosciences). Cells were passaged by trypsinization. All studies were done on cells cultivated for less than ten passages. SIRT6 knockout (KO) primary mouse embryonic fibroblast (MEFs) were generated from 13.5-day-old embryos as described (Mostoslavsky et al., 2006). These cells were immortalized by using the standard 3T3 protocol. Cells were cultured in high glucose Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 1% penicillin (100 U/ml)/streptomycin (100 Ug/ml) (Invitrogen), 2mM L-glutamine, 0.1mM NEAA, 1mM sodium pyruvate and 20mM HEPES.

**Glucose Uptake Assay.** Cells were grown under normal conditions for 24 hr and 100 μM 2-NBDG (Invitrogen) was added to the media for 2 hrs. Fluorescence was measured by flow cytometry using a FACSCalibur Analyzer (BD). Data are shown as mean ± *std* between duplicates and are representative of two independent experiments.

**Proliferation Assay.** Cells were plated in duplicate on collagen-coated 6-well dishes ($1 \times 10^4$ per well) in culture medium. Adherent cells were harvested, trypsinized and counted by trypan-blue exclusion using a Countess Automated Cell Counter (Invitrogen) 24, 72 or 120 h later. Proliferation assays were performed in duplicate and are represented as mean ± s.e.m. between three independent experiments. Alternatively, cells were plated in triplicate in 96-well plates (2000 cells/well for human PDAC cells and 500 cells/well on collagen coated plates for murine PDAC cells) in culture medium. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) assay was performed each day for six days. MTT (1.25 mg/mL final concentration) was added to the culture media and incubated for 3 h. Formazan crystals were solubilized with 100 μl /well of DMSO and absorbance was read at 570 nm. To determine the sensitivity of cells to dichloroacetate, 500 cells/well were seeded on collagen-coated plates in culture medium. The following day dichloroacetate was added to the culture medium and cells were allowed to grow for five days after which MTT was added to the culture medium as described above. MTT proliferation assays were performed in triplicate and are represented as mean ± s.e.m. between three independent experiments unless otherwise noted in the figure legend.

**Constructs and Viral infection.** Full-length wild-type SIRT6 cDNA was amplified from the HPDE cells using the following primers (CA**GGATCC** TTGTTCCCGTGGGGCAGTCGAGG; bold sequence indicates BamHI site) and (CA**GAATTC**CTACAAAAAGCCCCACCCTCCC; bold sequence indicates EcoRI site). Following PCR amplification and subcloning into pGEMT (Promega), SIRT6 constructs were digested with BamHI and EcoRI, and purified with the QIAquick Gel extraction kit (Qiagen). Digested SIRT6 was subcloned into pRetroX-TIGHT-Pur plasmid (Clontech) and site-directed mutagenesis of wild-type SIRT6 using the QuikChange Lightning site-directed mutagenesis kit (Stratagene, La Jolla, CA, USA) to generate the H133Y, catalytic dead mutant. pLVX-Tet-On was obtained from Clontech. All lentiviral shRNA plasmid target sequences are listed in Table S5. pMSCV-3xFlag-SIRT6 was previously described in (Sebastian et al., 2012). Human pTRIPz-shSIRT6 (Dharmacon RHS4740) and negative control shRNA vector was a kind gift from David Lombard and pBabe let-7g 7S21L mutant construct was a kind gift from Richard Gregory.

Viral particles containing the above mentioned plasmids were synthesized using either lentiviral (pCMV-dR8.91) or retroviral (pCL-ECO) packaging plasmids with pCMV-VSV-G (Addgene). Cells were infected by incubating with virus and 10 μg/ml polybrene. Twenty-four hours later, cells were selected in 2.5 μg/ml puromycin for at least two days and the pooled populations were used for various experiments. For all experiments involving

the Dox-inducible pRetro construct cells were treated with 1μg/mL dox for 48 hrs and for the Dox-inducible shSIRT6 cells were treated with 1μg/mL dox for 72 hrs unless otherwise indicated.

**siRNA and let-7 mimetics.** Silencer Select siRNA were purchased from Ambion and 10 nM was transfected into cells with Lipofectamine RNAiMax (Invitrogen). Negative control #1 (4390843), mouse siLin28b #1 (4390771 s117291), mouse siLin28b #2 (4390771 s117292), mouse siIgf2bp3 (4390771 s100444) human siLin28b #1 (4392420 s52477) and human siLin28b #2 (4392420 s52478) were used. miRCURY LNA Let-7 mimetics were purchased from Exiquon and 50 nM was reverse transfected into cells with Lipofectamine RNAiMax (Invitrogen). Negative control mimetic (479903-001), hsa-let7c-5p (471696-001) and hsa-let7d-5p (470030-001) were used.

**Real-Time RTPCR Analysis.** Total RNA was extracted with the TriPure Isolation Reagent (Roche) as described by the manufacturer. For cDNA synthesis, 1μg of total RNA was reverse-transcribed using the QuantiTect Reverse Transcription Kit (Qiagen). Real-time PCR was run in duplicate using SYBR green master mix (Roche), following the manufacturer's instructions, with the exception that the final volume was 12.5 μl of SYBR green reaction mix. Real-time monitoring of PCR amplification was performed using the LightCycler 480 detection system (Roche). Data were expressed as relative mRNA levels normalized to the β-actin expression level in each sample and are represented as mean ± s.e.m. between two independent experiments unless otherwise indicated in the figure legend. The primer sequences are listed in Table S4.

**Chromatin isolation and western blot.** Chromatin fractions were prepared by resuspending the cell pellet in lysis buffer containing 10mM HEPES pH 7.4, 10 mM KCl, 0.05% NP-40 supplemented with a protease inhibitor cocktail (Complete EDTA-free, Roche Applied Science), 5μM TSA, 5mM sodium butyrate, 1mM DTT, 1mM PMSF, 50mM NaF, 0.2mM sodium orthovanadate and phosphatase inhibitors (Phosphatase Inhibitor Cocktail Sets I and II, Calbiochem) and incubated on ice for 20 mins. The lysate was then centrifuged at 14,000 rpm for 10 mins at 4°C. The supernatant was removed (cytosolic fraction) and the pellet (nuclei) was acid-extracted using 0.2N HCl and incubated on ice for 20 mins. The lysate was then centrifuged at 14,000 rpm for 10 mins at 4°C. The supernatant (contains acid soluble proteins) was neutralized using 1M Tris-HCl pH 8. For whole cell lysate (WCL), the cell pellet was resuspended in RIPA buffer supplemented with a protease inhibitor cocktail (Complete EDTA-free, Roche Applied Science), 5μM TSA, 5mM sodium butyrate, 1mM DTT, 1mM PMSF, 50mM NaF, 0.2mM sodium orthovanadate and phosphatase inhibitors (Phosphatase Inhibitor Cocktail Sets I and II, Calbiochem) and incubated on ice for 20 mins. The lysate was then centrifuged at 14,000 rpm for 10 mins at 4°C and the supernatant was harvested. Protein concentration was quantified by Biorad Protein Assay. Ten-micrograms protein (chromatin) 20 μg (WCL) was electrophoresed on a 10-20% gradient polyacrylamide gel with SDS (Biorad) and electroblotted onto polyvinylidene difluoride membranes (PVDF) (Millipore). Membranes were blocked in TBS with 5% non-fat milk and 0.1% Tween and probed with antibodies. Bound proteins were detected with horseradish-peroxidase-conjugated secondary antibodies (Vector Biolaboratories) and SuperSignal West Pico Luminol/Enhancer Solution (Thermo Scientific). Antibodies used were anti-SIRT6 (Abcam, ab62739), anti-H3K9Ac (Millipore 07-352), anti-H3K56Ac (ab76307), anti-Lin28b (ab71415 and Cell Signaling 4196), anti-PDK1 (Cell signaling #3820), anti-Myc (ab32072), anti-IGF2BP1 (Cell Signaling #8482), anti-HMGA2 (Cell Signaling #8179), anti-IGF2BP3 (Proteintech 14642-1-AP) and anti-β actin (Sigma A5316) or total-H3 (ab1791) as a loading control.

**MicroRNA sequencing analysis.** Next-generation sequencing of small RNA-Seq for control (PLKO) and shLIN28b knockdown samples (three replicates each) was performed using Illumina HiSeq 2000 instrument, resulting in approximately 35 million pairs of 50-bp reads per sample. The libraries were made with the NEBNext Multiplex Small RNA Library Prep and 15 cycles of amplification. The samples were run in 2 pools of 6 in 2 lanes. These reads were aligned and miRNA expression profiles were generated using miRExpress (Wang et al., 2009), followed by the analysis of differential expression using edgeR package (Robinson et al., 2010).

**Chromatin Immunoprecipitation.** Cells were cross-linked with 1% paraformaldehyde for 15 min at room temperature. The reaction was quenched for 5 min at room temperature by adding 0.125 M glycine. After three washes with 1X PBS, cells were lysed with lysis buffer (1% SDS, 10 mM EDTA pH 8, 50 mM Tris-HCl pH 8) supplemented with protease and deacetylase (TSA) inhibitors. Lysates were sonicated on ice using a Branson Sonifier 250 sonicator (10 second pulses of output 3 at constant duty repeated 5 times at 4°C, keep on ice between cycles of sonication). Size of fragments obtained (between 200 and 1,200 bp) was confirmed by electrophoresis. Soluble chromatin was collected after centrifugation at 14,000 rpm at 4°C for 10 min and 1 million cells was diluted to 1/5 in dilution buffer (1% Triton X-100, 2 mM EDTA, 150 mM NaCl, 20 mM Tris-HCl pH 8.1) supplemented

with protease and deacetylase inhibitors. Soluble chromatin (1%) was kept as input control. Soluble chromatin was precleared with 100 µg/ml of salmon sperm (Amersham Biosciences), 2.5 µg/ml of unspecific IgGs, and protein-A-Sepharose at 50% overnight at 4°C in rotation. After centrifugation, supernatants were collected and specific antibodies were added. Mixtures were incubated at 4°C for 8 hrs in rotation and then incubated overnight at 4°C in rotation with protein-A-Sepharose at 50% (Roche). Beads were collected and washed sequentially at 4°C for 10 min with TSE I (150 mM NaCl, 0.1% SDS, 1% Triton X-100, 2 mM EDTA, and 20 mM Tris-HCl (pH 8.1)), TSE II (500 mM NaCl, 0.1% SDS, 1% Triton X-100, 2 mM EDTA, and 20 mM Tris-HCl (pH 8.1)), and buffer III (0.25 LiCl, 1% Nonidet P-40, 1% deoxycholate, 1 mM EDTA, and 10 mM Tris-HCl (pH 8.1)). Beads were washed once with 1X PBS by pipetting and immunoprecipitates were eluted two times (20 min incubation) with elution buffer (0.1 M $NaHCO_3$ and 1% SDS). Reversion of cross-linking was performed overnight by adding 0.2M NaCl and heating samples and input controls at 65°C. Samples were then treated with 0.2 mg/mL RNAse A (Qiagen) and incubated for 1hr at 37°C followed by addition of 0.01M EDTA, 0.04M Tris-HCl pH 6.5 and 4 U/mL of Proteinase K (Promega) and samples were incubated at 45°C for 1 hr. DNA was then purified using the QIAquick spin kit (Qiagen). Real time RT-PCR was performed with primers listed in Supplemental Table 4.

**Chromatin Immunoprecipitation Sequencing.** The steps of ChIP followed by sequencing (ChIP-seq) were performed using a modified version of our previous protocols adapted to the Bravo liquid handling platform (Agilent) as previously described (Etchegaray et al., 2015). Mouse PDAC cells were crosslinked, fixed cells were lysed and the chromatin was then sheared on Covaris E-220 to a size range between 200 and 800 bp. We used anti-H3K56Ac (ab76307) antibody. The antibody was incubated with a mix of Protein-A and Protein-G Dynabeads (Invitrogen) then incubated overnight. Next, samples were washed eluted, reverse crosslinked, treated with RNaseA (Roche) and Proteinase K (NEB). Illumina library construction reactions were performed as we described previously (Etchegaray et al., 2015), using the Bravo liquid handling platform (Agilent).

**H3K56ac ChIP-Seq Data Analysis.** Reads from H3K56ac ChIP-Seq for RP07 SIRT6 wild type (S6WT), SK03 SIRT6 knock-out (S6KO), and SK03 SIRT6 knock-out with SIRT6 restored (S6WT) (referred to as samples S1, S2, and S3 respectively) from mouse pancreatic cancer cell lines were aligned to mouse genome mm9 using bwa (Li and Durbin, 2009) and duplicate reads were marked with Picard tools (http://picard.sourceforge.net). Peaks were called using MACS2 (version 2.0.10) with a False Discovery Rate (FDR) set to 0.01 (Zhang et al., 2008). UCSC Mus musculus mm9 refGene gene annotation was used to generate a list of transcription start sites (TSS) for all genes and used to generate a bed file with TSS +/- 1kb regions for all genes. The bedtools program intersectBed (http://bedtools.readthedocs.org/en/latest/index.html) was used to associate the MACS2 peaks from the three H3K56ac ChIP-Seq samples with the TSS +/- 1kb regions and identify genes with peaks. Intersections of these gene lists were used to generate the Venn diagrams of Figure 3a. Genes from the 184 gene subset with TSS +/- 1kb peaks in S2 SK03 S6KO but not in S1 RP07 S6WT and not it S3 SK03 S6WT were prioritized for follow-up according to differential binding of H3K56ac ChIP-Seq reads from S2 SK03 S6KO relative to S1 RP07 S6WT. The R Bioconductor program DBChIP (Liang and Keles, 2012) was used to analyze the differential binding at the TSS locations associated with the 184 S2 but not S1 or S3 peaks shown in Table S1. DBChIP was run with a window size of 1000, fragment lengths of 229 and 219 from the MACS2 estimate of fragment length for S1 and S2 respectively, and library sizes of 19319155 and19059445 from the number of tags after filtering.

**Gene Expression Analysis and GSEA.** Gene expression data from pancreatic cancer datasets used for the Gene Set Enrichment Analysis (GSEA) in Figures 7B-D and S7A) are accessible from GEO (http://www.ncbi.nlm.nih.gov/gds/) (91 pancreatic cancer tumor samples from Perez-Mancera et al. 2012 (GSE36294) (Perez-Mancera et al., 2012), 36 pancreatic cancer tumor samples from Pei et al. 2009 (GSE16515) (Pei et al., 2009), 45 pancreatic cancer tumor samples from Zhang et al. 2012 (GSE28735) (Zhang et al., 2012), and 36 pancreatic ductal adenocarcinoma tumor samples from Badea et al. 2008 (GSE15471) (Badea et al., 2008)), 177 pancreatic adenocarcinoma (PAAD) primary tumor samples from TCGA (http://cancergenome.nih.gov/), 269 pancreatic cancer ductal adenocarcinoma (PACA-AU v18) tumor samples from Australian pancreatic ICGC (https://icgc.org) (Waddell et al., 2015), and 43 pancreatic cancer cell line samples from CCLE (http://www.broadinstitute.org/software/cprg/?q=node/11) (Barretina et al., 2012). For the GEO patient sample data sets GSE16515, GSE28735, and GSE15471 and the CCLE data set, raw expression values in the form of CEL files were collected and then processed using RMA in the R Bioconductor package. For the GEO patient sample data set, GSE36924, the series matrix file for the Illumina HumanHT-12 V4.0 expression beadchip data was downloaded. For TCGA data, expression data sets were created by combining RNASeqV2 Level3 normalized gene result files for individual samples and producing tables with genes in rows and samples in columns. ICGC data was read in from

the ICGC PACA-AU v18 array file exp_array.PACA-AU.tsv.gz. Gene Set Enrichment Analysis (Mootha et al., 2003; Subramanian et al., 2005) was used to evaluate the association of LIN28B expression with known pathways and phenotypes. GSEA was run using Pearson correlation with LIN28B to rank genes and p-values were obtained from 2500 permutations of the LIN28B expression phenotype. GSEA was performed using two libraries from version 4.0 of the molecular signature database (MolSigDB) (http://www.broadinstitute.org/gsea/msigdb/index.jsp): the c2 curated gene sets from online pathway databases, PubMed publications, knowledge of domain experts and the c3 motif gene sets.

**Histology and immunostaining.** Murine pancreata were harvested, submitted for histological examination, and analyzed in a blinded fashion by pathologist (V.D.). For quantification of PanIN and PDAC, we used a grading scheme endorsed by the WHO (Aaltonen et al., 2000), which is based primarily on the extent of gland formation. Tissue samples were fixed overnight in 4% buffered formaldehyde, and then embedded in paraffin and sectioned (5 μm thickness) by the DF/HCC Research Pathology Core. Haematoxylin and eosin staining was performed using standard methods. Human PDAC tissue microarrays were constructed from formalin-fixed paraffin embedded tissue with each core measuring 3 mm in diameter per our IRB-approved protocol (#2015P002328). Immunohistochemistry was performed as previously described (Fitamant et al., 2015). Primary antibodies used were as follows: anti-Lin28b (LS Bio LS-B3423) 1:200 for mouse and human tissues; anti-SIRT6 (Cell Signalling #12486) 1:300 for mouse tissues and 1:200 for human tissues. Stained slides were photographed with an Olympus DP72 microscope.

Immunohistochemistry was scored semi quantitatively, in a blinded fashion by pathologist (V.D.) on a 0 (no staining) to 3 (strongest intensity) scale based on the intensity of reactivity. A score of 0 was considered $SIRT6^{low}$ while 1-3 was considered $SIRT6^{high}$. For LIN28B staining 0-1 was considered $LIN28B^{low}$ and 2-3 was considered $LIN28B^{high}$.

**Apoptosis Assay.** Cells were washed with PBS and resuspended in 50 μl of 1X Binding Buffer (10 mM HEPES, pH 7.4; 140 mM NaCl; 2.5 mM CaCl2). 2.5 μl of Annexin V-FITC was added to each sample and incubated 15 min in the dark. After this time, 450 μl of 1X Binding Buffer was added and Annexin V positive cells analyzed by flow cytometry. Data are shown as mean ± *std* between triplicates and are representative of two independent experiments.

**Caspase 3/7 activity.** Cells were plated at confluency (10,000 cells/well) and allowed to adhere for 24 h in 96-well plate format. The following day caspase 3/7 activity was assessed using a Caspase-Glo® 3/7 Assay (G8090, Promega) per the manufacturer's recommended protocol. Data are shown as mean ± *std* between triplicates.

**Cell Cycle Analysis.** Briefly, cells were resuspended in 500 μl of PBS and fixed in ethanol by adding drop-wise 1 ml of 95 % ethanol. Fixed cells were incubated at 4°C overnight, washed with PBS and resuspended in 500 μl of PBS-0.1% Triton-X-100 supplemented with 1 μg/ml of RNAse A and 20 μg/ml of propidium iodide. Samples were incubated at 37°C for 20 min followed by 1h at 4°C and DNA content analyzed by flow cytometry. Cell cycle analysis was performed using the ModFit LT software. Data are shown as mean ± *std* between triplicates and are representative of two independent experiments.

**RNA In situ Hybridization (RISH) Assay.** For the manual (nonautomated) format for ISH, formalin-fixed paraffin-embedded (FFPE) baked tissue sections were subjected to Histoclear deparaffinization (National Diagnosics, Atlanta, GA), followed by ethanol dehydration. To unmask the RNA targets, dewaxed sections were incubated in 1X pre-treatment buffer (Affymetrix) (at 90 to 95°C for 10 minutes and digested with 1:100 dilution protease at 40°C for 10 minutes, followed by fixation with 10% neutral buffered formalin at room temperature for 5 minutes. Unmasked tissue sections were subsequently hybridized with 1:30 dilution of the Let7a (Affymetrix VM1-10266) probe for 3 hours at 40°C, followed by a series of post-hybridization washes. Signal amplification was achieved by a series of sequential hybridizations and washes as described in the View-RNA user manual (see link below). The specific conditions were as follow: pre-AMP: 25 minutes at 40°C; AMP: 15 minutes at 40°C; hybridization with labeled probe: 1:1000 dilution for 15 minutes at 40°C; signal detection with fast-red substrate: 30 minutes at 40°C. Slides were counterstained with Gill hematoxylin and mounted using Dako Ultramount (Dako, Carpinteria,CA).

For the automated Housekeeping gene (HKG) ISH, the assay was performed by using View- RNA eZL Detection Kit (Affymetrix) on the Bond RX immunohistochemistry and ISH Staining System with BDZ 6.0 software (Leica Biosystems). FFPE tissue sections on slides were processed automatically from deparaffinization, through ISH staining to hematoxylin counterstaining. Briefly, 5 mm-thick sections of formalin-fixed tissue were

baked for 1 hour at 60°C and placed on the Bond RX for processing. The Bond RX user-selectable settings were as follows: ViewRNA eZ-l Detection 1-plex (Red) protocol; ViewRNA Dewax1 Preparation protocol; View RNA HIER 10 minutes, ER1 (setting 95); ViewRNA Enzyme 2 (setting 10); ViewRNA Probe Hybridization. With these settings, the RNA unmasking conditions for the FFPE tissue consisted of a 10-minute incubation at 95°C in Bond Epitope Retrieval Solution 1 (Leica Biosystems), followed by 10-minute incubation with Proteinase K from the Bond Enzyme Pretreatment Kit at 1:1000 dilution (Leica Biosystems). ViewRNA eZ Check - Human TYPE 1 (Affymetrix Cat # DVA1-16742) (a cocktail of GAPDH, PPIB, and ACTB) was diluted 1:40 in ViewRNA Probe Diluent (Affymetrix). Post run, slides were rinsed with water, air dried for 30 minutes at room temperature and mounted using Dako Ultramount (Dako, Carpinteria,CA), and visualized and photographed with an Olympus DP72 microscope. Punctate like red color hybridization signals in the cell nuclei and cytoplasm were defined as positive signal. Slides were scored semi quantitatively in a blinded manner on a 0-3 scale based on the intensity of reactivity. If punctate red dots could be visualized using the 2x or 4x microscope objective then the section was given a score of +3, at 10x a score of +2, at 20x or 40x a score of +1 and finally no signal at 40x was given a score of zero. A score of zero was considered let-7a low and a score of 1-3 was considered let-7a high.

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