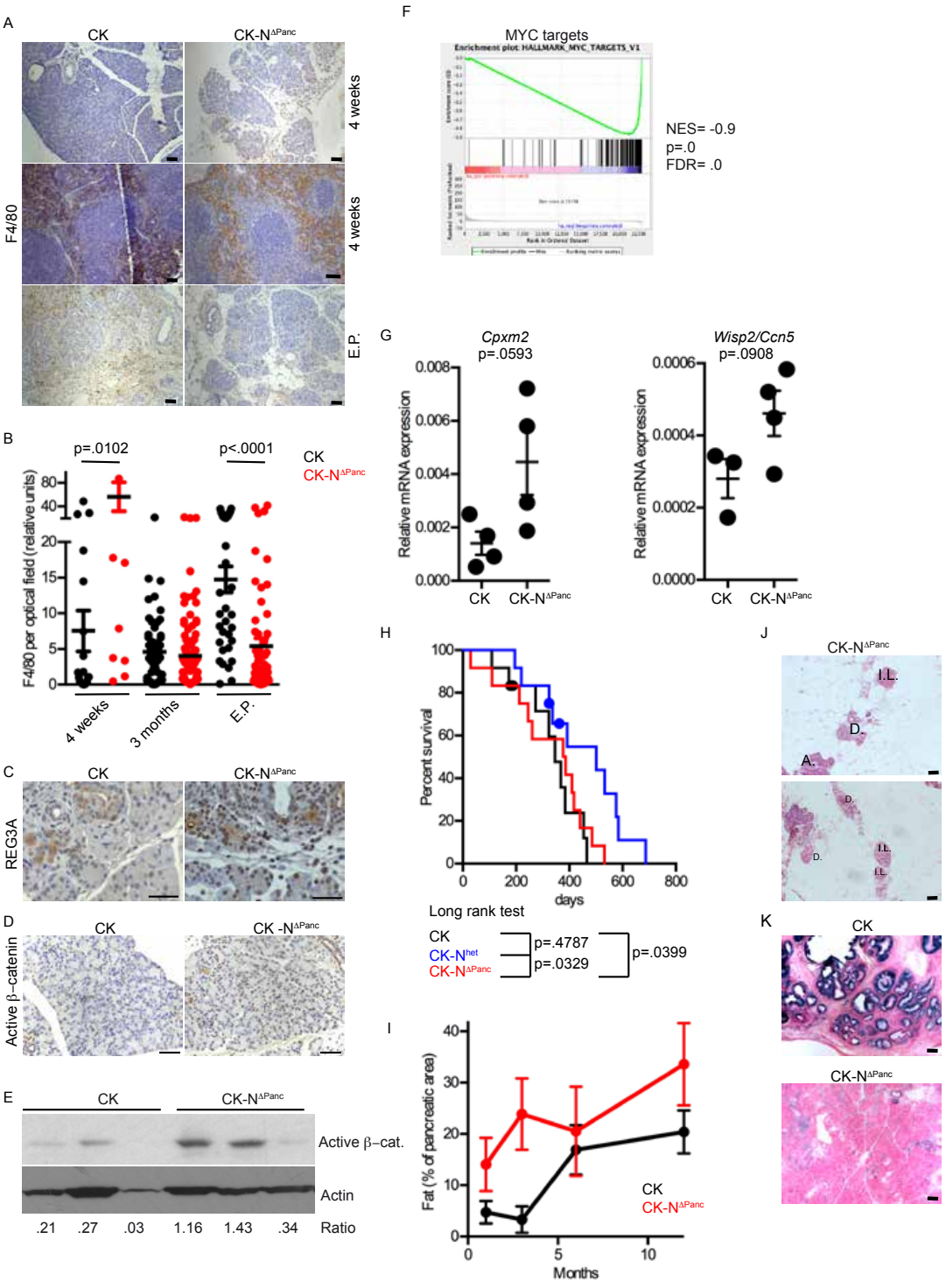
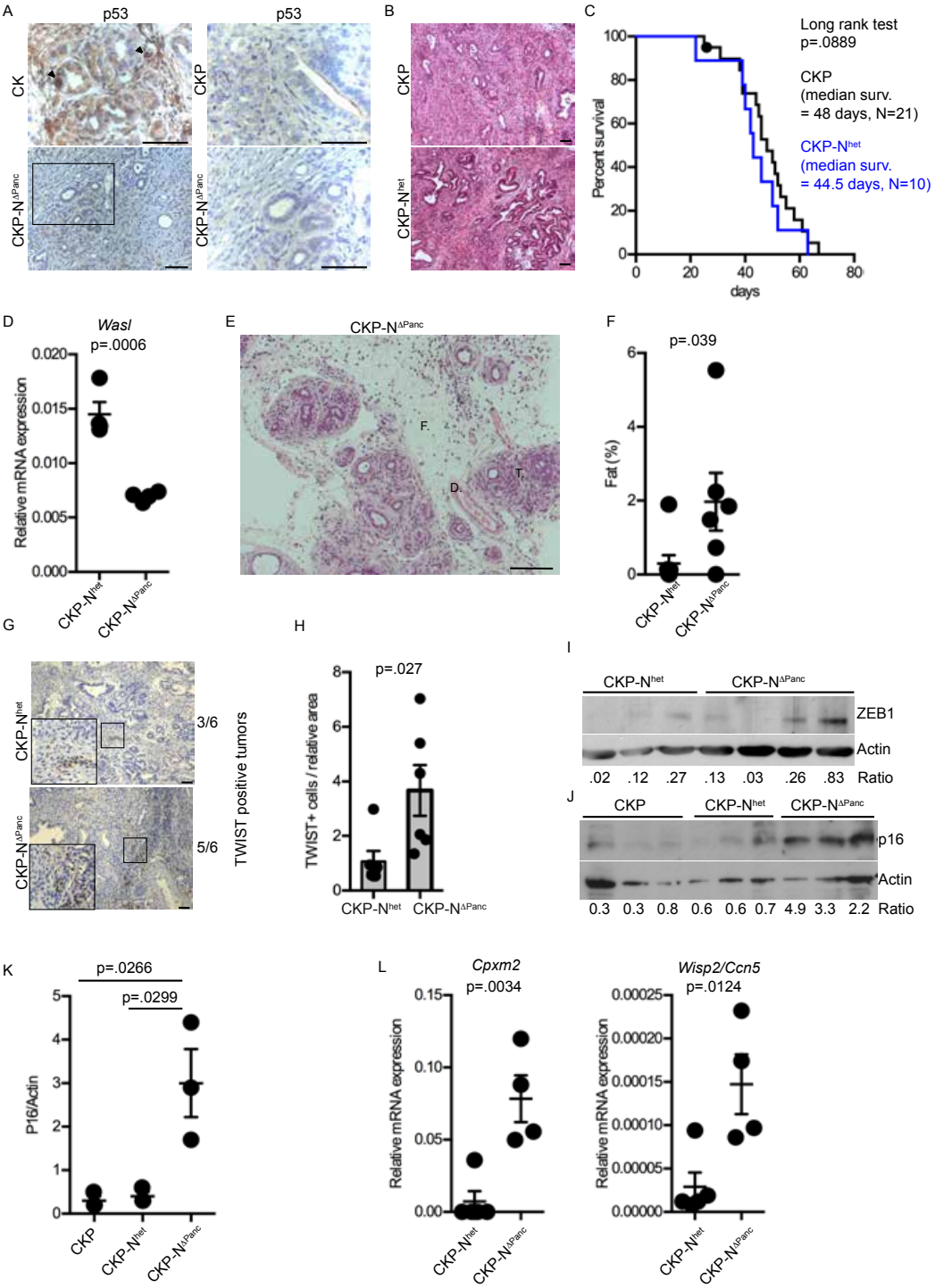
Supp. Fig. 1


A
CK
CK-N^ΔPanc
4 weeks
F4/80
4 weeks
E.P.
B
p=.0102
p<.0001
CK
CK-N^ΔPanc
F4/80 per optical field (relative units)
4 weeks
3 months
E.P.
C
CK
CK-N^ΔPanc
REG3A
D
CK
CK -N^ΔPanc
Active β−catenin
E
CK
CK-N^ΔPanc
Active β−cat.
Actin
.21 .27 .03 1.16 1.43 .34 Ratio
F
MYC targets
Enrichment plot: HALLMARK_MYC_TARGETS_V1
NES= -0.9
p=.0
FDR= .0
G
Cpxm2
p=.0593
Wisp2/Ccn5
p=.0908
Relative mRNA expression
CK
CK-N^ΔPanc
H
Percent survival
days
Long rank test
CK
CK-N^het
CK-N^ΔPanc
p=.4787
p=.0329
p=.0399
I
Fat (% of pancreatic area)
Months
CK
CK-N^ΔPanc
J
CK-N^ΔPanc
I.L.
D.
A.
K
CK
CK-N^ΔPanc

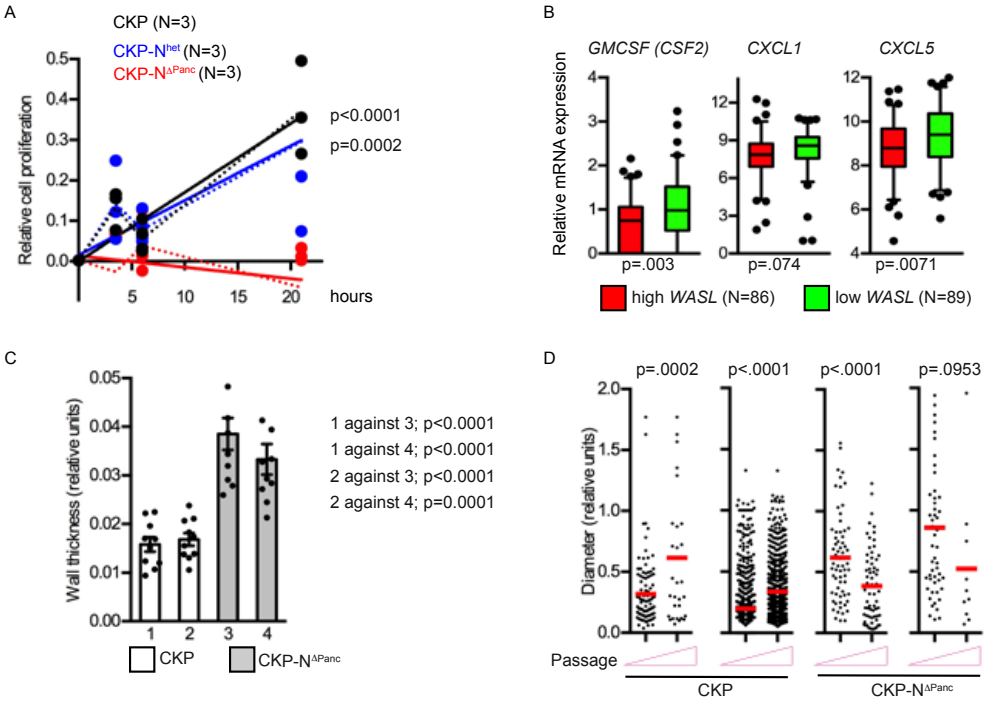
Supplementary Fig. 1: A. Immunohistochemical stainings for the macrophage marker F4/80. Upper and lower panel show pancreatic tissue; the middle panels show the spleen as an internal positive control. E.P.= human endpoints. Scale bars = 50 µM. B. Morphometric quantification of the amount of F4/80-positive macrophages per optical field within pancreatic tissue (3 to 5 mice per genotype) at the indicated time points. The mean of all optical fields and SEM are shown. Student´s t-test. C. Immunohistochemical staining for the pancreatic marker REG3A in pancreata of four weeks old mice. Scale bars = 50 µM. D. Immunohistochemical staining for active β-catenin in murine tissue. E. Western blot analysis of pancreatic tissue of four weeks old mice. F. Enrichment plots generated by the GSEA tool showing downregulations of MYC target genes in the CK-N$^{\Delta Panc}$ tissue. G. RT-PCR analyses for *Cpxm2* and *Wisp2* expression confirms a slight upregulation of these genes. The mean of 3/4 mice per group and SEM are shown. Student´s t-test. H. Kaplan-Meier survival curves, 12 mice per group. Long rank test. I. Quantification of the fatty metaplasia within the pancreatic tissue in mice of the indicated genotypes (CK 1-month N=7; CK-N$^{\Delta Panc}$ 1-month N=4; CK 3-months N=2; CK-N$^{\Delta Panc}$ 3-months N=4; CK 6-months N=3; CK-N$^{\Delta Panc}$ 6-months N=3; CK endpoints (E.P.) n=2 and CK-N$^{\Delta Panc}$ endpoints n=7. J. Representative pictures of a CK-N$^{\Delta Panc}$ tissue with fatty metaplasia. The presence of sparse Islets of Langerhans (I.L.) and acinar tissue (A.) highlights the fatty metaplasia. D. = duct; F. = fatty tissue; T. = tumor. Scale bars = 50 µM. K. SA-β-galactosidase staining of cryosections of pancreatic tissue of 4 weeks old mice. Scale bars = 50 µM.

Supp. Fig. 2


A
p53
p53
CK
CKP
CKP-N ΔPanc
CKP-N ΔPanc
B
CKP
CKP-N het
C
Long rank test
p=.0889
CKP
(median surv.
= 48 days, N=21)
CKP-N het
(median surv.
= 44.5 days, N=10)
Percent survival
days
D
Wasl
p=.0006
Relative mRNA expression
CKP-N het
CKP-N ΔPanc
E
CKP-N ΔPanc
F.
D.
T.
F
p=.039
Fat (%)
CKP-N het
CKP-N ΔPanc
G
CKP-N het
CKP-N ΔPanc
3/6
5/6
TWIST positive tumors
H
p=.027
TWIST+ cells / relative area
CKP-N het
CKP-N ΔPanc
I
CKP-N het
CKP-N ΔPanc
ZEB1
Actin
.02 .12 .27 .13 .03 .26 .83 Ratio
J
CKP
CKP-N het
CKP-N ΔPanc
p16
Actin
0.3 0.3 0.8 0.6 0.6 0.7 4.9 3.3 2.2 Ratio
K
p=.0266
p=.0299
P16/Actin
CKP
CKP-N het
CKP-N ΔPanc
L
Cpxm2
p=.0034
Relative mRNA expression
CKP-N het
CKP-N ΔPanc
Wisp2/Ccn5
p=.0124
Relative mRNA expression
CKP-N het
CKP-N ΔPanc

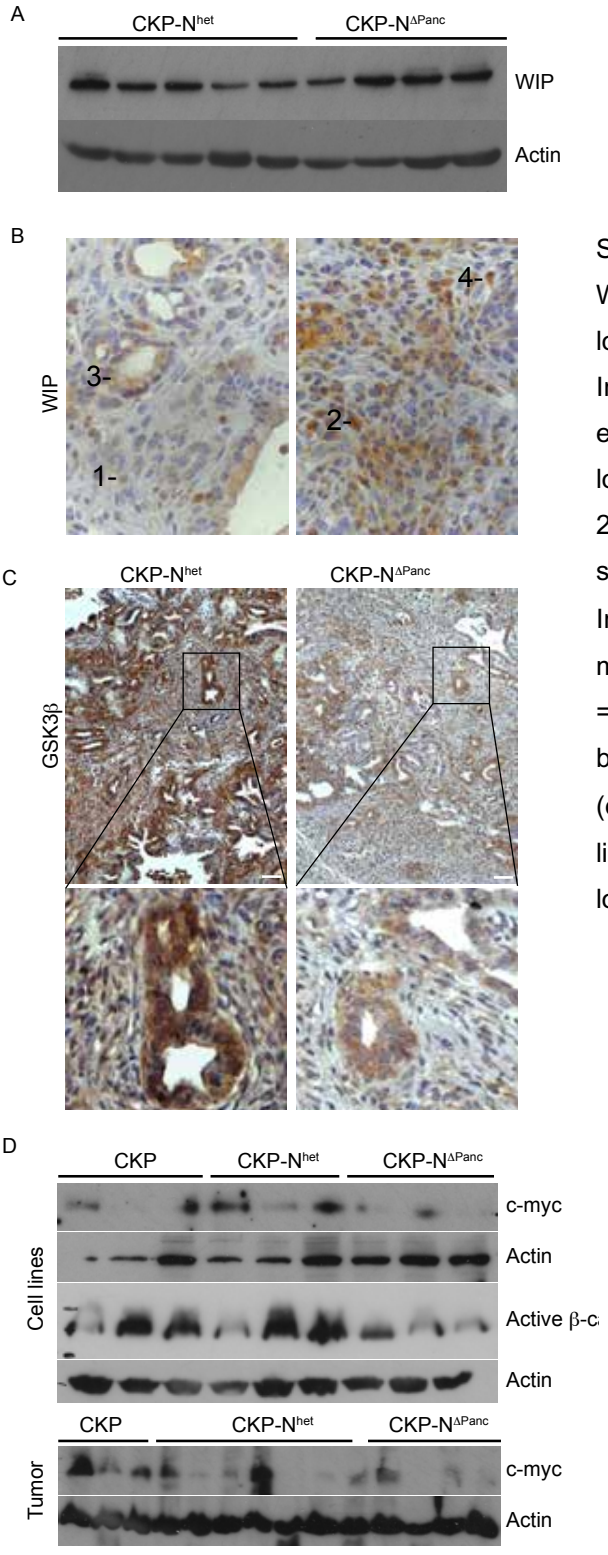
Supplementary Fig. 2: A. Immunohistochemical staining for p53 (arrowheads) showing lack of p53 expression in the CKP-N$^{\Delta Panc}$ pancreata (the right panel shows magnification of the black box). Scale bars = 50 µM. B. Histology from endpoint mice of the indicated genotypes. Scale bars = 50 µM. C. Kaplan-Meier survival curves for mice of the indicated genotypes. Long rank test. D. *Wasl* expression was analyzed in tumors from mice of the indicated genotypes by RT-PCR; Data represent mean of 4 mice/group ± SEM; Student´s t-test. E. Representative picture of the fatty metaplasia in a CKP-N$^{\Delta Panc}$ tumor. D = duct; F = fatty tissue; T. = tumor. Scale bar = 50 µM. F. Morphometric analysis of the fat content in tumors from mice of the indicated genotypes (blinded quantification). The mean and SEM are shown. Student´s t-test. G. Immunohistochemical staining for TWIST in murine tumors of the indicated genotype. The ratio below the panels indicates the number of positive stained tumors per total number of tumors that were analyzed. Scale bars = 50 µM. Inserts show magnification of the black boxes. H. Quantification of the staining shown in G. The mean (6 mice per group) and SEM are shown. Student´s t-test. I. Western blot analysis for ZEB1 in murine tumors. Actin shows equal protein loading. J. Western blot analysis for p16 in tumors from murine mice. K. quantification of the Western blot shown in H. The mean and SEM are shown. Student´s t-test. L. Analysis of gene expression by RT-PCR confirms the upregulation of *Cpxm2* and *Wisp2/CCN5* in CKP-N$^{\Delta Panc}$ tumors. The mean (5/4 samples per group) and SEM are shown. Student´s t-test.

Supp. Fig. 3



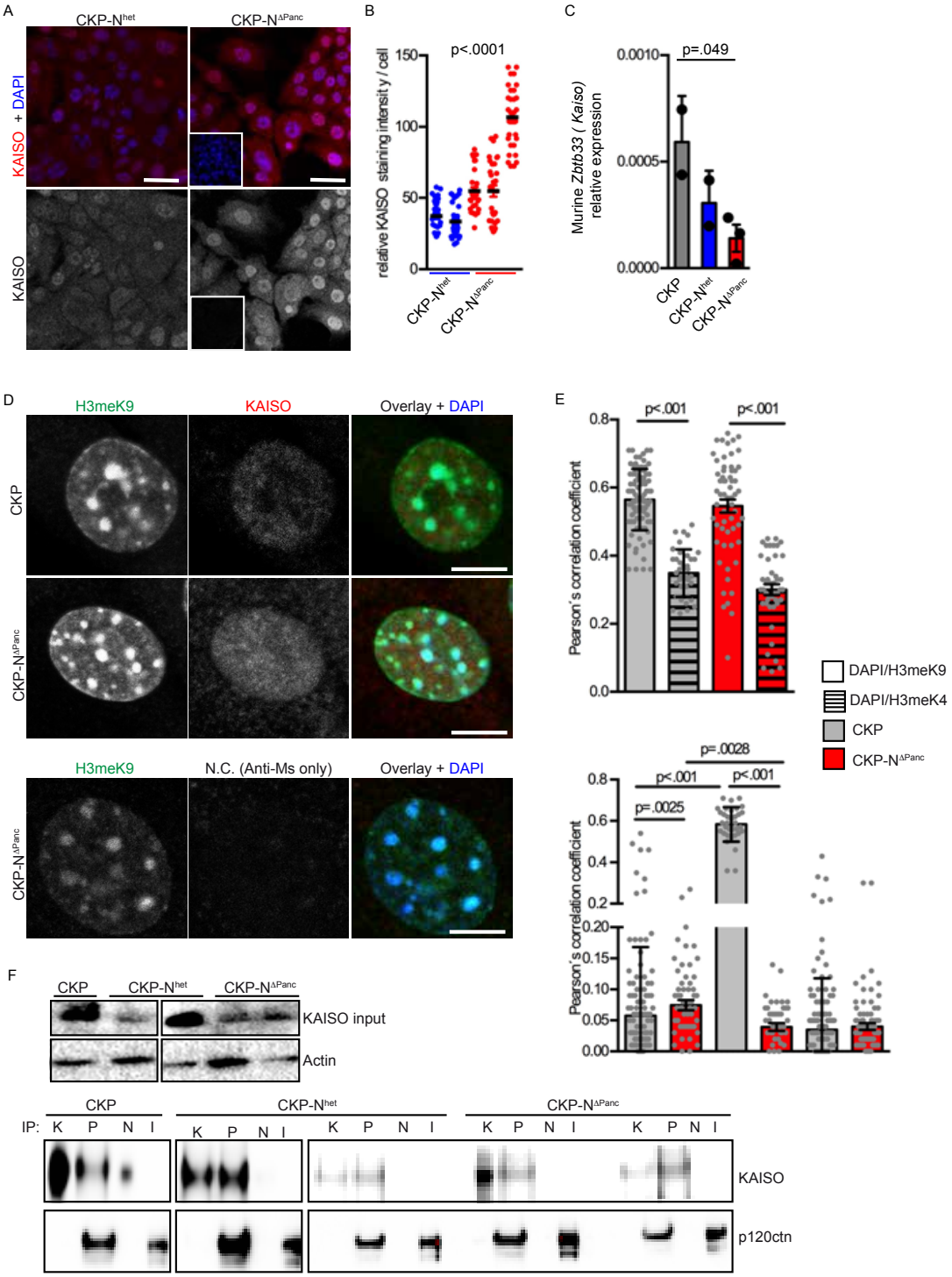
Supplementary Fig. 3: A. Cells were grown on a thin-layer of collagen and a BrdU proliferation assay was performed for 3 cell lines per genotype. Each point is the mean of three experiments. The values were normalized to time point 0. CKP-*N*$^{\Delta Panc}$ cells' growth was significantly slower than the control cells (linear regression). B. PDAC patients were stratified for *WASL* expression using the UCSC Xena genomic browser and the expression levels of the indicated genes were compared. In the box plots, the whiskers represent the 5th and 95th percentile and the central line is the median of the data, with the remaining dots being outliers. Unpaired t-test with Welch's correction. C. Organoids were generated from CKP and CKP-N$^{\Delta Panc}$ tumors and the wall thickness was measured. Data represent the mean of 10 organoids ± SEM. Student´s t-test. D. The diameter of the single organoids during in function of passage number is shown. Each scatter blot includes the mean of 50 to 600 organoids. Student´s t-test.

Supp. Fig. 4



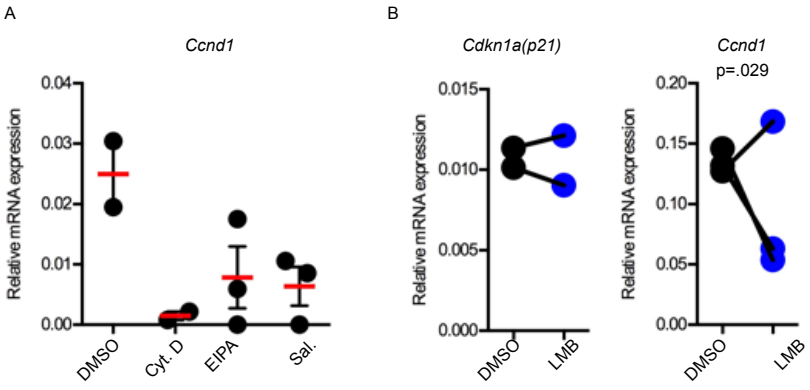
Supplementary Fig. 4: A. Western blot analysis for WIP in murine tumors. Actin shows equal protein loading. B. Representative pictures for Immunohistochemical staining for WIP with an example of the different WIP subcellular localization. 1=weak cytoplasmic staining (+), 2=strong cytoplasmic staining (++), 3=membranous staining and 4=nuclear staining. C. Immunohistochemical stainings for GSK3β in murine tumors of the indicated genotype. Scale bars = 50 μM. Inserts show magnification of the black boxes. D. Western blot analysis for Myc and active (dephosphorylated) β-catenin in tumor-derived cell lines and tumor tissue. Actin shows equal protein loading.

Supp. Fig. 5


A
CKP-N^het
CKP-N^ΔPanc
KAISO + DAPI
KAISO
B
p<.0001
relative KAISO staining intensity / cell
150
100
50
0
CKP-N^het
CKP-N^ΔPanc
C
p=.049
Murine Zbtb33 (Kaiso) relative expression
0.0010
0.0005
0.0000
CKP
CKP-N^het
CKP-N^ΔPanc
D
H3meK9
KAISO
Overlay + DAPI
CKP
CKP-N^ΔPanc
H3meK9
N.C. (Anti-Ms only)
Overlay + DAPI
CKP-N^ΔPanc
E
p<.001
p<.001
Pearson's correlation coefficient
0.8
0.6
0.4
0.2
0.0
DAPI/H3meK9
DAPI/H3meK4
CKP
CKP-N^ΔPanc
p=.0028
p<.001
p<.001
p=.0025
0.20
0.15
0.10
0.05
0.00
F
CKP
CKP-N^het
CKP-N^ΔPanc
KAISO input
Actin
IP: K P N I
KAISO
p120ctn

Supplementary Fig. 5: A. Cell lines of the indicated genotypes were stained for KAISO by immunofluorescence. Scale bars = 50 µM. B. Quantification of the staining described in B. Data represents the mean of 30 cells per cell line ± SEM. KAISO is significantly expressed higher in CKP-N$^{\Delta Panc}$ cells, two-way ANOVA. C. Analysis of *Zbtb33*(*Kaiso)* gene expression by RT-PCR. Data represent the mean of 2/3 cell lines ± SEM. Student´s t-test. D. Immunofluorescence staining for KAISO, the inactive transcriptional marker H3meK9 and heterochromatin (stained with DAPI). The pictures show the nuclei of the cells. Scale bars 10 µM. E. Quantification of immunofluorescence stainings for KAISO, the inactive transcriptional marker H3meK9, the active transcriptional marker H3meK4, and heterochromatin. Upper panel: a stronger colocalization of DAPI with H3meK9 was used as a validation of the method. Shown are the colocalization rates of the indicated proteins. Data represent the mean of 40 to 120 nuclei ± SEM. Mann-Whitney test. F. Western blot showing co-immunoprecipitation of KAISO and p120ctn. K=KAISO, P=p120ctn, N=negative control (IgG) and I=Input. Since the amount of KAISO was very low, we loaded 40 µg of cell lysates used for the IP on a separate Western blot (upper panel).

Supp. Fig. 6



Supplementary Fig. 6: A, B. CKP-N$^{\Delta Panc}$ cells were grown on a thin-layer of collagen and treated with the indicated drugs. Gene expression was analyzed by RT-PCR. Data represent 2/3 cell lines ± SEM. Student´s t-test.

Supplementary Table 1: Pancreata of four weeks-old CK (N = 3) and CK-N$^{\Delta Panc}$ (N=4) mice were analyzed by RNA-Seq. We identified 155 differentially expressed genes with log2 (fold change)>4 and 100 genes with log2 (fold change) <-1.6. Gene enrichment was analyzed with Enrichr. The table shows the top up-regulated and down-regulated pathways and ontologies (old normalized *p*-value <.005).

Supplementary Table 1

Comparison Pancreas 4 weeks CK-N Dpanc / CK

GeneName	baseMean	log2FoldChan	lfcSE	stat	pvalue	padj
Gm5409	16,667	5,245	0,728	7,206	5,768E-13	4,557E-11
Lrrn4	4,671	5,141	0,804	6,393	1,629E-10	6,998E-09
Klk1b3	10,787	5,122	0,671	7,635	2,257E-14	2,427E-12
Klk1b4	20,959	5,061	0,726	6,967	3,232E-12	2,129E-10
Klk1b5	58,789	5,033	0,710	7,089	1,346E-12	1,006E-10
Ifi44	3,843	5,029	0,832	6,041	1,527E-09	5,260E-08
Hsd17b13	24,175	5,028	0,792	6,349	2,164E-10	8,974E-09
Efs	4,627	5,004	0,791	6,330	2,450E-10	9,986E-09
1810010K12I	6,301	4,990	0,807	6,182	6,330E-10	2,371E-08
Mgll	82,120	4,936	0,288	17,126	9,578E-66	1,597E-61
Serpina10	3,425	4,934	0,881	5,603	2,101E-08	5,456E-07
Tff2	1503,813	4,910	0,458	10,710	9,087E-27	8,416E-24
Egf	4,177	4,903	0,743	6,598	4,159E-11	2,137E-09
Clec3b	12,829	4,903	0,656	7,478	7,560E-14	7,284E-12
Dmbt1	1706,564	4,859	0,756	6,429	1,284E-10	5,752E-09
Try5	24415,253	4,797	0,672	7,132	9,865E-13	7,614E-11
Slc22a1	2,142	4,772	0,882	5,409	6,326E-08	1,459E-06
Cdo1	9,288	4,755	0,740	6,427	1,303E-10	5,806E-09
Arfgef3	13,044	4,746	0,534	8,882	6,559E-19	1,822E-16
Lgals12	2,760	4,741	0,894	5,301	1,152E-07	2,448E-06
Reg2	2485,284	4,739	0,910	5,205	1,939E-07	3,843E-06
Pigr	15,814	4,728	0,856	5,522	3,353E-08	8,444E-07
Gabra4	9,118	4,721	0,552	8,552	1,210E-17	2,507E-15
Car3	124,869	4,718	0,831	5,676	1,375E-08	3,773E-07
Reg3d	144,353	4,712	0,854	5,521	3,373E-08	8,481E-07
2210010C04I	13221,219	4,697	0,676	6,947	3,735E-12	2,404E-10
Klk1	2354,573	4,686	0,669	7,000	2,558E-12	1,748E-10
Zg16	2603,128	4,681	0,738	6,343	2,259E-10	9,275E-09
Cuzd1	399,922	4,671	0,732	6,377	1,811E-10	7,720E-09
Fabp4	50,599	4,644	0,678	6,846	7,585E-12	4,615E-10
Evi2a	8,776	4,631	0,620	7,468	8,131E-14	7,658E-12
Ces1d	8,717	4,627	0,772	5,994	2,052E-09	6,843E-08
Slc7a8	10,733	4,622	0,631	7,322	2,443E-13	2,057E-11
Derl3	73,379	4,617	0,516	8,948	3,634E-19	1,027E-16
Try4	18196,535	4,611	0,763	6,043	1,517E-09	5,246E-08
Spink1	805,989	4,574	0,679	6,734	1,647E-11	9,184E-10
Phactr1	3,188	4,563	0,835	5,463	4,684E-08	1,132E-06
Mettl21b	3,716	4,560	0,853	5,347	8,923E-08	1,957E-06
Lyz1	54,106	4,555	0,757	6,020	1,742E-09	5,938E-08
Rnase1	11068,226	4,551	0,599	7,597	3,036E-14	3,163E-12
Try10	1980,696	4,541	0,614	7,401	1,350E-13	1,210E-11
Bcl11a	4,703	4,524	0,704	6,425	1,321E-10	5,855E-09
Cd209g	0,857	4,519	0,941	4,804	1,554E-06	2,405E-05
Fam13c	2,317	4,514	0,798	5,654	1,570E-08	4,234E-07
Adamts5	9,208	4,507	0,541	8,326	8,343E-17	1,495E-14
Cela3a	5,529	4,494	0,716	6,278	3,434E-10	1,350E-08
Gm13010	1,831	4,487	0,904	4,961	6,996E-07	1,186E-05
Gal	13,013	4,481	0,573	7,826	5,053E-15	6,104E-13
Cela3b	16403,001	4,469	0,597	7,491	6,833E-14	6,701E-12
Cpb1	8677,835	4,457	0,632	7,048	1,815E-12	1,304E-10
4930415O20	3,152	4,456	0,844	5,283	1,273E-07	2,669E-06
Reg3g	369,081	4,455	0,877	5,080	3,783E-07	6,847E-06
Ggt1	41,896	4,446	0,562	7,917	2,426E-15	3,236E-13
Chdh	1,954	4,439	0,888	4,997	5,810E-07	1,008E-05
Reg3a	1206,017	4,433	0,904	4,905	9,354E-07	1,539E-05
Sycn	3117,084	4,432	0,701	6,322	2,589E-10	1,048E-08
Cd209f	5,011	4,432	0,856	5,175	2,284E-07	4,454E-06
Stox2	8,143	4,425	0,643	6,877	6,116E-12	3,748E-10
Fam174b	45,721	4,415	0,508	8,693	3,525E-18	8,517E-16
Clec4a3	12,277	4,413	0,579	7,616	2,615E-14	2,742E-12
Slc12a8	14,622	4,408	0,676	6,521	7,006E-11	3,370E-09
Lama2	5,575	4,405	0,762	5,783	7,357E-09	2,163E-07
Ms4a7	9,651	4,398	0,576	7,629	2,369E-14	2,516E-12
Klk1b11	5,576	4,391	0,814	5,394	6,882E-08	1,569E-06
C4b	142,292	4,379	0,574	7,627	2,407E-14	2,539E-12
P2rx1	31,104	4,379	0,646	6,775	1,243E-11	7,218E-10
Hmgcs2	53,963	4,376	0,666	6,572	4,957E-11	2,482E-09
Atp2c2	13,182	4,376	0,501	8,731	2,525E-18	6,377E-16
Ccr2	18,138	4,366	0,526	8,299	1,047E-16	1,837E-14
Lmo2	5,781	4,362	0,722	6,046	1,484E-09	5,142E-08
Slc16a7	2,601	4,362	0,859	5,076	3,857E-07	6,951E-06
Tmed6	137,285	4,359	0,518	8,411	4,072E-17	7,627E-15
Cd37	18,452	4,346	0,514	8,451	2,895E-17	5,548E-15
Oas1a	2,282	4,341	0,811	5,350	8,819E-08	1,937E-06
Serpini2	110,357	4,321	0,658	6,568	5,097E-11	2,536E-09
F2	3,503	4,315	0,879	4,912	9,034E-07	1,493E-05
Cpa1	15151,565	4,306	0,594	7,255	4,020E-13	3,237E-11
Cldn10	43,729	4,304	0,551	7,808	5,796E-15	6,951E-13
Ces1e	1,743	4,300	0,866	4,967	6,803E-07	1,157E-05
Msmp	2,091	4,296	0,843	5,096	3,463E-07	6,350E-06
Wdfy4	3,105	4,296	0,799	5,374	7,711E-08	1,732E-06
Abca1	7,631	4,294	0,581	7,397	1,394E-13	1,242E-11
Reg1	17300,429	4,287	0,615	6,974	3,091E-12	2,061E-10
Cela2a	1285,250	4,287	0,588	7,292	3,055E-13	2,521E-11

Comparison Pancreas 4 weeks CK-N Dpanc / CK

GeneName	baseMean	log2FoldChan	lfcSE	stat	pvalue	padj
Unc5a	1,559	4,074	0,874	4,663	3,110E-06	4,424E-05
Aoc3	3,689	4,068	0,795	5,115	3,135E-07	5,827E-06
Fetub	12,573	4,064	0,822	4,944	7,635E-07	1,283E-05
Gm2663	73,190	4,053	0,851	4,762	1,921E-06	2,919E-05
Ero1lb	21,495	4,052	0,530	7,651	1,987E-14	2,179E-12
Slit3	13,449	4,052	0,563	7,203	5,888E-13	4,608E-11
Rai2	3,957	4,051	0,787	5,146	2,656E-07	5,055E-06
Tmem116	2,492	4,051	0,802	5,050	4,428E-07	7,878E-06
Thrsp	9,606	4,043	0,842	4,803	1,562E-06	2,416E-05
Mat1a	4,553	4,040	0,792	5,104	3,329E-07	6,145E-06
Cd48	6,286	4,040	0,775	5,215	1,839E-07	3,698E-06
Asb16	1,499	4,038	0,923	4,374	1,217E-05	1,454E-04
Myh13	1,058	4,038	0,919	4,394	1,113E-05	1,346E-04
Ednrb	11,070	4,035	0,528	7,646	2,066E-14	2,236E-12
Erp27	242,834	4,034	0,622	6,485	8,847E-11	4,108E-09
F13a1	27,005	4,029	0,487	8,265	1,396E-16	2,389E-14
Reg3b	4513,974	4,028	0,863	4,670	3,011E-06	4,300E-05
Trpv6	1,568	4,027	0,917	4,393	1,117E-05	1,348E-04
Prss2	40006,349	4,022	0,532	7,562	3,965E-14	4,030E-12
Hpn	31,122	4,018	0,433	9,272	1,834E-20	6,505E-18
Ins2	3457,946	4,017	0,522	7,703	1,334E-14	1,523E-12
Apbb1ip	8,289	4,016	0,699	5,748	9,031E-09	2,600E-07
2610528J11R	3,771	4,015	0,846	4,746	2,070E-06	3,114E-05
Anpep	12,597	4,010	0,662	6,059	1,373E-09	4,799E-08
Tie1	6,001	4,009	0,737	5,437	5,419E-08	1,274E-06
Sp140	4,153	4,005	0,688	5,823	5,793E-09	1,753E-07
Fam13a	8,675	4,000	0,662	6,039	1,549E-09	5,322E-08
Npm1	358,254	-1,603	0,152	-10,579	3,745E-26	3,286E-23
Ppil1	78,371	-1,603	0,244	-6,573	4,941E-11	2,482E-09
Ugdh	68,555	-1,604	0,293	-5,480	4,256E-08	1,045E-06
Rdh10	100,850	-1,616	0,285	-5,666	1,462E-08	3,977E-07
Me1	15,734	-1,618	0,429	-3,773	1,613E-04	1,324E-03
Wdr3	17,506	-1,624	0,379	-4,282	1,850E-05	2,078E-04
Fscn1	82,966	-1,628	0,444	-3,663	2,490E-04	1,913E-03
Cenpe	28,751	-1,630	0,361	-4,516	6,310E-06	8,274E-05
Plscr1	35,948	-1,632	0,390	-4,179	2,934E-05	3,111E-04
Mcm2	37,931	-1,632	0,325	-5,029	4,942E-07	8,691E-06
Elovl6	22,296	-1,633	0,327	-4,990	6,047E-07	1,043E-05
Dnph1	25,805	-1,640	0,335	-4,889	1,012E-06	1,648E-05
Fhl2	33,881	-1,650	0,318	-5,185	2,165E-07	4,246E-06
Nup107	12,312	-1,653	0,437	-3,779	1,575E-04	1,299E-03
Akr1c13	18,450	-1,667	0,435	-3,829	1,288E-04	1,097E-03
Fads3	26,701	-1,671	0,363	-4,608	4,074E-06	5,627E-05
Nop56	31,924	-1,673	0,314	-5,329	9,901E-08	2,146E-06
Akr1b8	42,165	-1,684	0,403	-4,183	2,872E-05	3,050E-04
Slc38a1	22,098	-1,684	0,444	-3,795	1,477E-04	1,231E-03
Shq1	10,873	-1,690	0,460	-3,677	2,356E-04	1,828E-03
Med30	15,010	-1,692	0,416	-4,065	4,806E-05	4,777E-04
Hsd17b14	24,687	-1,700	0,459	-3,705	2,114E-04	1,668E-03
Rpa3	13,852	-1,704	0,426	-3,997	6,427E-05	6,112E-04
Bag2	29,203	-1,704	0,315	-5,415	6,121E-08	1,419E-06
Shcbp1	15,081	-1,704	0,427	-3,992	6,543E-05	6,205E-04
Fosl1	44,016	-1,705	0,385	-4,433	9,287E-06	1,148E-04
Asf1b	27,812	-1,708	0,312	-5,472	4,455E-08	1,083E-06
Myef2	13,471	-1,722	0,411	-4,192	2,760E-05	2,943E-04
Casp3	34,465	-1,725	0,305	-5,648	1,621E-08	4,338E-07
Rrm2	123,415	-1,728	0,274	-6,312	2,747E-10	1,101E-08
Msmo1	75,275	-1,728	0,274	-6,313	2,735E-10	1,098E-08
Cdt1	44,554	-1,736	0,332	-5,225	1,739E-07	3,500E-06
Tcp11l1	21,672	-1,737	0,414	-4,193	2,751E-05	2,938E-04
Ctgf	101,893	-1,741	0,468	-3,722	1,975E-04	1,572E-03
Tipin	27,270	-1,748	0,335	-5,212	1,867E-07	3,738E-06
Bdnf	18,088	-1,756	0,415	-4,227	2,372E-05	2,603E-04
Tk1	44,427	-1,757	0,282	-6,221	4,941E-10	1,894E-08
1700037H04I	50,673	-1,763	0,266	-6,637	3,206E-11	1,697E-09
Anln	12,554	-1,773	0,442	-4,009	6,110E-05	5,857E-04
Foxq1	31,664	-1,782	0,481	-3,706	2,102E-04	1,661E-03
Magohb	21,794	-1,801	0,354	-5,085	3,686E-07	6,715E-06
Cdk2	9,858	-1,814	0,481	-3,770	1,632E-04	1,338E-03
Ncapd2	14,938	-1,819	0,437	-4,166	3,101E-05	3,257E-04
Mcm3	38,093	-1,825	0,313	-5,825	5,726E-09	1,739E-07
Cdk1	42,804	-1,826	0,271	-6,741	1,577E-11	8,941E-10
F2r	52,163	-1,836	0,441	-4,162	3,157E-05	3,308E-04
Hes1	33,469	-1,840	0,358	-5,145	2,676E-07	5,087E-06
Ccna2	54,762	-1,851	0,317	-5,841	5,174E-09	1,588E-07
Tlcd1	23,304	-1,897	0,405	-4,680	2,875E-06	4,135E-05
F2rl1	25,045	-1,922	0,491	-3,913	9,134E-05	8,208E-04
Nup85	35,997	-1,923	0,270	-7,115	1,118E-12	8,508E-11
Ran	84,252	-1,929	0,238	-8,096	5,699E-16	8,559E-14
Cdca7	9,536	-1,934	0,490	-3,947	7,924E-05	7,262E-04
Dbf4	11,118	-1,957	0,473	-4,142	3,448E-05	3,586E-04
Cdca2	14,045	-1,960	0,419	-4,677	2,911E-06	4,180E-05
Psmc3ip	7,664	-1,965	0,537	-3,658	2,542E-04	1,949E-03
Tmem138	13,325	-2,000	0,444	-4,503	6,687E-06	8,655E-05

Ctrl	8807,915	4,269	0,456	9,369	7,291E-21	2,826E-18
Nfasc	13,429	4,269	0,656	6,504	7,841E-11	3,682E-09
Pdia2	775,057	4,255	0,569	7,473	7,860E-14	7,487E-12
Aqp12	116,293	4,239	0,602	7,040	1,924E-12	1,377E-10
Dcn	324,320	4,232	0,358	11,827	2,845E-32	5,584E-29
Gbp3	5,577	4,224	0,737	5,732	9,916E-09	2,834E-07
Abcd2	4,914	4,221	0,782	5,396	6,800E-08	1,557E-06
Pla2g1b	489,374	4,220	0,842	5,012	5,378E-07	9,397E-06
Themis2	5,514	4,216	0,766	5,500	3,792E-08	9,434E-07
2510009E07I	8,646	4,208	0,574	7,326	2,363E-13	1,999E-11
Art3	3,103	4,207	0,832	5,058	4,226E-07	7,559E-06
Tox	5,900	4,190	0,643	6,518	7,142E-11	3,411E-09
Gp2	1169,142	4,182	0,790	5,292	1,209E-07	2,552E-06
Nr5a2	11,210	4,181	0,671	6,236	4,503E-10	1,742E-08
Foxp2	3,459	4,181	0,793	5,270	1,366E-07	2,825E-06
Nsg1	6,704	4,172	0,753	5,542	2,992E-08	7,592E-07
Oasl2	9,909	4,171	0,627	6,657	2,803E-11	1,488E-09
Edaradd	4,960	4,169	0,723	5,763	8,271E-09	2,415E-07
Amy1	39,570	4,160	0,771	5,396	6,812E-08	1,558E-06
Cd93	15,942	4,157	0,486	8,546	1,275E-17	2,531E-15
2210407C18I	8,542	4,157	0,743	5,591	2,253E-08	5,813E-07
Ppp1r3d	2,107	4,150	0,838	4,951	7,380E-07	1,245E-05
Vipr2	2,105	4,150	0,833	4,980	6,359E-07	1,093E-05
Cyfip2	6,651	4,143	0,628	6,598	4,167E-11	2,137E-09
Pnliprp2	1536,180	4,142	0,654	6,332	2,426E-10	9,910E-09
Entpd1	43,085	4,141	0,360	11,500	1,320E-30	2,001E-27
Ctrb1	44223,817	4,139	0,602	6,874	6,255E-12	3,819E-10
Dpt	19,358	4,137	0,667	6,202	5,587E-10	2,131E-08
Srpx	9,353	4,137	0,626	6,612	3,781E-11	1,970E-09
Slco2b1	7,347	4,127	0,633	6,515	7,264E-11	3,450E-09
Trim30d	2,041	4,122	0,909	4,537	5,703E-06	7,587E-05
Ptger3	37,137	4,122	0,432	9,548	1,319E-21	5,944E-19
Ifi27l2a	45,289	4,113	0,688	5,975	2,299E-09	7,605E-08
Myo1g	8,252	4,113	0,742	5,544	2,950E-08	7,496E-07
Klf15	15,953	4,113	0,651	6,322	2,585E-10	1,048E-08
Fxyd1	21,601	4,112	0,441	9,318	1,183E-20	4,285E-18
Slc11a1	5,758	4,107	0,678	6,059	1,372E-09	4,799E-08
Amy2a5	6,541	4,106	0,799	5,140	2,745E-07	5,195E-06
Fcgr1	6,846	4,105	0,609	6,740	1,588E-11	8,973E-10
Slc6a4	2,046	4,102	0,884	4,639	3,500E-06	4,919E-05
Cd36	7,290	4,101	0,777	5,275	1,326E-07	2,755E-06
Slc39a5	51,239	4,097	0,721	5,683	1,326E-08	3,654E-07
Rab11fip4	3,001	4,080	0,712	5,729	1,008E-08	2,863E-07
Fam46c	32,924	4,077	0,484	8,430	3,470E-17	6,574E-15
Adipoq	21,498	4,077	0,904	4,509	6,524E-06	8,496E-05
Dctd	20,957	-2,003	0,368	-5,450	5,038E-08	1,201E-06
Chtf18	10,801	-2,044	0,463	-4,417	1,001E-05	1,225E-04
Acsl3	19,376	-2,053	0,394	-5,212	1,868E-07	3,738E-06
Trip13	17,090	-2,054	0,374	-5,491	4,003E-08	9,901E-07
Tmem171	12,250	-2,057	0,460	-4,473	7,716E-06	9,834E-05
Ckap2l	15,853	-2,082	0,443	-4,702	2,572E-06	3,745E-05
Plk1	44,018	-2,087	0,320	-6,520	7,049E-11	3,377E-09
Ska2	10,814	-2,093	0,532	-3,932	8,408E-05	7,641E-04
Cyr61	39,907	-2,103	0,477	-4,408	1,041E-05	1,269E-04
Ect2	8,802	-2,130	0,507	-4,197	2,705E-05	2,900E-04
Nup93	8,723	-2,156	0,547	-3,942	8,076E-05	7,377E-04
Pnpt1	8,278	-2,163	0,554	-3,903	9,517E-05	8,493E-04
Trim59	19,295	-2,164	0,404	-5,358	8,436E-08	1,867E-06
Cks1b	65,877	-2,168	0,238	-9,118	7,651E-20	2,407E-17
Slc16a1	14,080	-2,174	0,447	-4,860	1,172E-06	1,880E-05
Rbpms2	12,854	-2,185	0,595	-3,673	2,396E-04	1,855E-03
Prim1	12,652	-2,240	0,475	-4,716	2,404E-06	3,524E-05
Hist1h1b	25,673	-2,273	0,444	-5,121	3,036E-07	5,673E-06
Nrn1	17,568	-2,274	0,511	-4,454	8,431E-06	1,062E-04
Gchfr	35,644	-2,280	0,351	-6,505	7,790E-11	3,679E-09
Ffar4	10,029	-2,287	0,568	-4,029	5,608E-05	5,473E-04
Exo1	5,833	-2,302	0,628	-3,665	2,472E-04	1,902E-03
1110038B12I	14,073	-2,303	0,494	-4,660	3,161E-06	4,489E-05
Vsig1	9,763	-2,308	0,581	-3,975	7,039E-05	6,599E-04
Igf2bp1	15,395	-2,310	0,501	-4,613	3,977E-06	5,506E-05
Gtf2h3	10,846	-2,319	0,513	-4,523	6,091E-06	8,039E-05
Slco4a1	12,806	-2,330	0,589	-3,956	7,634E-05	7,051E-04
Kifc1	5,503	-2,381	0,628	-3,788	1,520E-04	1,261E-03
Cdc45	7,574	-2,384	0,585	-4,077	4,553E-05	4,567E-04
Cdkn2a	18,070	-2,441	0,530	-4,606	4,096E-06	5,652E-05
Lpcat4	14,387	-2,493	0,510	-4,891	1,002E-06	1,636E-05
Ccnf	15,680	-2,500	0,491	-5,090	3,586E-07	6,555E-06
Nup37	11,942	-2,517	0,490	-5,134	2,833E-07	5,318E-06
Ptgds	7,856	-2,551	0,575	-4,437	9,126E-06	1,131E-04
Ankrd1	29,011	-2,736	0,475	-5,763	8,269E-09	2,415E-07
Fignl1	7,553	-2,741	0,629	-4,357	1,319E-05	1,553E-04
Foxg1	12,179	-2,811	0,627	-4,485	7,288E-06	9,360E-05
2810408I11R	2,610	-2,915	0,785	-3,715	2,032E-04	1,612E-03
Bora	5,576	-3,014	0,711	-4,236	2,275E-05	2,510E-04
Serp2	4,359	-3,020	0,719	-4,200	2,675E-05	2,882E-04
Fam83d	5,253	-3,148	0,710	-4,430	9,403E-06	1,161E-04
A630076J17F	0,783	-3,261	0,868	-3,755	1,732E-04	1,412E-03
Gm10036	9,848	-3,879	0,770	-5,035	4,790E-07	8,468E-06

Supplementary Table 2: Pancreata from four weeks-old CK-N*ΔPanc* (N=4) and CK mice (N=4) were analyzed by RNA-Seq.
The differentially expressed genes with p adjusted <.02 and with log2 (fold change)>4 and with log2 (fold change) <-1.6 are listed.

Ontology	Jensen TISSUES							
Term	**Overlap**	**P-value**	**Adjusted P-value**	**Old P-value**	**Old Adjusted P-value**	**Z-score**	**Combined Score**	**Genes**
Immune_system	20/1046	0,0002	0,0156	0,0000	0,0007	-6,8202	59,0626	ABCA1;AOC3;PIGR;ENTPD1;CD93;PLA2G1B;EGF;SLC11A1;ADIPOQ;LMO2;GP2;DPT;F2;C4B;FABP4;CTRL;ANPEP;CD48;GGT1;CCR2
Pancreatic_juice	7/33	0,0000	0,0000	0,0000	0,0000	-2,9109	55,4768	CELA3A;REG3A;CELA3B;SPINK1;CPB1;CTRB1;GP2
Plasma_cell	10/286	0,0001	0,0097	0,0000	0,0011	-4,8281	45,4833	C4B;AOC3;PIGR;CLEC3B;LAMA2;ANPEP;SERPINA10;F13A1;FETUB;F2
Artery	10/336	0,0003	0,0205	0,0000	0,0028	-5,3248	43,2069	ABCA1;EDNRB;KLK1;PLA2G1B;P2RX1;ADIPOQ;PTGER3;F2;DCN;CCR2
Blood_vessel_endothelium	7/124	0,0001	0,0093	0,0000	0,0011	-4,0238	39,7144	ABCA1;EDNRB;PLA2G1B;ADIPOQ;F2;DCN;CCR2
Bile	3/18	0,0003	0,0205	0,0002	0,0126	-3,0777	24,5622	PIGR;ANPEP;GGT1
Mesenchymal_stem_cell	5/159	0,0080	0,2164	0,0029	0,0689	-4,3135	20,8169	FABP4;EGF;ANPEP;ADIPOQ;DCN
Atherosclerotic_plaque	4/69	0,0020	0,0913	0,0009	0,0327	-3,1964	19,8183	ABCA1;PLA2G1B;ADIPOQ;CCR2
Urine	3/26	0,0010	0,0536	0,0006	0,0260	-2,4668	16,9403	KLK1;F2;RNASE1
Diseases	Jensen DISEASES							
Term	**Overlap**	**P-value**	**Adjusted P-value**	**Old P-value**	**Old Adjusted P-value**	**Z-score**	**Combined Score**	**Genes**
Pancreatitis	7/84	0,0000	0,0011	0,0000	0,0007	-3,61E+14	4,4790E+15	REG3A;CELA3A;CPA1;CELA3B;SPINK1;CPB1;GGT1
Coronary_artery_disease	9/205	0,0000	0,0044	0,0000	0,0019	-4,29E+15	4,4310E+15	ABCA1;EFS;PLA2G1B;ADIPOQ;PHACTR1;CD36;F2;GGT1;CCR2
Exocrine_pancreatic_insufficiency	3/20	0,0005	0,0428	0,0005	0,0434	-3,21E+15	2,4568E+16	CELA3A;CELA2A;CELA3B
Pathways	Wiki Patways 2016							
Term	**Overlap**	**P-value**	**Adjusted P-value**	**Old P-value**	**Old Adjusted P-value**	**Z-score**	**Combined Score**	**Genes**
DNA Replication_Mus musculus_WP150	8/40	0,0000	0,0000	0,0000	0,0000	-2,17E+16	5,3488E+15	CDT1;DBF4;CDC45;RPA3;PRIM1;CDK2;MCM3;MCM2
G1 to S cell cycle control_Mus musculus_	8/60	0,0000	0,0000	0,0000	0,0000	-1,94E+16	4,1172E+16	CDC45;CDKN2A;RPA3;PRIM1;CDK2;CDK1;MCM3;MCM2
p53 signaling_Mus musculus_WP2902	5/64	0,0000	0,0003	0,0002	0,0049	-1,71E+16	1,8791E+16	RRM2;CDKN2A;CASP3;CDK2;CDK1

Supplementary Table 3.

RNA from pancreata of 4 weeks old CK (N=4) and CK-N$^{\Delta Panc}$ (N=4) mice were sequenced.

The table shows a summary of the differential expression of b-catenin target genes.

	log2FoldChange	pvalue
Axin2	3,25	6,922E-05
Apc	1,35	2,219E-02
Mmp7	1,97	3,748E-06
Cpxm2	1,78	1,200E-03
Wisp2/Ccn5	2,26	0,000E+00
Ccnd1	-1,53	9,008E-10
Myc	-1,60	7,101E-07

Supplementary Table 4: Summary of the histology of the tumors collected from mice of the indicated ***genotype.***

Mouse N	Genotype	Sex	Age (days)	Tumor	Histology				RNAseq
					Adenoca.	Sarcomatoid	Anaplastic	Other	
1	CKP-NΔPanc	m	74	Y	x				x
2	CKP-NΔPanc	f	52	Y	x		x		
3	CKP-NΔPanc	m	71	Y	x		x		x
4	CKP-NΔPanc	m	52	Y			x		x
5	CKP-NΔPanc	f	51	Y	x				x
6	CKP-NΔPanc	m	57	Y	x		x		x
7	CKP-NΔPanc	f	45	leg paralysis	x	x			x
8	CKP-NΔPanc	m	57	Y	*No histology available*				
9	CKP-NΔPanc	m	80	Y	*No histology available*				
10	CKP-NΔPanc	m	76	Y	*No histology available*				
11	CKP-NΔPanc	f	57	Y	x	x			x
12	CKP-NΔPanc	f	22	leg paralysis					
13	CKP-NΔPanc		used for tumor organoids		x				
14	CKP-NΔPanc		used for tumor organoids		x		x		
15	CKP-NΔPanc		used for tumor organoids		x				
1	CKP-Nhet	f	52	Y	x	x			x
2	CKP-Nhet	f	46	Y	x				
3	CKP-Nhet	f	39	Y	x				x
4	CKP-Nhet	m	43	Y	x				x
5	CKP-Nhet	f	40	Y	x				x
6	CKP-Nhet	f	42	Y	x				x
7	CKP-Nhet	f	63	Y					x
8	CKP-Nhet	f	22	Y	x				
9	CKP-Nhet	m	50	Y	x				
10	CKP-Nhet	m	53	Y	x				
11	CKP-NΔPanc		used for tumor organoids		x				
				Tumors					
Sum	CKP-NΔPanc			14,0	10 (7%)	7 (50%)	4 (2.8%)		
Sum	CKP-Nhet			10,0	10 (100%)	2 (20%)	2 (20%)		

Supplementary Table 5: Tumors from CKP-N^{het} (n=6) and CKP-N$^{\Delta Panc}$ (N=7) mice and derived cell lines grown on a thin layer of collagen (N=3/group) were analyzed by RNA-Seq. The differentially expressed genes with p-adjusted <.05 are listed.

Supplementary Table 3

Comparison Tumors CKP-N Dpanc / CKP-Nhet						
GeneName	**baseMean**	**log2FoldChar**	**lfcSE**	**stat**	**pvalue**	**padj**
Mcpt2	34,226	-1,48	0,219	-6,748	0,0000	0,00000
Mcpt1	15,076	-1,36	0,237	-5,735	0,0000	0,00006
Phgr1	23,996	-1,35	0,238	-5,661	0,0000	0,00006
Cwh43	11,722	-1,29	0,232	-5,553	0,0000	0,00008
Ctse	412,983	-0,98	0,186	-5,291	0,0000	0,00029
Cpxm2	40,514	1,12	0,218	5,139	0,0000	0,00047
Krt20	82,730	-0,99	0,191	-5,161	0,0000	0,00047
Car2	42,103	-1,05	0,215	-4,871	0,0000	0,00153
Ifitm1	30,222	1,01	0,207	4,861	0,0000	0,00153
Wisp2	40,051	0,96	0,202	4,758	0,0000	0,00231
Cd24a	315,355	-0,63	0,140	-4,510	0,0000	0,00638
Mgp	435,985	0,94	0,207	4,524	0,0000	0,00638
Elf3	73,820	-0,80	0,179	-4,487	0,0000	0,00639
Tspan32	23,437	0,87	0,195	4,477	0,0000	0,00639
Il33	38,197	1,02	0,235	4,331	0,0000	0,01168
Akr1b7	24,468	-1,01	0,236	-4,278	0,0000	0,01310
Sptssb	9,902	-1,08	0,252	-4,284	0,0000	0,01310
Onecut3	17,514	-0,92	0,216	-4,245	0,0000	0,01438
Pdxdc1	80,828	-0,52	0,124	-4,187	0,0000	0,01760
1700027J19R	93,308	-0,51	0,123	-4,164	0,0000	0,01761
Krt19	1648,828	-0,54	0,130	-4,173	0,0000	0,01761
Ptgis	45,279	0,89	0,215	4,129	0,0000	0,01955
Mest	27,032	-0,94	0,228	-4,111	0,0000	0,02025
St8sia3	19,237	-0,99	0,243	-4,081	0,0000	0,02208
Sftpd	40,346	-1,01	0,249	-4,062	0,0000	0,02302
Dsp	28,531	-0,73	0,182	-3,996	0,0001	0,02928
Mecom	10,172	-0,98	0,246	-3,985	0,0001	0,02958
Kank1	6,790	0,95	0,246	3,854	0,0001	0,04900
Gkn2	6,032	-0,89	0,233	-3,837	0,0001	0,04978
Jam2	13,016	0,82	0,214	3,834	0,0001	0,04978

Comparison Cells CKP-N Dpanc / CKP-Nhet						
GeneName	**baseMean**	**log2FoldChar**	**lfcSE**	**stat**	**pvalue**	**padj**
Nkx6-3	7,380	4,08	0,780	5,229	0,0000	0,00388
Rpl3	66,091	-2,53	0,543	-4,663	0,0000	0,03556

Comparison Cells CKP-N Dpanc / CKP						
GeneName	**baseMean**	**log2FoldChar**	**lfcSE**	**stat**	**pvalue**	**padj**
Gm10036	9,848	-4,45	0,714	-6,228	0,0000	0,00001
Rpl3	66,091	-2,81	0,542	-5,184	0,0000	0,00248
A630076J17I	0,783	-4,26	0,857	-4,973	0,0000	0,00500
Unc13d	4,909	2,80	0,600	4,673	0,0000	0,01694

Comparison Cells CKP-N het / CKP						
GeneName	**baseMean**	**log2FoldChar**	**lfcSE**	**stat**	**pvalue**	**padj**
Cxcl5	90,605	2,97	0,663	4,476	0,0000	0,04346

Supplementary Table 6

List of antibodies used for Western blot, immunohistochemistry and immunofluorescence

Supplementary Table 6

	Company	**Cat Nr**	**Dilution**
immunofluore	Cell signaling	9402	1:1000
YAP	Cell signaling	D8H1X	1:1000
p120ctn	Thermo fisher	339700	1:1000
E-cadherin	Cell signaling	3195	1:500
ACTIN-HRP	Sigma	A3854	1:60.000
ERK1	Santa Cruz	sc-93	1:1000
ERK2	Santa Cruz	sc-154	1:1000
WIP (WIPF1	biobyt	orb318836	1:500
P-ß-CATENI	Cell signaling	9561	1:1000

Immunoistochemistry

Ab	**Company**	**Cat Nr**	**Dilution**
TWIST	Abcam	AB50887	1:250
WIP (WIPF1	biobyt	orb318836	1:400
GSK3ß	Cell signaling	D5C5Z	1:800
P-ß-CATENI	Cell signaling	9561	1:500
KAISO	Merck	05-659	1:500
N-WASP	Abcam	ab126626	1:100
P53	P53-CM5P_L	Leica	1:500

Immunofluorescence

Ab	**Company**	**Cat Nr**	
E-cadherin	Cell signaling	3195	1:200
p120ctn	Thermo fisher	339700	1:200
GSK3ß	Cell signaling	D5C5Z	1:200
KAISO	Merck	05-659	1:200
H3K9me3	Abcam	ab8898	1:500
H3K4me3	Active Motif	39159	1:500

Supplementary Table 7: List of primers used for RT-PCR.

Gene	**Gene Bank ID**	**Forward primer**	**Reverse primer**
c-Myc	NM_001177353.1	AAGCTGGTCTCGGAGAA	GGTTTGCCTCTTCTCCAC
Rplp0 (XS13)	NM_007475.5	TGGGCAAGAACACCATGATG	AGTTTCTCCAGAGCTGGGTTGT
Trp53	NM_001127233.1	agatccgcgggcgtaaac	tctgtagcatgggcatccttt
Cdkn1a	AH011321.2	ccccaaacagaaggaa	ccagacagtccactaa
Wasl	NM_028459.2	GCTCCAAATGGTCCCAATCT	ACATGCCCAATGTGCTGGAA
Ccdn1	NM_007631.2	CTGTGCCACAGATGTGAAGTTC	AGTCCGGGTCACACTTGATGA
p19Arf (Cdkn2a transcript variant 1)	NM_009877.2; NM_001040654.1	GCCGCACCGGAATCCT	TTGAGCAGAAGAGCTGCTGCTACG
p16(INK4a) (;Cdkn2a transcript variant 2)	NM_001040654.1	CCCAACGCCCCGAACT	GCAGAAGAGCTGCTACGTGAA
Wisp2/CCN5	XM_006499169.3	AATTGCAGGGTTTTGTGCCG	CTAGCAAAGGCCGACGTTGT
Rpl3	NM_013762.2	TCGCTCTCTATCTGCGGCG	AATGCCCACAACCACCATTG
Cpxm2	NM_018867.5	TTGGTGTGCTGGTAGGAACG	CCATGTGTGGCTGTCATTGC
Phgr1	NM_001145644.1	TCAGCCTTCCTGTTCCTACTCTA	GCCACCTGGATGCATCTTTACA
Tff2	NM_009363.3	ATGCTCTGGTAGAGGGCGAG	CCACAATTCTTGCGAGCTGA
Zbtb33 (Kaiso)	NM_020256.2	GCGTGGCCATGGTCTCTTT	GGGCCCGGAATTTTCG