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Supplementary Table 1. Provided as an Excel file.

Supplementary Table 2. Provided as an Excel file.

Supplemental Materials and Methods

Quantification of DCLK1+ cells

A. From spontaneous mouse model: DCLK1+ cells were counted per PanIN or ADM lesion. Data was shown as mean % TSA +/- SEM. To adequately identify the type of lesion in which DCLK1 is quantified, we have performed H&E stainings on parallel sections of DCLK1 Immunofluorescence-stained slides which allows distinction between the preneoplastic lesions (Fig S3A). For some slides that didn't have a clear parallel section we did IHC staining for DCLK1 with counterstaining for hematoxilin that allows distinction between the preneoplastic lesions (Fig S3B).

B. From human PDAC tumors: To quantify DCLK1 and ALDH1A1 stained by IHC we used the Allred scoring system which accounts for both the intensity of staining (0 = none, 1 = weak, 2 = moderate, 3 = strong) and the proportion of stained cells (0 = 0%, 1 = < 1%, 2 = 1 to 10%, 3 = 11 to 33%, 4 = 34 to 66%, 5 = > 66%) producing a sum score of the two values (intensity + proportion = 0 to 8)[1].

IL-17A stimulation

For IL-17A *in vitro* treatment, murine recombinant IL-17A proteins (R&D system, Minneapolis, MN) were using to stimulate cells at concentration of 10 ng/ml. To inhibit cell signaling, U0126 (Cell Signaling Technology, Danvers, MA), and BAY11-7082 (InvivoGen, San Diego, CA) were administered in cell culture medium (10 and 5 μM) for five days.

Tumor initiation assay

1, 5, or 10 $x10^3$ KPC cells or KPC cells treated with IL17 cytokine for 7 days suspended in 100 μl of PBS were injected subcutaneously into the flank of C57BL/6 mice. Tumor incidents were monitored every 10 days for 30 days total. Assays were repeated three times. Limiting dilution

assays were performed with several cells concentration in murine experiments and 5x10e3 cells/injection have been found to be the minimal concentration of cells required for forming tumors. If lower concentrations of cells were used, no tumors were formed in either the treatment or control groups.

Cell proliferation assay

To determine cell proliferation of KPC cells, 2,000 cells were plated per well in 96-well plates. Murine IL-17A cytokine recombinant protein (R&D system, Minneapolis, MN) at concentration of 0 and 10 ng/ml in full DMEM was added after deprivation of FBS 24h. WST-1 Cell Proliferation reagent (Clontech, Mountain View, CA) was used to measure cell proliferation for 0 to 7 days after IL-17A incubation following manufacturer's instructions. Assays were performed in triplicate and repeated three times. This is a colorimetric assay based on the cleavage of the WST-1 tetrazolium salt by mitochondrial dehydrogenases. Absorbance is then measured at 450 nm versus a 650 nm reference by using a plate reader.

Wound healing assay

KPC cells were plated into 6-well plates and cultured until 90% confluent. Cell monolayers were wounded with a sterile 200 µl pipet tip and then incubated with DMEM containing 1% FBS and Murine IL-17A cytokine recombinant protein at concentration of 0 and 10ng/ml for 6, 12, 18 or 24 h in an atmosphere of 5% CO2 at 37℃. Representa tive areas of wounded monolayers containing wounds of the same width were marked and photographed. After incubation, the same areas were photographed. The extent of wound repair was evaluated by measuring the wound area using the Image J (NIH).Each experiment was performed in triplicate wells and repeated three times.

Western blot

Cell pellets were harvested and washed twice with pre-cold 1X PBS (Corning, Corning, N.Y). Pellets were then lysed with RIPA buffer (Thermo Scientific, Waltham, MA) to prepare protein extracts and analyzed by immunoblotting. Nuclear and cytosolic proteins were extracted from cell pellets using a NE-PER Nuclear and Cytoplasmic Extraction Reagent (Thermo Scientific, Waltham, MA). Antibodies against the following proteins were used as probes: Dclk1 (Abcam, Cambridge, MA), Ac-α-tubulin (SIGMA, St. Louis, MO), Lamin A/C, ALDH1A1, NFkB-p65, Ikkβ, p-Erk, Erk, p-p38, p38, p-JNK, JNK, p-Akt-S473, Tak1 (all from Cell Signaling Technology, Danvers, MA). The blots were incubated with primary antibody (1:1000) overnight at 4℃, washed three times with PBS/0.05% Tween® 20, followed by HRP-conjugated secondary antibody (Bio-Rad, Hercules, CA)(1:5000) for 1 hour at room temperature. The blots were visualized using a Clarity Western ECL substrate kit (Bio-Rad, Hercules, CA). As internal controls for equal protein loading, blots were stripped and probed with antibodies against beta-Actin (Abcam, Cambridge, MA).

NF-κB Binding Activity Assay

Mouse and human pancreatic adenocarcinoma cell line KPC and Capan-2 cells were plated into 100-mm culture dish, and grown to about 80% confluence. Human or murine recombinant IL-17A proteins (R&D system, Minneapolis, MN) were used to stimulate cells at concentration of 10 ng/ml. Nuclear protein was extracted at 0, 15, 30, 60, 120, 240, 480 minutes after IL-17A stimulation using a NE-PER™ Nuclear and Cytoplasmic Extraction kit (Thermo Scientific, 78833) following the product manuals. Then NF-κB binding activity was examined in nuclear protein extracts by NF-kB p65 Transcription Factor Assay Kit (Abcam ab133112) following manufacturer's instructions.

ALDH Activity Assay

An ALDH Activity Assay Kit (Colorimetric) (ab155893) from Abcam was performed. KPC cells were pre-stimulated with 10ng/ml IL17 for 7 days.

ALDH activity assay was performed according to manufacturer's instruction. In brief, 2X10^6 KPC control and IL-17 stimulated cells were homogenized with 400 ul ALDH Assay buffer using Dounce homogenizer and 50 ul cell lysates were used to examine the ALDH activity and samples were measured in a kinetic mode (every 3 min) for up to 60 min.

RNA isolation and quantitative reverse transcription polymerase chain reaction (qRT-PCR)

Total RNA was extracted with RNeasy RNA isolation kit (Qiagen, Valencia, CA) and reverse transcribed with a cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA), then amplified by TaqMan™ PreAmp Master Mix Kit (Applied Biosystems, Foster City, CA) following following manufacturer's instructions. qRT-PCR was performed with TaqMan® Gene Expression Assays and TaqMan® Fast Advanced Master Mix (Applied Biosystems, Foster City, CA) on an ViiA™ 7 Real-Time PCR System machine (Applied Biosystems, Foster City, CA). GAPDH were used for normalization. Assays were run in triplicates.

Histopathology

Tumor-bearing mice were humanely sacrificed and the pancreas, or subcutaneously implanted tumors were excised, fixed in freshly prepared 4 % paraformaldehyde in PBS, pH 7.2. Tissues were embedded in paraffin, 5-µm sections obtained, and stained with hematoxylin and eosin (H&E) (VWR, West Chester, PA) following standard protocols for visual examination. The stained slides were reviewed and screened for representative tumor regions by a pathologist.

Immunohistochemistry

Paraformaldehyde-fixed, paraffin-embedded tissue sections were deparaffinized, rehydrated, and then boiled in a microwave oven with 0.01 M citrate buffer pH 6.0 (Diagnostic Biosystems, Pleasanton, CA) for 10 min for antigen retrieval. Endogenous peroxidases were blocked with 3% H2O2 for 15 min. Nonspecific epitopes were blocked with normal horse serum (Jackson ImmunoResearch, West Grove, PA) for 30 min. The sections were incubated overnight at 4℃ with antibodies against one of the following proteins: Dclk1 (Abcam, Cambridge, MA), cleaved Caspase-3 (Cell Signaling Technology, Danvers, MA), Ki67, IL17RA (Santa Cruz Biotechnology, Santa Cruz, CA), IL17RC (Bioss-USA, Woburn, Massachusetts). This was followed by using a SuperPicture™ 3rd Gen IHC Detection Kit (Invitrogen, Frederick, MD) following manufacturer's instructions. Slides were then counterstained with hematoxylin, mounted in Acrymount (StatLab, Mckinney, TX), and visualized under a light microscope.

Immunofluorescence

Paraformaldehyde-fixed and paraffin-embedded sections were subjected to antigen retrieval and nonspecific epitopes blocking as described above, then incubated with antibodies against E-cadherin (Santa Cruz Biotechnology, Santa Cruz, CA) and Dclk1 (Abcam, Cambridge, MA). Samples were washed three times with PBS-Tween, followed by incubation with a fluorescence-conjugated secondary antibody (1:1000, Invitrogen). Nuclei were stained with 1:20,000 dilution of 4', 6-diamidino-2-phenylindole (DAPI) and slides were mounted in ProLong® Diamond Antifade Mountant (Invitrogen). Images were acquired using a Nikon confocal imaging microscope. A total of three slides per mouse were used, separated by 100 microns.

RNA sequencing

Total RNA from KPC cells exposed to IL17 or media was extracted. Each sample was assessed using Qubit 2.0 fluorometer and Agilent TapeStation 2200 for RNA quantity and quality. The cDNA libraries were pooled at a final concentration 1.8pM. Cluster generation and 75 bp single-

read dual-indexed sequencing was performed on Illumina NextSeq 500's. Total RNA libraries were generated using Illumina TruSeq Stranded mRNA sample preparation kit. The first step in the workflow involves purifying the poly-A containing mRNA molecules using poly-T oligo attached magnetic beads. Following purification, the mRNA is fragmented into small pieces using divalent cations. The cleaved RNA fragments are copied into first strand cDNA using reverse transcriptase and random primers. Strand specificity is achieved by using dUTP in the Second Strand Marking Mix, followed by second strand cDNA synthesis using DNA Polymerase I and RNase H. These cDNA fragments then have the addition of a single 'A' base and subsequent ligation of the adapter. The products are then purified and enriched with PCR to create the final cDNA library.The cDNA libraries are validated using KAPA Biosystems primer premix kit with Illumina-compatible DNA primers and Qubit 2.0 fluorometer. Quality is examined using Agilent Tapestation 2200.

Sequencing analysis was done using mRNA-seq Analysis on Maverix Analytic Platform (Maverix Biomics, Inc, San Mateo, CA). Raw sequencing reads from Illumina sequencing platform that was converted into FASTQ file format were quality checked for potential sequencing issues and contaminants using FastQC. Adapter sequences, primers, Ns, and reads with quality score below 28 were trimmed using fastq-mcf of ea-utils and Trimmomatic. Reads with a remaining length of fewer than 20bp after trimming were discarded. Single reads were mapped to the mouse genome (m10) using STAR in a strand specific manner. Pairwise differential expression was quantified using Cuffdiff. Cufflinks was used to determine FPKM levels for each gene from the STAR alignment and was used as input for Cuffdiff. Read counts were then normalized across all samples and significant differentially expressed genes were determined by adjusted P-value with a threshold of 0.05. Principal Component analysis is a statistical tool that is useful for exploratory data analysis. It uses combinations of the gene expression values for each sample to define a new set of unrelated variables. Similarities

between the data sets correlate to the distance in the projection of the space delimited by the principal components. RNA Sequencing data has been deposited at Sequence Read Archive (SRA accession: SRP132695).

Dissociation of Adult Mouse Pancreas

Whole adult mouse pancreas was harvested in sterile conditions and digested using collagenase as previously described [2].

Gene Array Analysis

RNA amplification, labeling and hybridization were conducted using Affymetrix GeneChip Hyb, Wash, and Stain kit as previously described[2]. For systematic bioinformatics analysis, IPA was used to assess functional correlations within the different groups. IPA can analyze the gene expression patterns using a build-in scientific literature based database. Stemchecker is a stemness analysis tool that was used to assess for the presence of stemness signatures[3].

SUPPLEMENTAL REFERENCE

1. Fedchenko N, Reifenrath J. Different approaches for interpretation and reporting of immunohistochemistry analysis results in the bone tissue - a review. Diagn Pathol 2014;9:221.
2. McAllister F, Bailey JM, Alsina J, et al. Oncogenic Kras activates a hematopoietic-to-epithelial IL-17 signaling axis in preinvasive pancreatic neoplasia. Cancer Cell 2014;25:621-37.
3. Pinto JP, Kalathur RK, Oliveira DV, et al. StemChecker: a web-based tool to discover and explore stemness signatures in gene sets. Nucleic Acids Res 2015;43:W72-7.

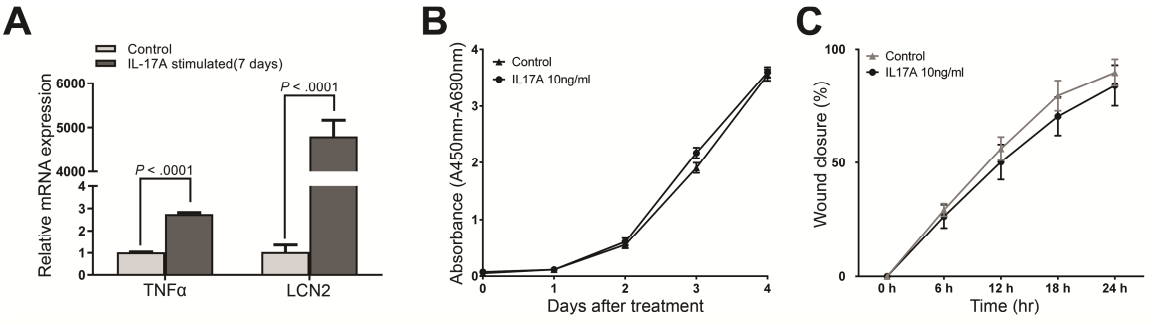
Cell movement	Cell development	Cellular growth and proliferation	Cell to cell signaling	Asembly and organization
ADAMTS1	ADAM28	ABCC3	AGT	AGT
AGT	ADAMTS1	ADAM28	ALOX5	AVIL
ALOX5	AGT	ADAMTS1	ATP1B1	BAG3
AQP1	Akr1b7	AGT	BCAM	CAV2
BAG3	ALOX5	ALOX5	CCK	CCK
BMX	AQP1	AQP1	CDH1	CDC42BPA
C1GALT1	BMX	BMX	CDHR5	CDH1
CA9	BTG3	BTG3	CEACAM1	CGN
CADPS2	C1GALT1	C1GALT1	CHGA	CHGA
CCK	CA9	CA9	CLDN2	CLDN2
CDH1	CADPS2	CAV2	CLDN4	CLDN4
CEACAM1	CDH1	CCK	CLU	CLMN
CFTR	CDHR5	CDC42BPA	CTNND1	CLU
CHGA	CEACAM1	CDH1	CXADR	CTNND1
CLDN4	CGN	CDHR5	CXCL6	CTTN
CLU	CHGA	CEACAM1	CYR61	CXADR
CTBP2	CHKA	CFTR	DCLK1	CYR61
CTNND1	CLDN4	CGN	DSP	DCLK1
CTSE	CLDN18	CHGA	EFNA1	DLG5
CTTN	CLU	CHKA	EFNB2	DSP
CXCL6	CTBP2	CLDN4	EPCAM	DSTN
CYP2J2	CTNND1	CLMN	ERBB2	EFNA1
CYR61	CTSE	CLU	ERBB3	EFNB2
DCLK1	CYP2C9	CTNND1	F3	EHD2
DSTN	CYR61	CXADR	F5	EPS8L2
EFEMP1	DCLK1	CYP2C9	F2RL1	ERBB2
EFNA1	DDX6	CYR61	FERMT1	F3
EFNB2	DLG5	DCLK1	FLNB	F2RL1
EPCAM	EFNA1	EFEMP1	FLRT3	FLNB
ERBB2	EFNB2	EFNA1	GSK3B	FLRT3
ERBB3	ELF3	EFNB2	HBEGF	GSK3B
F3	ENC1	ENC1	HNF4A	HNF1B
F11R	EPCAM	EPCAM	HSPA1A/HSPA1B	HNF4A
F2RL1	ERBB2	ERBB2	ITGA2	HSPA1A/HSPA1B
FLNB	ERBB3	ERBB3	ITGB6	KLF5
GRB7	F3	F3	KRT8	KRT8
GSK3B	F11R	F2RL1	LAMA5	KRT18
HBEGF	F2RL1	FERMT1	LBP	KRT20
HSPA1A/HSPA1B	FERMT1	FLNB	LCN2	LAMA5
HYAL1	FLNB	GALNT3	LEPR	LCN2
ID1	GALNT3	GKN1	let-7	LIMA1
ITGA2	GATA5	Gkn3	LIMA1	LTF
KCNE3	GOLM1	GOLM1	LTF	MAL
KLF5	GPRC5B	GRB7	Mcpt1	MET
KRT8	GSK3B	GSK3B	MET	MMP7
LAMA5	HBEGF	HBEGF	MST1R	MST1R
LAMC2	HNF1B	HNF1B	MYO6	MTM1
LBP	HNF4A	HNF4A	NDFIP2	MYO6
LCN2	HPGD	HPGD	NEU1	MYO10
let-7	HSPA1A/HSPA1B	HSPA1A/HSPA1B	PCDH1	MYO1A
LGR4	ID1	ID1	PENK	NDFIP2
LIMA1	IGFBP7	IGFBP7	PKP2	ONECUT2
LTF	ITGA2	ITGA2	PLA2G4A	PENK
Mcpt1	KDM2A	ITGB6	PML	PLD1

MET	KLF5	KDM2A	PRKCZ	PLS1
MMP7	KRT8	KLF5	Ptprd	PRKCZ
MST1R	KRT18	KRT8	PYY	Ptprd
MUC20	KRT19	KRT18	RAPGEF6	RAB5B
NT5E	LAMA5	KRT19	RHOB	RHOB
ONECUT2	LCN2	KRT23	SCARA3	SEMA5A
OSMR	LEPR	LAMA5	SDC1	SERPINB5
PENK	let-7	LCN2	SERPINB5	SHH
PLA2G16	LGR4	LEPR	SFTPD	SLC12A2
PLA2G4A	LTF	let-7	SHH	SPP1
PLD1	MET	LGR4	SLC12A2	TJP1
PML	MLPH	LIMA1	SLC44A4	VTCN1
PRAP1	MST1R	LTF	SPP1	
PRDX1	Muc4	MET	TJP1	
PRKCZ	MYO6	MMP7	VNN1	
PYY	OGN	MST1R	VTCN1	
RBP1	ONECUT2	MUC13		
RHOB	PENK	MYO10		
SDC1	PLA2G4A	NT5E		
SEMA5A	PLD1	ONECUT2		
SERPINB5	PML	PENK		
SFTPD	POU2F3	PIGR		
SHH	Ppp1cc	PLA2G16		
SLC12A2	PRAP1	PLA2G4A		
SPP1	PRKCZ	PLD1		
TFF1	Ptprd	PML		
TIMP3	RBP1	PRDX1		
TJP1	RHOB	PRKCZ		
TM4SF4	SDC1	RBP1		
TM4SF5	SEMA5A	RHOB		
TMEM102	SFN	S100A14		
TMPRSS4	SHH	SDC1		
TNS4	SIN3A	SEMA5A		
TSPAN8	SLC12A2	SERPINB5		
VIL1	SMPD3	SFN		
VTCN1	SPP1	SFTPD		
	TFF1	SGPP2		
	TIMP3	SHH		
	TJP1	SIN3A		
	TMEM54	SLC12A2		
	VSIG1	SPP1		
	VTCN1	SPRR1A		
		TFF1		
		TIMP3		
		TJP1		
		TM4SF4		
		VSIG1		
		VTCN1		

Supplementary Table 2.
RNA Seq on KPC Cells exposed to IL-17 vs media for 24 hrs

gene ID	gene symbol	IL17vsControl. Fold change	IL17vsControl pVal
16819	Lcn2	8.21993	0.000936025
17002	Ltf	6.93085	0.000338283
20762	Sprr2h	6.23378	0.000338283
76509	1600029D21Rik	5.68675	0.000338283
229927	Clca4	5.61399	0.000338283
100303738	D030025P21Rik	5.27872	0.000338283
26464	Vnn3	4.90676	0.000338283
16165	Il13ra2	4.82743	0.000338283
20311	Cxcl5	4.57577	0.000338283
18173	Slc11a1	4.46182	0.025101
17063	Muc13	4.44134	0.000936025
13661	Ehf	4.20139	0.000338283
330122	Cxcl3	4.14562	0.000338283
12985	Csf3	4.14315	0.000338283
16997	Ltbp2	4.07701	0.000338283
18987	Pou2f2	4.066	0.000338283
213696	Duoxa1	3.82423	0.000338283
80797	Clca2	3.79902	0.000338283
19415	Rasal1	3.7223	0.000338283
12291	Cacna1g	3.65439	0.000338283
104886	Rab15	3.5739	0.00199449
80885	Niacr1	3.51825	0.000338283
241275	Noxa1	3.43897	0.000338283
20731	Spink4	3.31326	0.030448
21926	Tnf	3.28706	0.000338283
230738	Zc3h12a	3.28589	0.000338283
12409	Cbr2	3.28453	0.003225
12609	Cebpd	3.19615	0.000338283
16193	Il6	3.08352	0.003225
20297	Ccl20	2.94563	0.000338283
17951	Naip5	2.87324	0.000338283
625286	Tmem236	2.86634	0.000338283
109335	9230102K24Rik	2.81648	0.00589477
14825	Cxcl1	2.80012	0.000338283
100502940	Gm684	2.78943	0.000338283
69583	Tnfsf13	2.77991	0.000338283
18383	Tnfrsf11b	2.77891	0.000338283
320563	Islr2	2.77372	0.000338283
16803	Lbp	2.76536	0.000338283
20322	Sord	2.63406	0.000338283
108995	Tbc1d10c	2.61843	0.000338283
11997	Akr1b7	2.61624	0.000338283
20765	Sprr2k	2.57946	0.000338283
12023	Barx2	2.54781	0.000338283
414084	Tnip3	2.545	0.000338283
54199	Ccrl2	2.53981	0.000338283
76974	Urah	2.51103	0.000338283
12837	Col8a1	2.48435	0.000338283
16175	Il1a	2.47925	0.000338283
108116	Slco3a1	2.447	0.000338283
80859	Nfkbiz	2.41498	0.000338283
20310	Cxcl2	2.39108	0.000338283
26365	Ceacam1	2.38132	0.000338283
57349	Ppbp	2.34183	0.000338283
18578	Pde4b	2.22972	0.000338283
239759	Liph	2.18374	0.000338283
71287	Cpvl	2.1282	0.00504837
18300	Oit1	2.1247	0.000338283

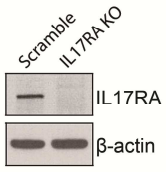
17952	Naip6	2.10649	0.000338283
18811	Prl2c2	2.08246	0.000338283
23844	Clca3	2.06328	0.000338283
100039239	Gm2115	2.05854	0.000338283
24099	Tnfsf13b	2.05445	0.000338283
216643	Gabrp	2.05357	0.000338283
67280	3110009F21Rik	2.05174	0.000338283
74424	Tmc5	2.04371	0.000338283
19085	Prkar1b	1.97934	0.000338283
70717	Medag	1.97453	0.000338283
12266	C3	1.9555	0.000338283
545902	Ptprh	1.92452	0.000338283
99662	Eps8l3	1.92223	0.000338283
20761	Sprr2g	1.8777	0.0252597
12981	Csf2	1.87653	0.000338283
11539	Adora1	1.84291	0.000338283
242122	Vtcn1	1.84286	0.000338283
19142	Prss12	1.8376	0.000338283
19200	Pstpip1	1.83313	0.000338283
244595	Ces1a	1.81091	0.000338283
209558	Enpp3	1.81064	0.000338283
57319	Smpdl3a	1.79786	0.000338283
71893	Noxo1	1.79405	0.000338283
106042	Prickle1	1.78357	0.000338283
20500	Slc13a2	1.77909	0.000338283
22436	Xdh	1.77858	0.000338283
18414	Osmr	1.77554	0.000338283
242125	Mab21l3	1.75295	0.000338283
23947	Mid2	1.74296	0.000338283
13615	Edn2	1.71523	0.000338283
100040462	Mndal	1.6999	0.000338283
20306	Ccl7	1.69342	0.0210892
70417	Megf10	1.68405	0.000338283
433470	AA467197	1.6838	0.000338283
21946	Pglyrp1	1.67707	0.000338283
107607	Nod1	1.66277	0.000338283
12494	Cd38	1.64779	0.000338283
12819	Col15a1	1.60217	0.000338283
28105	Trim36	1.60075	0.000338283
11647	Alpl	1.58373	0.000338283
233552	Gdpd5	1.58339	0.000338283
207686	A330021E22Rik	1.55277	0.000338283
11717	Ampd3	1.55058	0.000338283
69083	Sult1c2	1.53521	0.000338283
18585	Pde9a	1.52701	0.000338283
57425	U90926	1.52204	0.0378341
17857	Mx1	1.50934	0.000338283



D

No. Cell injected	KPC-Ctrl	KPC-IL17 stimulated
5 x 10^5	10/10	10/10
1 x 10^5	6/10	10/10
5 x 10^4	4/10	8/10
1 x 10^4	2/14	4/14
5 x 10^3	1/14	2/14
1 x 10^3	0/20	0/20
TIC Frequency	1/94701 (1/160768 -1/55784)	1/29614 (1/4743-1/18488)
P value	0.00126	

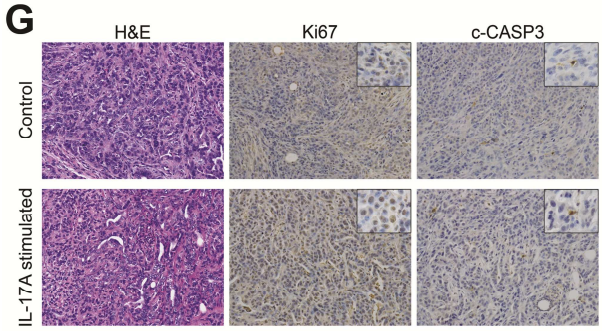
E



F

No. Cell injected	KPC-Scramble	KPC-IL17RA KO
5 x 10^5	10/10	7/10
1 x 10^5	8/10	5/10
5 x 10^4	5/10	3/10
1 x 10^4	2/10	0/10
5 x 10^3	1/10	0/10
1 x 10^3	0/10	0/10
TIC Frequency	1/62615 (1/105124 -1/37295)	1/270432 (1/479531-1/152511)
P value	0.000123	

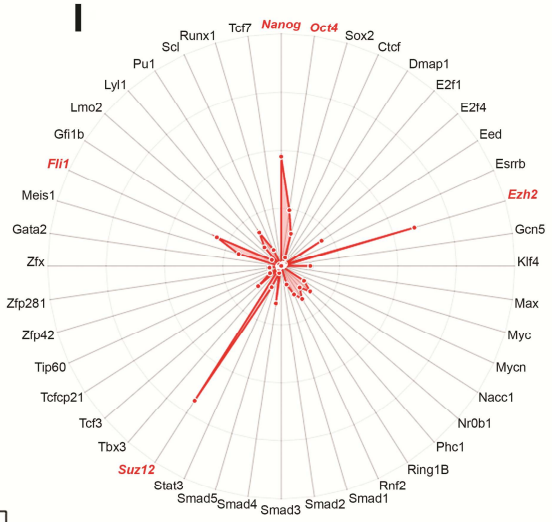
G



H

Cell Type	Set size	Overlapping Genes	p value	adjusted p value
Embryonic stem cells	3513	94	1.09 x 10^{-10}	9.84 x 10^{-10}
Hematopoietic stem cells	2475	63	1.27 x 10^{-6}	1.14 x 10^{-5}
Intestinal stem cells	483	17	4.03 x 10^{-4}	0.004

I



J

Transcription factor	Set size	Overlapping Genes	p value	adjusted p value
Ezh2	2436	78	1.32 x 10^{-12}	9.67 x 10^{-11}
Suz12	1908	59	3.97 x 10^{-9}	2.9 x 10^{-7}
Nanog	2177	61	7.6 x 10^{-8}	5.54 x 10^{-6}
Fli1	8990	169	8.69 x 10^{-7}	6.34 x 10^{-5}
Oct.4	4221	89	1.69 x 10^{-5}	0.001

Figure S1. (A) Relative mRNA expression of TNFα and LCN2 quantified by RT-PCR from KPC cells stimulated by IL-17A vs control for 7 days. (B,C) Representative quantification of IL-17A-stimulated KPC cells proliferation as measured by WST-1 cell proliferation test (B) and migration determined by wound healing assay (C). (D,F) In vivo limiting dilution assay. Tumor incidence at day 20 post-implantation using limiting dilution of KPC cells control vs IL-17A in vitro pre-treated (D) and KPC-Scramble vs KPC-IL17RA KO cells (F). TIC frequency and P values were calculated using the Extreme Limiting Dilution Analysis software. (E) Immunoblotting for IL17RA expression in KPC-Scramble vs KPC-IL17RA KO cells, Results are expressed as relative protein level normalized to β-actin. (G) Representative images of Hematoxylin-Eosin (H&E) histology, Ki67 and c-Caspase3 staining on tumors formed from subcutaneously injected KPC cells pre-incubated with IL-17A vs control. (H) List of Embryonic, Hematopoietic and Intestinal stem cells signatures that have significant overlap with the genes regulated by IL-17A on the microarray data. P value and adjusted p value provided for each signature. (I) Radar chart displaying the overlap between the IL-17A-regulated genes and the stemness-associated transcription factors. The values plotted represent the significance of the overlap (with each radar representing -log10 P-value). (J) List of transcription factors that have significant overlap with their target genes regulated by IL-17A on the microarray data. P value and adjusted p value provided for each signature.

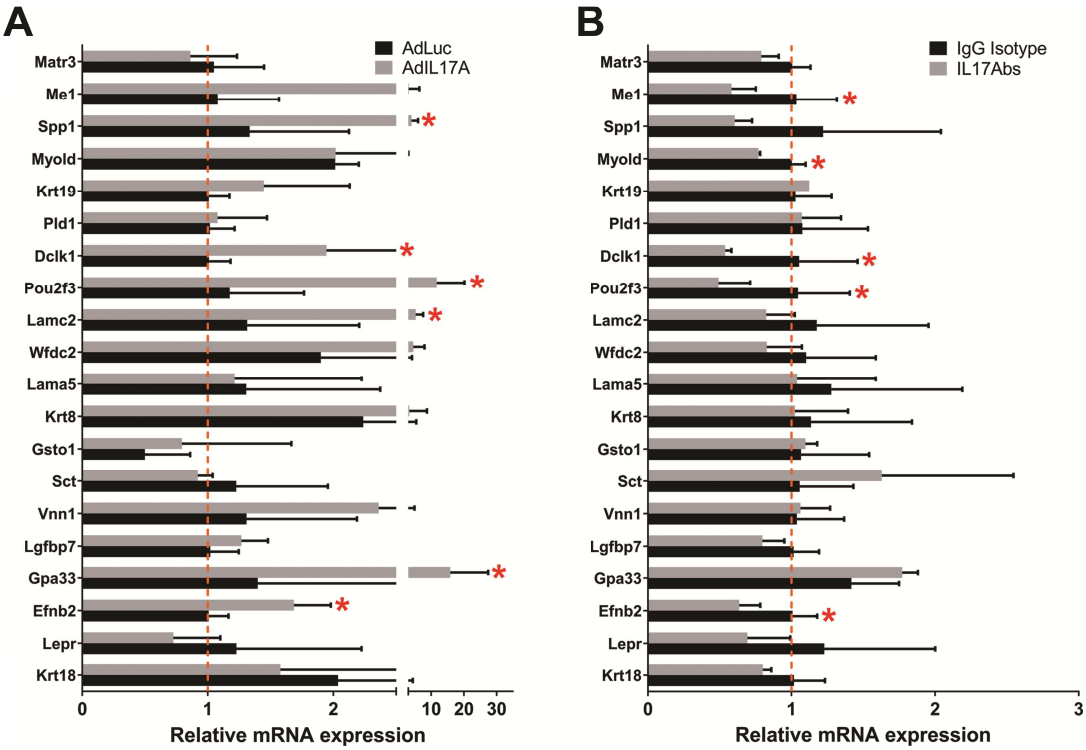


Figure S2. Relative mRNA expression of the top-20 individual ESC signature genes quantified by RT-PCR from pancreas RNA extraction from KC^{iMist1} Ad Luc and KC^{iMist1} AdIL-17 mice (A) and KC^{iMist1} mice received IL-17 neutralizing antibodies and isotype (B).

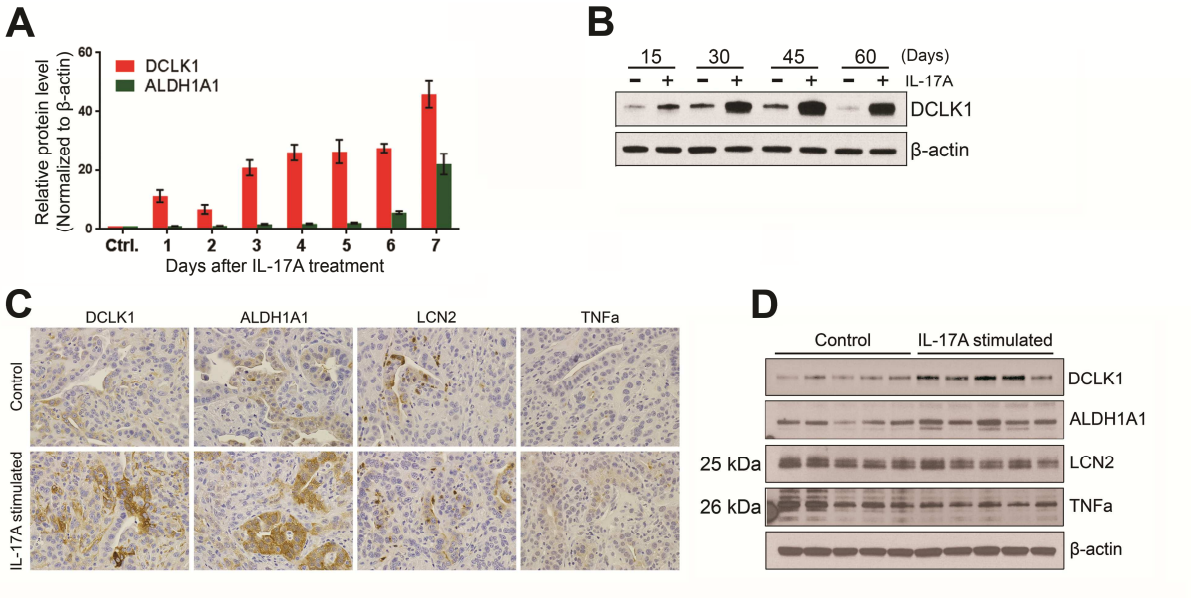


Figure S3. (A) Quantification of Dclk1 and Aldh1a1 Immunoblotting results expressed as relative protein level normalized to β-actin. Error bars indicate the SEM from two individual assays. (B) Immunoblotting for Dclk1 on KPC cells stimulated with IL-17A vs media alone for up to 60 days. (C) Representative figure of Dclk1, Aldh1a1, LCN2 and TNFα on subcutaneous tumors developed from IL-17A- stimulated vs control (exposed to media alone) KPC cells. (D) Immunoblotting for Dclk1, Aldh1a1, LCN2, and TNFα on tumors formed with subcutaneously injected KPC cells pre-incubated with IL-17A vs control. Tumors were removed 10 days after KPC cells injections.

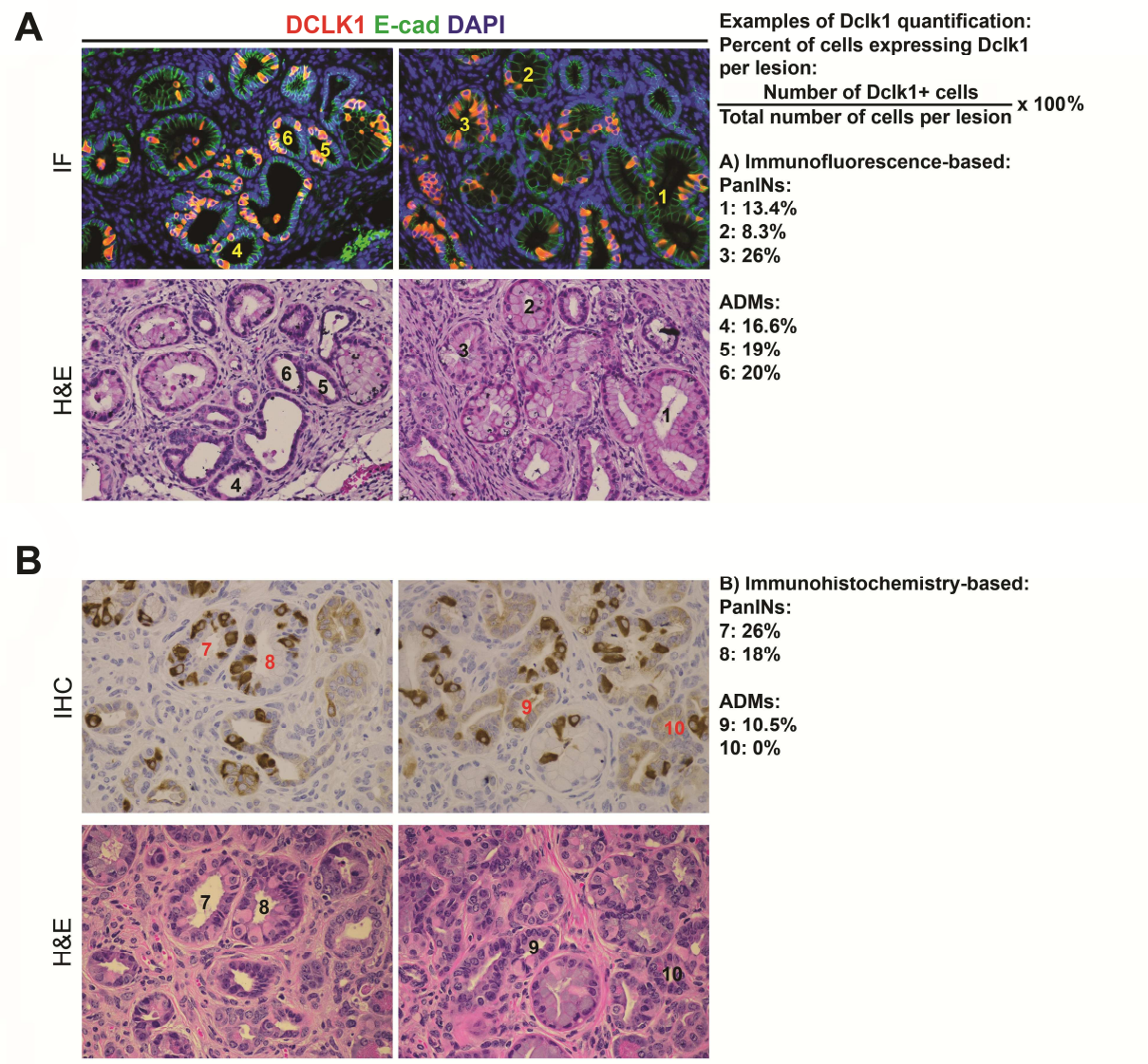
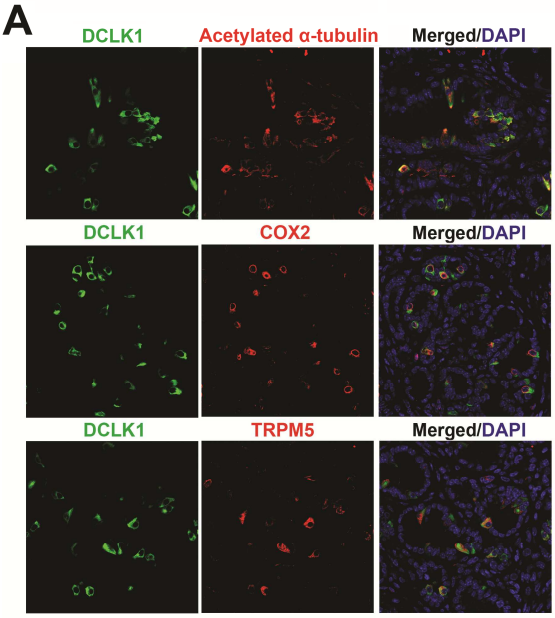


Figure S4. (A,B) Detail of immunofluorescent (A) or immunohistochemical (B) detection and quantification of Dclk1-expressing cells in images from KC^{iMist1} mice. Parallel sections stained with H&E were matched with each slide. For each image, 2-3 examples of Dclk1 quantification were given. The total number of cells per lesion (ADM or PanIN) and the number of Dclk1 expressing cells per lesion were quantified. Results were expressed as percent of Dclk1+ cells/lesion.

A



B

Percent of positive cells/Total Dclk1+ cells in PanINs	
Ac-α-Tubulin+	98
COX2+	93.75
TRPM5+	91.66666667

Figure S5. (A) Representative pictures of immunofluorescence co-staining of Dclk1 with Acetylated α-tubulin, COX2 and TRPM5 individually in ADMs or PanINs from KC^{iMist1} mice. (B) Table shows the quantification of percent of Dclk1+ cells expressing each of the tuft cell markers.

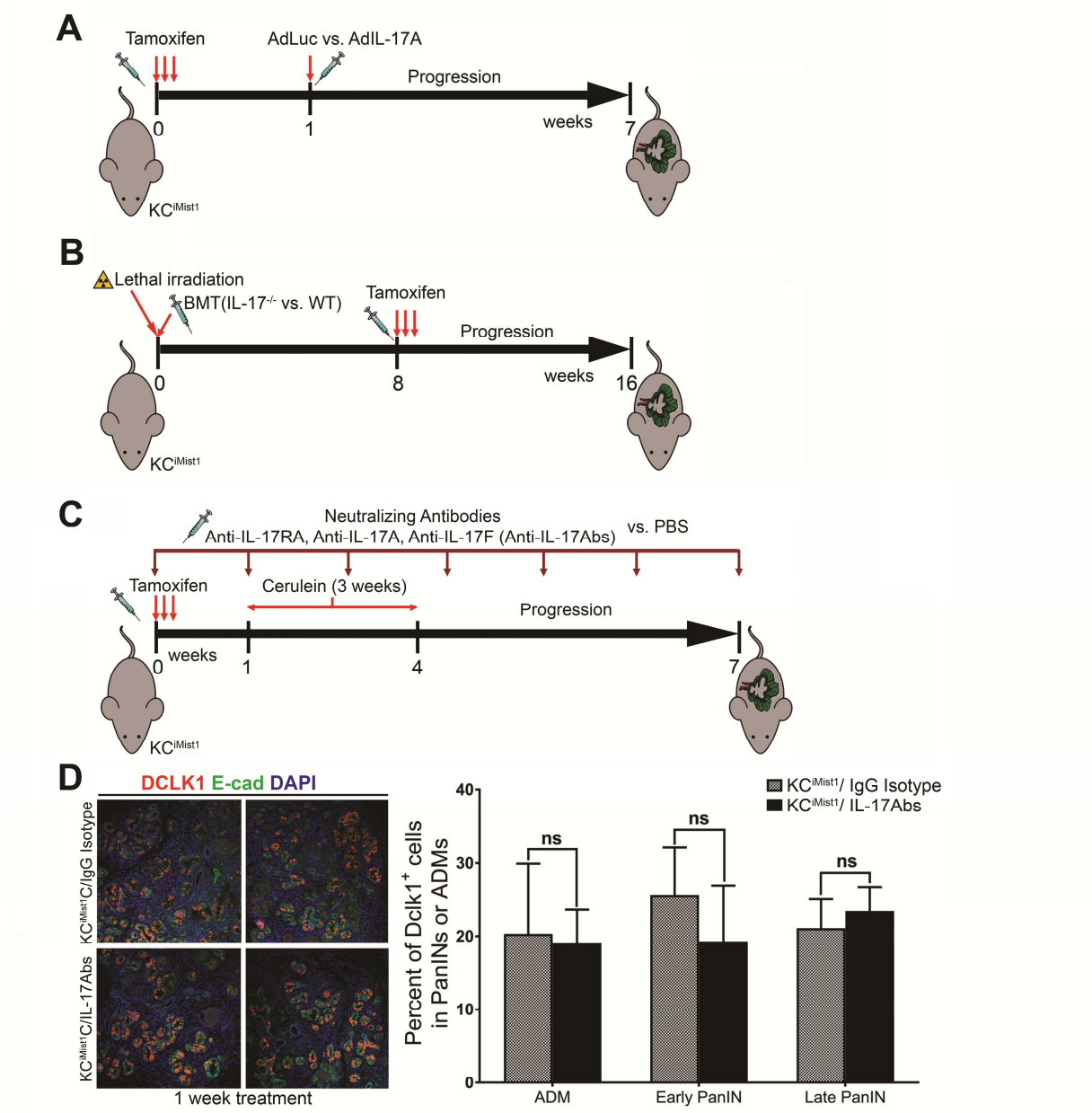


Figure S6. (A) Protocol for Kras activation and delivery of adenovirus encoding for IL-17A vs Luciferase (Luc) to KCi^{Mist1} mouse pancreas. (B) Protocol for the generation of KC^{iMist1}/IL-17AWT and KC^{iMist1}/IL-17AKO bone marrow (BM) chimeric animals. (C) Protocol for the treatment of KCi^{Mist1} mice with IL-17 neutralizing antibodies vs IgG isotype 7 weeks after cerulean inoculations. (D) Representative pictures of Dclk1 and e-cadherin immunofluorescence staining in ADMs or PanINs from KC^{iMist1} mice challenged with cerulean and treated for 1 week with IL-17 neutralizing antibodies vs IgG isotype (left); Quantification of the percent of cells expressing Dclk-1 per ADMs or PanIN (right).

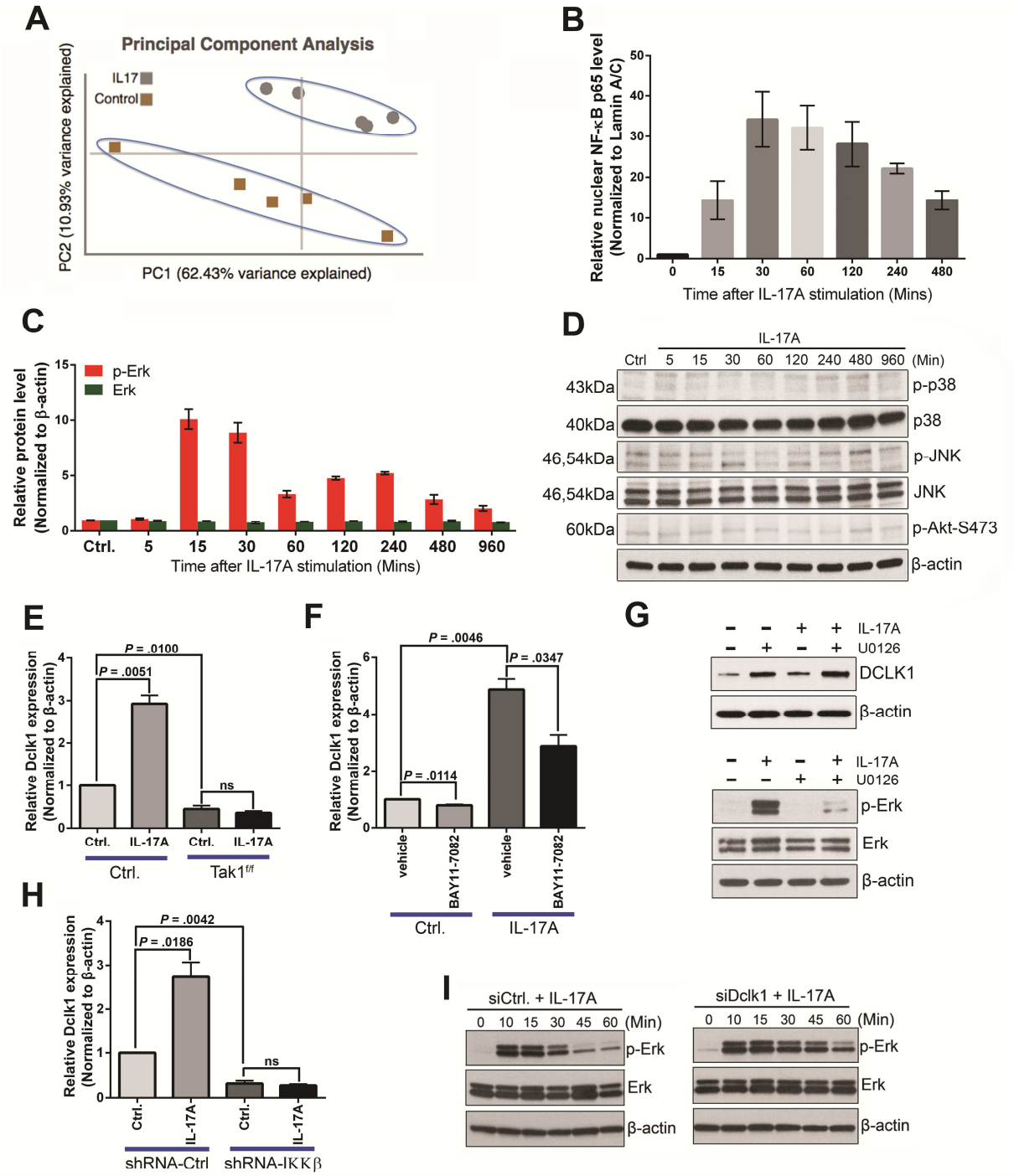


Figure S7. (A) Principal component analysis (PCA) showed the samples from KPC stimulated with IL-17A or control cluster together. (B) Quantification of nuclear NF-κB p65 immunoblotting results expressed as relative protein level normalized to Lamin A/C. Error bars indicate the SEM from two individual assays. (C) Quantification of p-Erk and total Erk immunoblotting results expressed as relative protein level normalized to β-actin. Error bars indicate the SEM from two individual assays. (D) Immunoblotting for p-p38, p38, p-JNK, JNK and P-Akt of KPC cells stimulated with IL-17A. (E, F, H) Quantification of Dclk1 immunoblotting results upon IL-17A stimulation using Tak$^{f/f}$ KPC cells (E), BAY11-7082 (F) and shRNA-IKKb (H). Results are expressed as relative protein level normalized to β-actin. Error bars indicate the SEM from two individual assays. (G) Immunoblotting for Dclk1 (upper), p-Erk and total Erk (lower) on KPC cells stimulated with IL-17A upon MAPK pathway inhibitor (U0126) for 5 days. (I) Immunoblotting for p-Erk and total Erk on KPC cells transfected with siRNA: siDCLK1(right) or siCtrl. (left) stimulated with IL-17A.

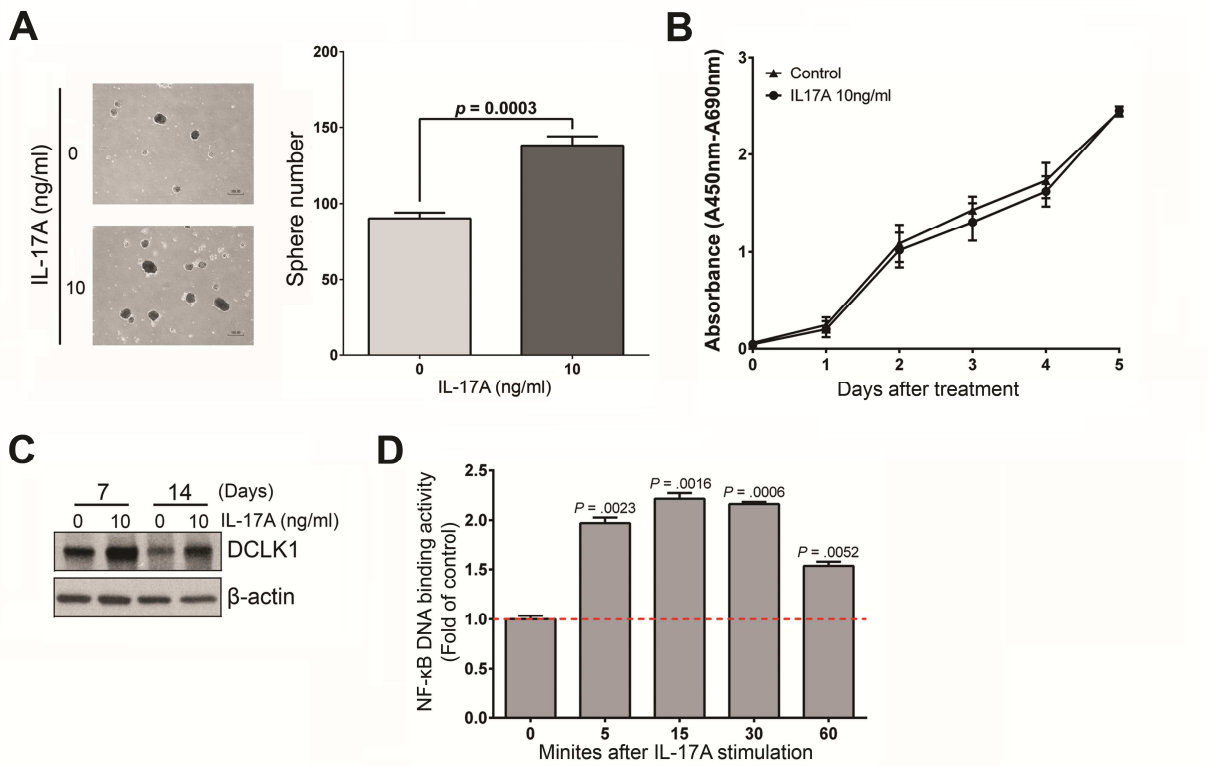


Figure S8. (A) Representative pictures (left) and quantification of tumorspheres (right) developed from Capan-2 cells *in vitro* stimulated with IL-17A (10 ng/ml). The tumorsphere assay has been repeated 3 times. Results of one representative experiment are shown. (B) Representative quantification of IL-17A-stimulated Capan-2 cells proliferation as measured by WST-1 cell proliferation test. (C) Immunoblotting for Dclk1 on Capan-2 cells stimulated with IL-17A (+) vs media alone for 7 and 14 days. (D) Time-dependent NF-κB DNA binding activity measured in Capan-2 cells stimulated with IL-17A. Results are expressed as fold changes over control Capan-2 cells untreated. This experiment was repeated 2 times and a representative experiment is shown.

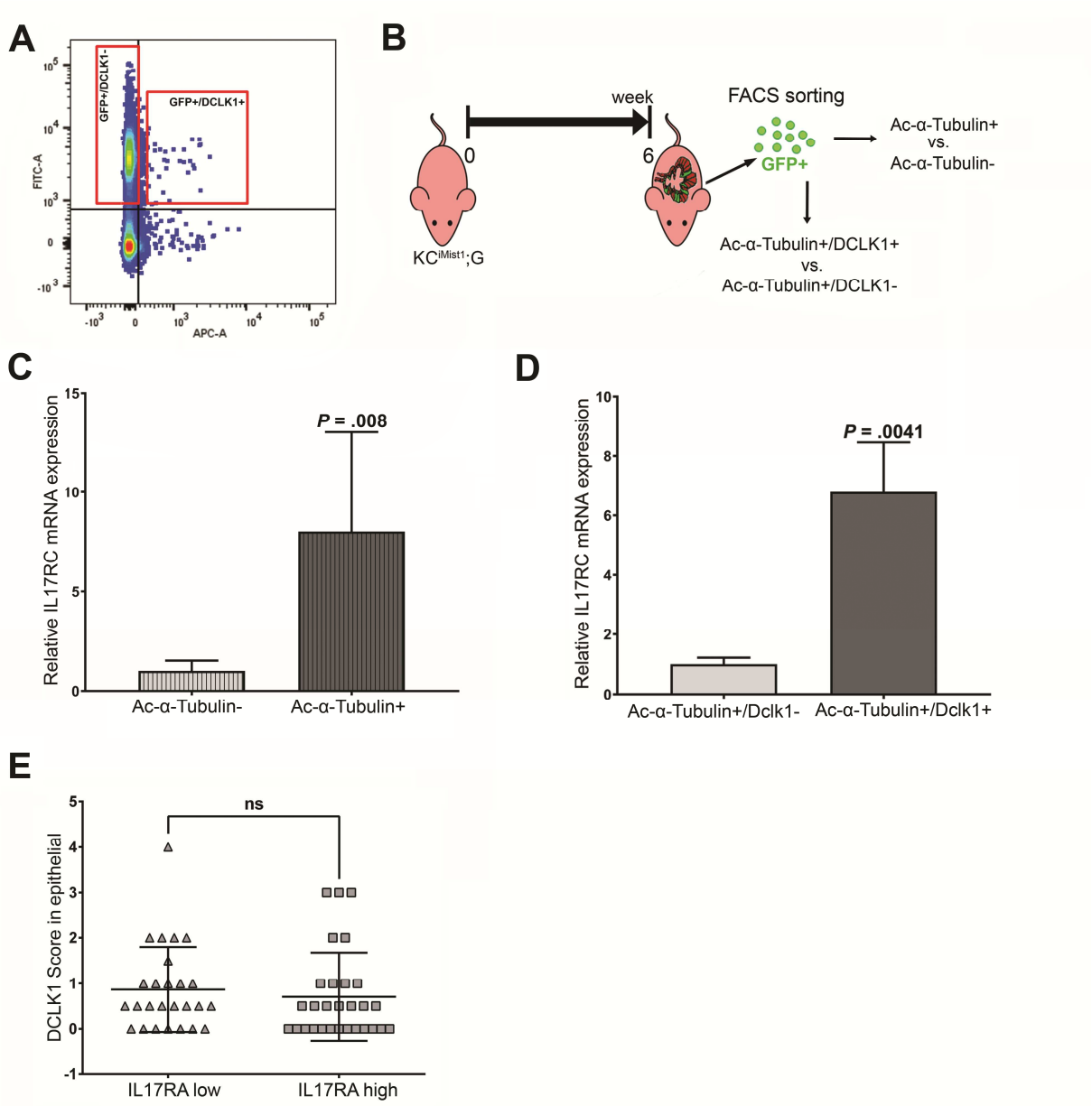


Figure S9. (A) Sorted fractions of GFP+/Dclk1+ and GFP+/Dclk1- cells from KC^{iMist1};G mice (expressed as percent of total GFP+ cells). (B) Protocol for sorting GFP+/Ac-α-Tubulin- vs GFP+/Ac-α-Tubulin+ cells or GFP+/Ac-α-Tubulin+/Dclk1- vs GFP+/ Ac-α-Tubulin+/Dclk1- cells from KPCiMist1;G mouse. (C, D) Taqman PCR for quantification of mRNA expression of IL-17RC in Ac-α-Tubulin-, Ac-α-Tubulin+ (C) and Ac-α-Tubulin+/Dclk1-, Ac-α-Tubulin+/Dclk1+ (D) expressing GFP+ KPC cells. (E) Comparison of DCLK1 expression between human PDAC with IL17RA high expression and IL17RA low expression, based on immunohistochemistry staining score.