

SUPPLEMENTARY METHODS

Acinar Cell Isolation and Culture

Pancreata were harvested from 5 week old mice and digested with 2.5 mg/ml Collagenase D (Roche) at 37°C for 15 minutes. After multiple washes with Phosphate Buffered Saline (PBS) supplemented with 5% Fetal Bovine Serum (FBS), the collagenase digested tissue was filtered through a 100 µm Nylon mesh (BD Biosciences). The filtrate was centrifuged through 20 ml PBS supplemented with 30% FBS. The pellet was resuspended in RPMI1640 Medium (Gibco) supplemented with 10% FBS, penicillin G, streptomycin, 0.1 mg/ml Soybean Trypsin Inhibitor (Sigma-Aldrich), 1 µg/ml dexamethasone (Sigma-Aldrich), 2% Matrigel (BD Biosciences) and 1% glucose. Cells were plated in 24 well plates (4×10^4 cells/well) and maintained with Matrigel at 37°C and 5% CO₂. Medium was changed on day 1 and day 3. At given time points, cells were recovered with Cell Recovery Solution (BD Biosciences).

Primer sequences

The primers used for both quantitative and non quantitative PCR are: human Sin3B forward (5'-AAG CCG GGA AAT TGA TTA TG-3') and reverse (5' - CTC CAA TGG TCA AGC TCC TT -3'), mouse Sin3B forward (5'-AGA GCA TCG ACA CTC CTG GT-3') and reverse (5'-TTG AAG TCC TCC CCA CAG TC-3'), mouse α-Amylase forward (5'- TTC TGC TGC TTT CCC TCA TT-3') and reverse (5'-CAT TGT TGC ACC TTG TCA CC-3'), mouse insulin forward (5'-AAC CAC AAA GGT GCT GCT TGA C-3') and reverse (5'-CCT AAG TGA TCC GCT ACA AT -3'), mouse GAPDH forward (5'-TGC ACC ACC

AAC TGC TTA G-3') and reverse (5'-GGA TGC AGG GAT GAT GTT C-3'), mouse Il-1a forward (5'-TGAG TCG GCA AAG AAA TCA A-3') and reverse (5'-GAG AGA TGG TCA ATG GCA GA -3'), human Il-1a forward (5'-CAG TGC TGC TGA AGG AGA TG-3') and reverse (5'-AGT TTG GAT GGG CAA CTG AT -3'), mouse Il-6 forward (5'-AGA CAA AGC CAG AGT CCT TCA G-3') and reverse (5'-AGC CAC TCC TTC TGT GAC TCC-3'), mouse p15^{INK4B} forward (5'-CGG CGA GGA CCA TTT CTG-3') and reverse (5'-GTT CAG GGC GTT GGG ATC-3'), mouse Dec1 forward (5'-AGC GAA GAC AGC AAG GAA AC-3') and reverse (5'-TCG GGT AGG AGA TCC TTC AG-3'), mouse p53 forward (5'-TGA ACCG CCG ACC TAT CCT TAC C-3') and reverse (5'-CCC AGG GCA GGC ACA AAC AC-3') and mouse p21 forward (5'-CAG ACA TTC AGA GCC ACA GG-3') and reverse (5'-AGA GAC AAC GGC ACA CTT TG-3').

SUPPLEMENTAL FIGURE LEGENDS

Supplementary Figure 1: Related to Figure 1. Genetic inactivation of *Sin3B* delays progression of KRAS^{G12D} driven PanINs.

(A) Paraffin sections of pancreas from *Sin3B*^{+/-}p48-Cre (*Sin3B*^{p+/-}) and *Sin3B*^{-/-}p48-Cre (*Sin3B*^{p-/-}) mice were stained with H&E or antibodies against SIN3B. Scale bar represent 50 μ m.

(B) Quantitative PCR for Sin3B mRNA expression in pancreas from Sin3B^{p+/-} (black bar, n=3) and Sin3B^{p-/-} (gray bar, n=4) pancreas. Sin3B^{p-/-} expression is relative to Sin3B^{p+/-} expression (*p<0.01).

(C) Immunohistochemistry for α -Amylase (Amylase) using paraffin sections of pancreas from Sin3B^{p+/-} and Sin3B^{p-/-} mice. Scale bar represent 50 μ m.

(D) PCR for Sin3B, Insulin, Amylase and Gapdh in 3T3 cells (3T3), Mouse Embryonic fibroblasts (MEF), Wild type (WT) pancreas, Sin3B^{p+/-}, and Sin3B^{p-/-} pancreas.

(E) Immunohistochemistry for Sin3B using paraffin sections of pancreas obtained from 8 week old Sin3B^{p+/-}Kras^{pG12D} and Sin3B^{p-/-}Kras^{pG12D} mice. Scale bar represent 50 μ m.

(F) Quantitative PCR for Sin3B expression in pancreas obtained from Sin3B^{p+/-}Kras^{pG12D} (black bar, n=5) and Sin3B^{p-/-}Kras^{pG12D} (gray bar, n=4) pancreas. Sin3B^{p-/-}Kras^{pG12D} expression is relative to Sin3B^{p+/-}Kras^{pG12D} expression (*p<0.0001).

(G) Immunohistochemistry for Sin3B using paraffin sections of pancreas obtained from 12 month-old sick animals Sin3B^{p+/-}Kras^{pG12D} and Sin3B^{p-/-}Kras^{pG12D} mice. Scale bar represent 50 μ m.

Supplementary Figure 2: Related to figure 2. *Sin3B* deletion impairs the establishment but not the initiation of acinar-to-ductal metaplasia in vivo.

(A) H&E of paraffin sections from 5 week old *Sin3B^{p+/-}Kras^{pG12D}* and *Sin3B^{p-/-}Kras^{pG12D}* mice used for acinar 3D cultures. Scale bar represent 50 μ m.

(B) Quantitative PCR for *Sin3B* mRNA expression in acinar 3D cultures obtained from *Sin3B^{p+/-}Kras^{pG12D}* and *Sin3B^{p-/-}Kras^{pG12D}* mouse pancreas one day (d1), 3 days (d3) and 5 days (d5) after plating in 3D culture. Black bars represent *Sin3B^{p+/-}Kras^{pG12D}* cells and gray bars represent *Sin3B^{p-/-}Kras^{pG12D}* cells. *Sin3B^{p-/-}Kras^{pG12D}* levels for *Sin3B* are relative to *Sin3B^{p+/-}Kras^{pG12D}* levels. *p<0.001 for d1, *p<0.05 for d3 and *p<0.001 for d5.

Supplementary Figure 3: Related to figure 3. *Sin3B* deletion impairs oncogene KRAS-induced senescence in vivo.

(A) Immunohistochemistry for Phospho-HP1 γ (P-HP1 γ) on paraffin sections of 24 week old *Sin3B^{p+/-}Kras^{pG12D}* and *Sin3B^{p-/-}Kras^{pG12D}* pancreata.. Scale bar represent 50 μ m.

(B) Immunohistochemistry for Sin3B and DEC1 on one 12 month old *Sin3B^{p+/-}Kras^{pG12D}* and three different 12 month-old *Sin3B^{p-/-}Kras^{pG12D}* pancreata. Scale bar represent 50 μ m.

Supplementary Figure 4: Related to figure 4. Loss of SIN3B mitigates oncogenic KRAS-driven inflammatory response in vivo.

- (A) Immunohistochemistry for phosphorylated-STAT3 (P-STAT3), phosphorylated-ERK1/2 (P-ERK1/2) and active P65 staining of 6 week old *Sin3B^{p+/-}Kras^{pG12D}* and *Sin3B^{p-/-}Kras^{pG12D}* pancreata. Scale bar represent 50 μ m.
- (B) Western Blot for phosphorylated-ERK1/2 (P-ERK1/2) and total ERK1/2 and for phosphorylated-Stat3 (P-STAT3) and total STAT3 on *Sin3B^{p+/-}Kras^{pG12D}* and *Sin3B^{p-/-}Kras^{pG12D}* 6 week and 24 week old pancreata. Lanes were run on the same gel but were noncontiguous.
- (C) Quantitative PCR for *Il-1a* and *Il-6* mRNA expression in pancreas obtained from 6 to 12 month (6-12 months) and 12 month *Sin3B^{p+/-}Kras^{pG12D}* and *Sin3B^{p-/-}Kras^{pG12D}* mice. Black bars represent *Sin3B^{p+/-}Kras^{pG12D}* pancreas and grey bars represent *Sin3B^{p-/-}Kras^{pG12D}* pancreas. *Sin3B^{p-/-}Kras^{pG12D}* mRNA expression are relative to the *Sin3B^{p+/-}Kras^{pG12D}* expression.

Supplementary Figure 5: Related to Figure 5. SIN3B is required for cell autonomous *Il-1a* expression.

- (A) Pie chart showing the percentage of genes related to the immune system, which are down-regulated (left) and up-regulated (right) in *Sin3B^{p-/-}Kras^{pG12D}* pancreas. This was made using the pie chart viewer from the Panther Classification System.
- (B) Quantitative PCR for *Il-6* mRNA expression in pancreatic duct cell (PDEC) cultures obtained from *Sin3B^{p+/-}Kras^{pG12D}* and *Sin3B^{p-/-}Kras^{pG12D}* pancreas. Black

bars represent $Sin3B^{p+/-} Kras^{pG12D}$ PDEC lines and gray bars represent $Sin3B^{p-/-} Kras^{pG12D}$ PDEC lines. $Sin3B^{p-/-} Kras^{pG12D}$ mRNA levels are relative to $Sin3B^{p+/-} Kras^{pG12D}$ levels.

(C) Quantitative PCR for *Il-6* mRNA expression in acinar 3D cultures obtained from $Sin3B^{p+/-} Kras^{pG12D}$ and $Sin3B^{p-/-} Kras^{pG12D}$ mice one day (d1), 3 days (d3) and 5 days (d5) after plating in 3D culture. Black bars represent $Sin3B^{p+/-} Kras^{pG12D}$ cells and gray bars represent $Sin3B^{p-/-} Kras^{pG12D}$ cells. $Sin3B^{p-/-} Kras^{pG12D}$ mRNA levels are relative to $Sin3B^{p+/-} Kras^{pG12D}$ levels.

Supplementary Figure 6: IL-1 α expression correlates with senescence in the pancreas.

(A) Kaplan Meier Survival curve of $Sin3B^{p+/-} Kras^{pG12D} Ink4a^{p-/-}$ mice (black, n=23) and $Sin3B^{p-/-} Kras^{pG12D} Ink4a^{p-/-}$ mice (red, n=14).

(B) H&E staining on $Sin3B^{p+/-} Kras^{pG12D} Ink4a^{p-/-}$ and $Sin3B^{p-/-} Kras^{pG12D} Ink4a^{p-/-}$ pancreata. Scale bar represent 50 μ m.

(C) Immunohistochemistry for CK19 on $Sin3B^{p+/-} Kras^{pG12D} Ink4a^{p-/-}$ and $Sin3B^{p-/-} Kras^{pG12D} Ink4a^{p-/-}$ pancreata. Scale bar represent 50 μ m.

(D) Cryogenic sections stained for Senescence-associated β -galactosidase (SA- β -GAL) on $Sin3B^{p+/-} Kras^{pG12D} Ink4a^{p-/-}$ and $Sin3B^{p-/-} Kras^{pG12D} Ink4a^{p-/-}$ pancreata. Scale bar represent 50 μ m.

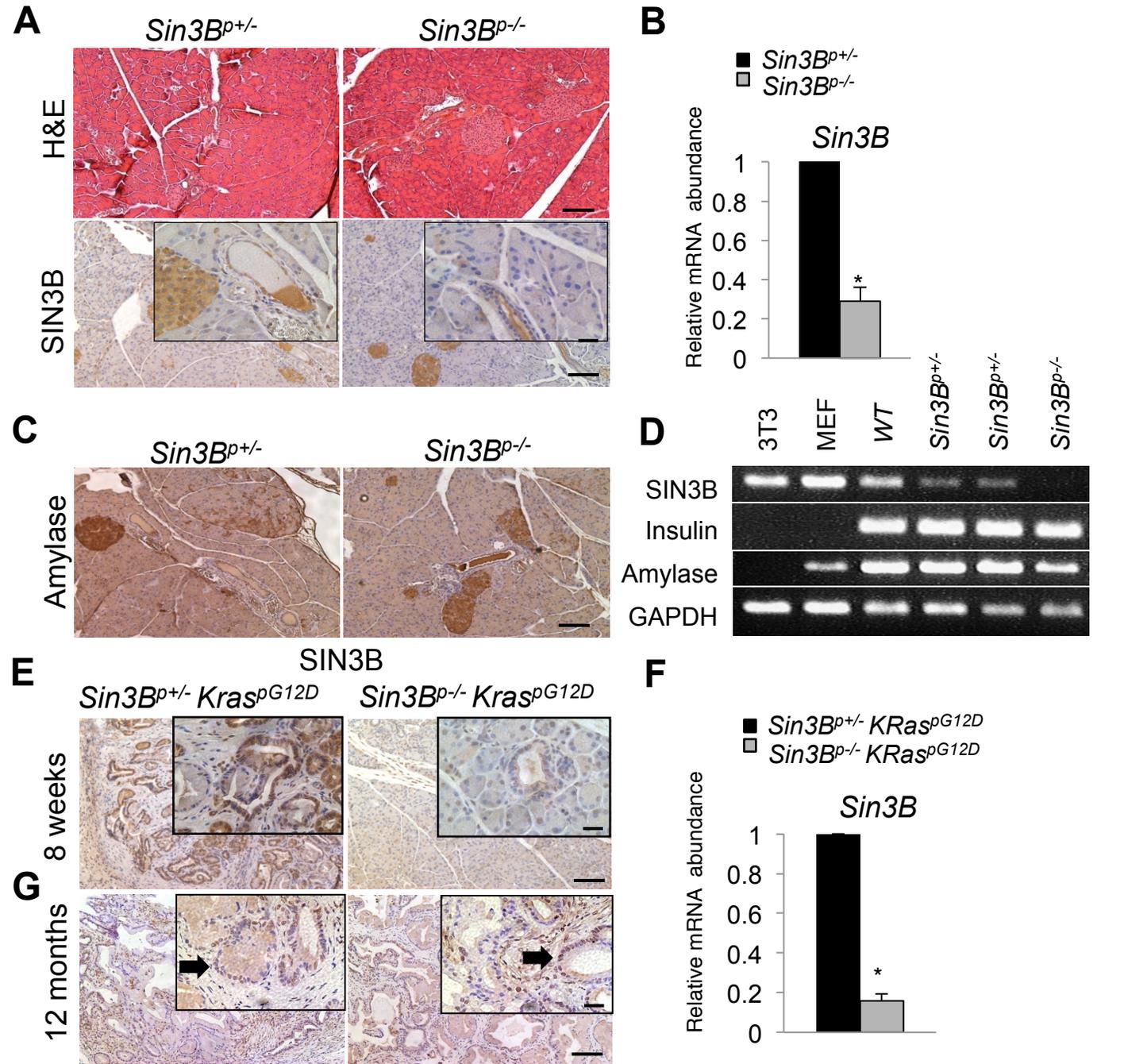
(E) Quantitative PCR for $p15^{INK4B}$ and *Dec1* mRNA expression in pancreas obtained from $Sin3B^{p+/-}Kras^{pG12D}$ (black bars, n=3), $Sin3B^{p+/-}Kras^{pG12D}Ink4a^{p-/-}$ (gray bars, n=3) and $Sin3B^{p-/-}Kras^{pG12D}Ink4a^{p-/-}$ (dark gray bars, n=2) mice. $Sin3B^{p+/-}Kras^{pG12D}Ink4a^{p-/-}$ and $Sin3B^{p-/-}Kras^{pG12D}Ink4a^{p-/-}$ values are relative to $Sin3B^{p+/-}Kras^{pG12D}$ value. *Dec1* (ND: not detected). $p15^{INK4B}$ (*p<0.05).

(F) Immunohistochemistry for CD45 and F4/80 on $Sin3B^{p+/-}Kras^{pG12D}Ink4a^{p-/-}$ and $Sin3B^{p-/-}Kras^{pG12D}Ink4a^{p-/-}$ pancreata. Scale bar represent 50 μ m.

(G) Quantitative PCR for *Il-6* and *Il-1a* mRNA expression in pancreas obtained from $Sin3B^{p+/-}Kras^{pG12D}$ (black bars, n=3), $Sin3B^{p+/-}Kras^{pG12D}Ink4a^{p-/-}$ (grey bars, n=3) and $Sin3B^{p-/-}Kras^{pG12D}Ink4a^{p-/-}$ (dark gray bars, n=2) mice. $Sin3B^{p+/-}Kras^{pG12D}Ink4a^{p-/-}$ and $Sin3B^{p-/-}Kras^{pG12D}Ink4a^{p-/-}$ values are relative to $Sin3B^{p+/-}Kras^{pG12D}$ values. ND: not detected.

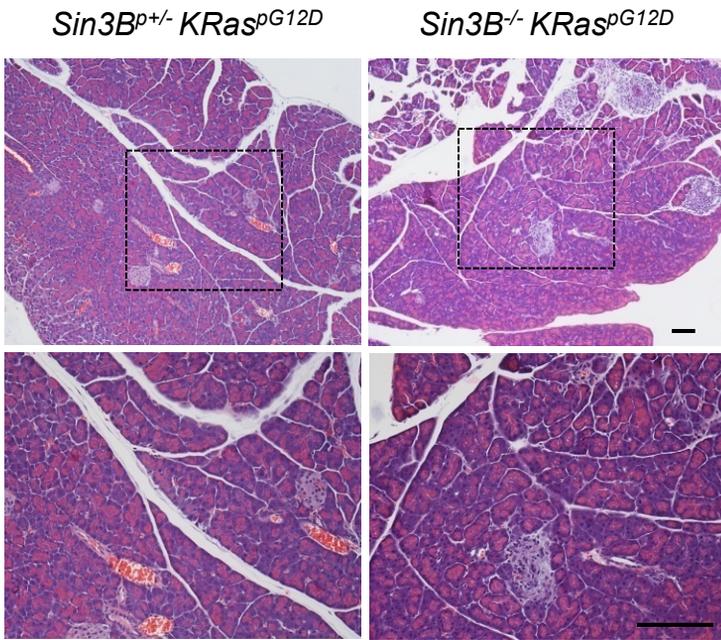
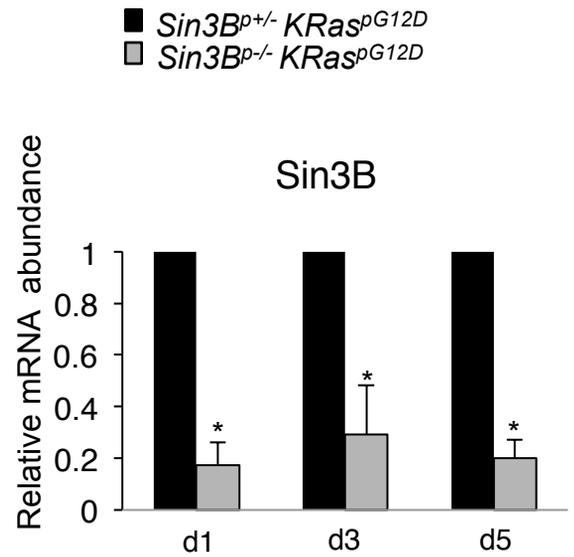
Supplementary Figure 7: Related to Figure 6. SIN3B levels correlate with an inflammatory response in both human pancreatic tissue and cancer cells.

Quantitative PCR for *SIN3B* (*p<0.005) and *IL-1 α* (*p<0.05) mRNA expression in BxPc3 cells infected with empty vector (black bars) or a shRNA against *SIN3B* (shSIN3B, gray bars). shSIN3B mRNA levels are relative to empty vector levels.



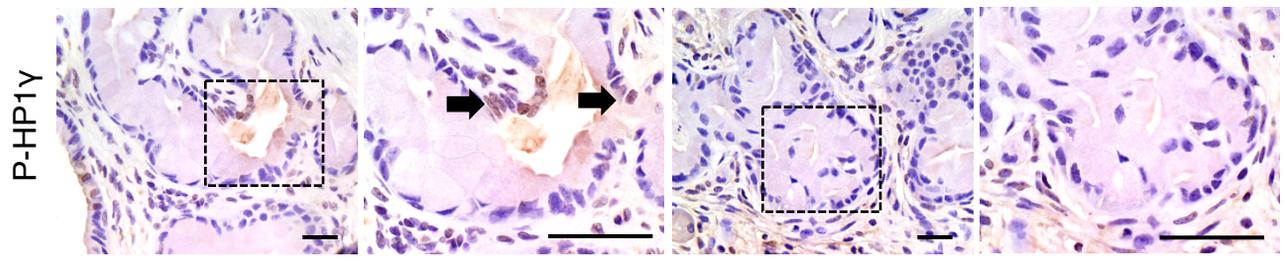
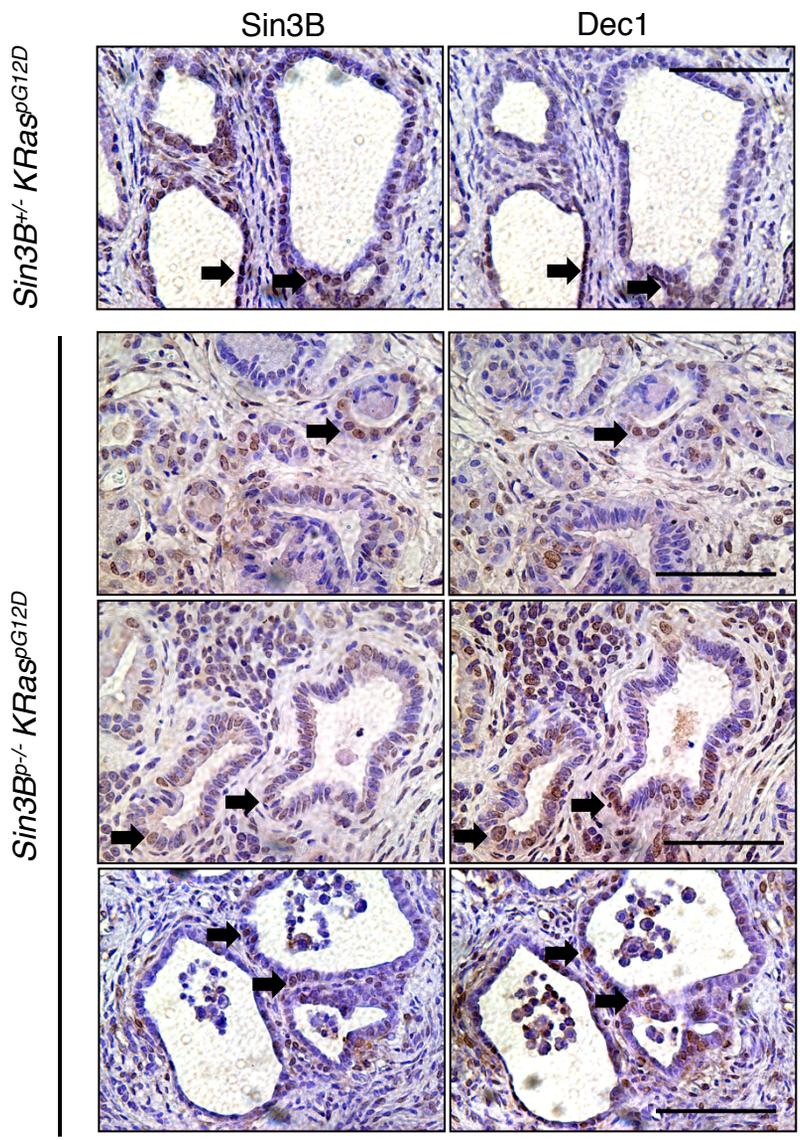
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(A) Paraffin sections of pancreas from *Sin3B*^{p+/+}p48-Cre (*Sin3B*^{p+/+}) and *Sin3B*^{p-/-}p48-Cre (*Sin3B*^{p-/-}) mice were stained with H&E or antibodies against SIN3B. Scale bar represent 50 μ m. (B) Quantitative PCR for *Sin3B* mRNA expression in pancreas from *Sin3B*^{p+/+} (black bar, n=3) and *Sin3B*^{p-/-} (gray bar, n=4) pancreas. *Sin3B*^{p-/-} expression is relative to *Sin3B*^{p+/+} expression (*p<0.01). (C) Immunohistochemistry for α -Amylase (Amylase) using paraffin sections of pancreas from *Sin3B*^{p+/+} and *Sin3B*^{p-/-} mice. Scale bar represent 50 μ m. (D) PCR for *Sin3B*, *Insulin*, *Amylase* and *Gapdh* in 3T3 cells (3T3), Mouse Embryonic fibroblasts (MEF), Wild type (WT) pancreas, *Sin3B*^{p+/+}, and *Sin3B*^{p-/-} pancreas. (E) Immunohistochemistry for *Sin3B* using paraffin sections of pancreas obtained from 8 week old *Sin3B*^{p+/+} *Kras*^{pG12D} and *Sin3B*^{p-/-} *Kras*^{pG12D} mice. Scale bar represent 50 μ m. (F) Quantitative PCR for *Sin3B* expression in pancreas obtained from *Sin3B*^{p+/+} *Kras*^{pG12D} (black bar, n=5) and *Sin3B*^{p-/-} *Kras*^{pG12D} (gray bar, n=4) pancreas. *Sin3B*^{p-/-} *Kras*^{pG12D} expression is relative to *Sin3B*^{p+/+} *Kras*^{pG12D} expression (*p<0.0001). (G) Immunohistochemistry for *Sin3B* using paraffin sections of pancreas obtained from 12 month-old sick animals *Sin3B*^{p+/+} *Kras*^{pG12D} and *Sin3B*^{p-/-} *Kras*^{pG12D} mice. Scale bar represent 50 μ m.

A**B**

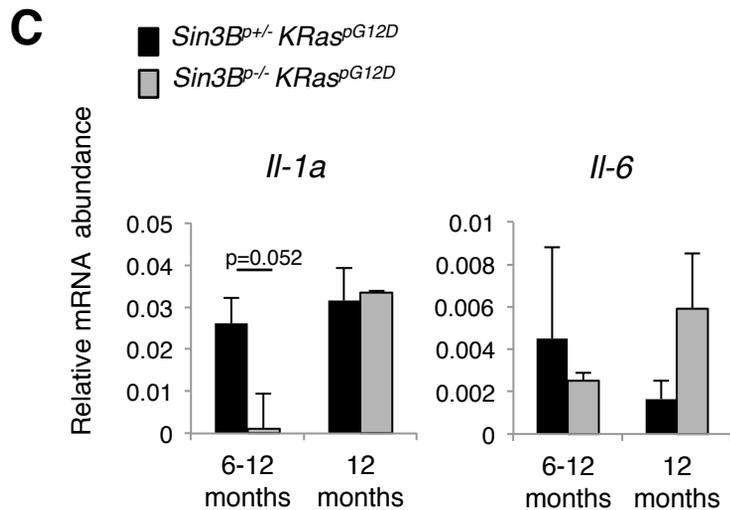
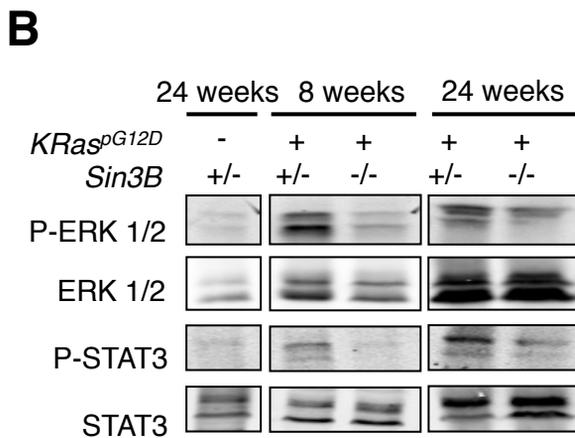
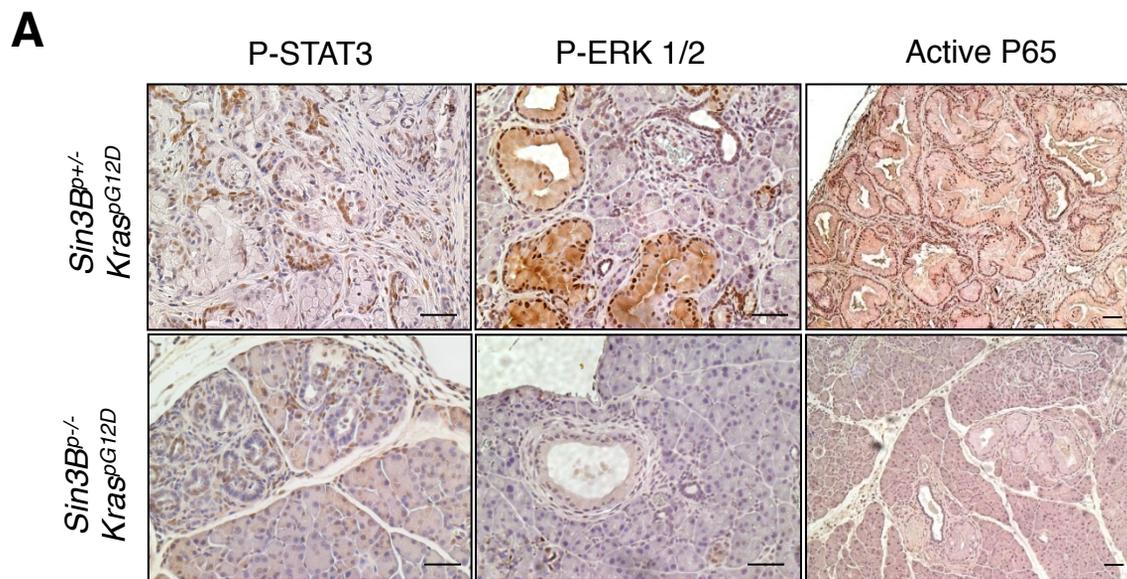
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(A) &E of paraffin sections from 5 week old *Sin3B*^{+/+} *Kras*^{pG12D} and *Sin3B*^{-/-} *Kras*^{pG12D} mice used for acinar 3D cultures. Scale bar represent 50 μ m. (B) Quantitative PCR for *Sin3B* mRNA expression in acinar 3D cultures obtained from *Sin3B*^{+/+} *Kras*^{pG12D} and *Sin3B*^{-/-} *Kras*^{pG12D} mouse pancreas one day (d1), 3 days (d3) and 5 days (d5) after plating in 3D culture. Black bars represent *Sin3B*^{+/+} *Kras*^{pG12D} cells and gray bars represent *Sin3B*^{-/-} *Kras*^{pG12D} cells. *Sin3B*^{-/-} *Kras*^{pG12D} levels for *Sin3B* are relative to *Sin3B*^{+/+} *Kras*^{pG12D} levels. * $p < 0.001$ for d1, * $p < 0.05$ for d3 and * $p < 0.001$ for d5.

A*Sin3B^{p/+} Kras^{pG12D}**Sin3B^{p/-} Kras^{pG12D}***B**

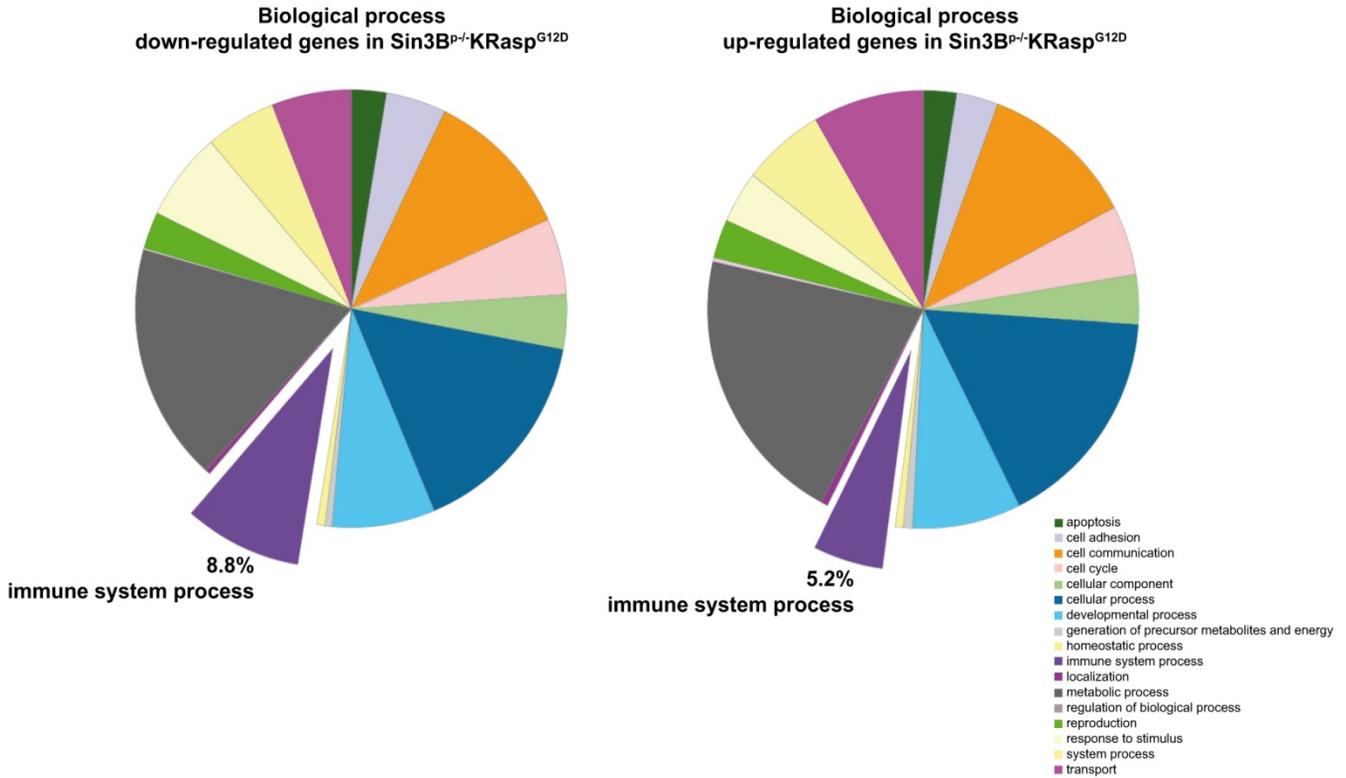
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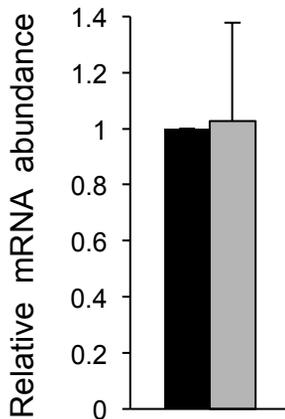


Supplementary Figure 4: Related to figure 4. Loss of SIN3B mitigates oncogenic KRAS-driven inflammatory response in vivo

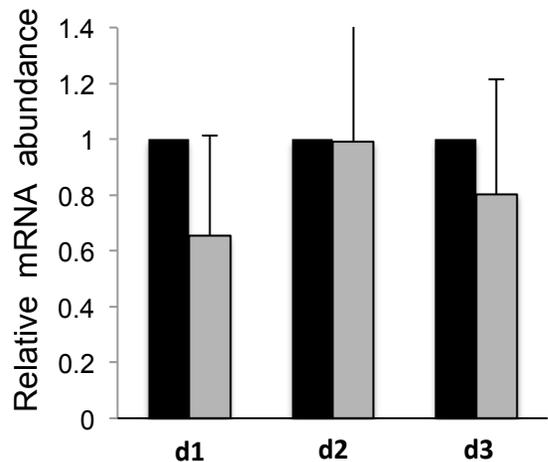
(A) Immunohistochemistry for phosphorylated-STAT3 (P-STAT3), phosphorylated-ERK1/2 (P-ERK1/2) and active P65 staining of 6 week old *Sin3B^{+/+}*-*Kras^{pG12D}* and *Sin3B^{-/-}*-*Kras^{pG12D}* pancreata. Scale bar represent 50 μ m. (B) Western Blot for phosphorylated-ERK1/2 (P-ERK1/2) and total ERK1/2 and for phosphorylated-Stat3 (P-STAT3) and total STAT3 on *Sin3B^{+/+}*-*Kras^{pG12D}* and *Sin3B^{-/-}*-*Kras^{pG12D}* 6 week and 24 week old pancreata. Lanes were run on the same gel but were noncontiguous. (C) Quantitative PCR for *Il-1a* and *Il-6* mRNA expression in pancreas obtained from 6 to 12 month (6-12 months) and 12 month *Sin3B^{+/+}*-*Kras^{pG12D}* and *Sin3B^{-/-}*-*Kras^{pG12D}* mice. Black bars represent *Sin3B^{+/+}*-*Kras^{pG12D}* pancreas and grey bars represent *Sin3B^{-/-}*-*Kras^{pG12D}* pancreas. *Sin3B^{-/-}*-*Kras^{pG12D}* mRNA expression are relative to the *Sin3B^{+/+}*-*Kras^{pG12D}* expression.

A**B**

■ $Sin3B^{p+/-}Kras^{pG12D}$
 ■ $Sin3B^{p-/-}Kras^{pG12D}$

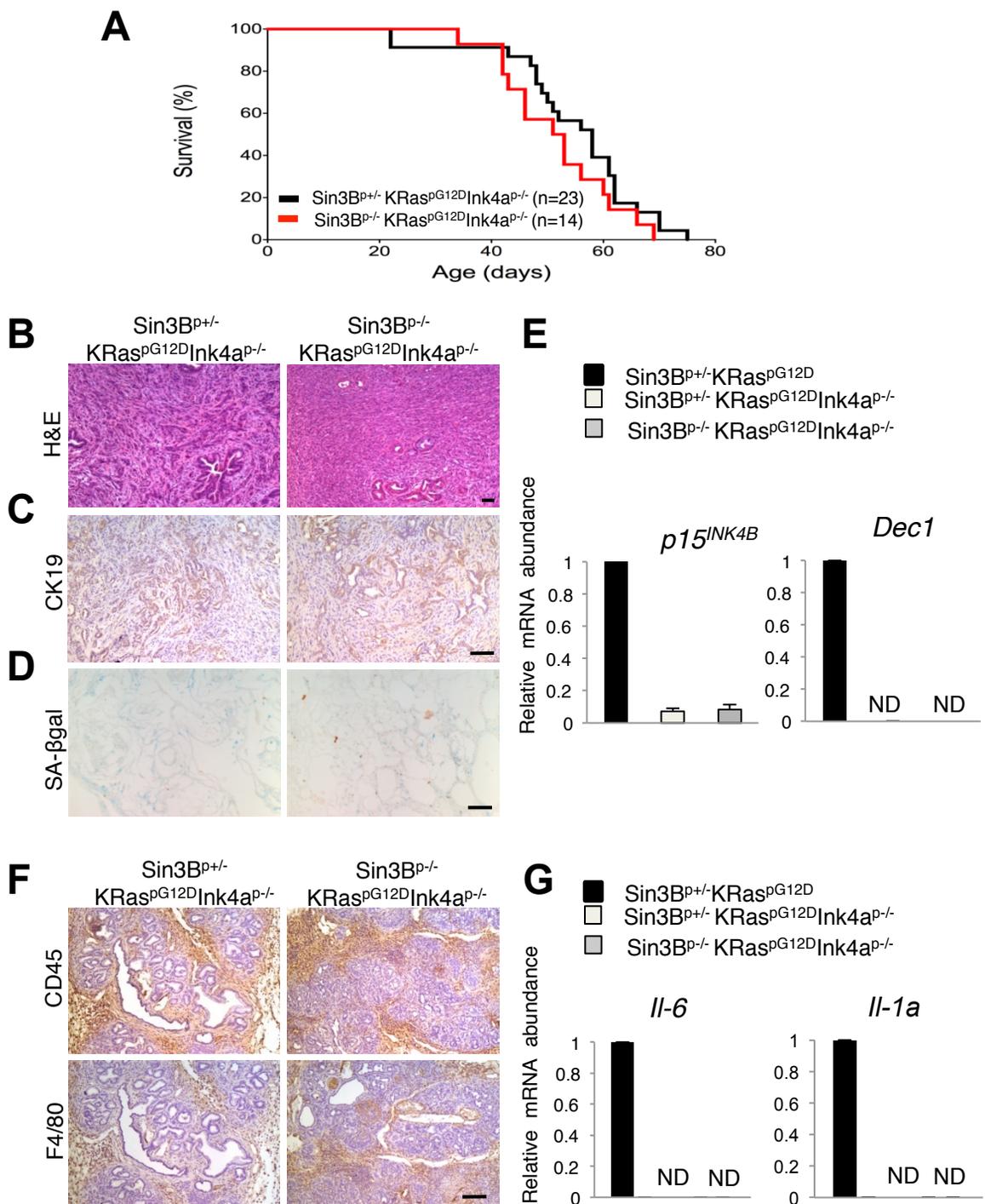
Il-6**C**

■ $Sin3B^{p+/-}Kras^{pG12D}$
 ■ $Sin3B^{p-/-}Kras^{pG12D}$

Il-6

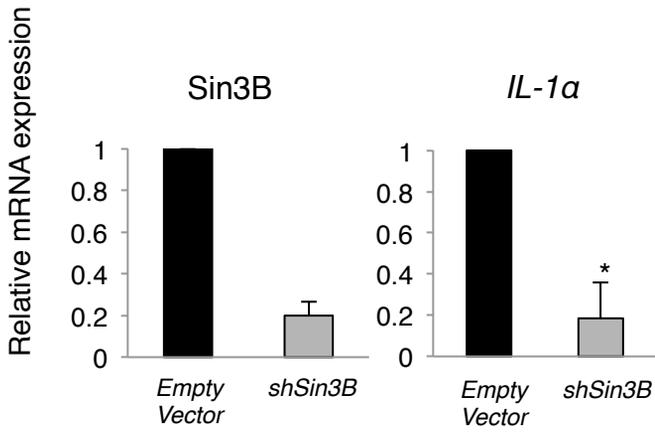
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(A) Pie chart showing the percentage of genes related to the immune system, which are down-regulated (left) and up-regulated (right) in $Sin3B^{p-/-}Kras^{pG12D}$ pancreas. This was made using the pie chart viewer from the Panther Classification System. (B) Quantitative PCR for *Il-6* mRNA expression in pancreatic duct cell (PDEC) cultures obtained from $Sin3B^{p+/-}Kras^{pG12D}$ and $Sin3B^{p-/-}Kras^{pG12D}$ pancreas. Black bars represent $Sin3B^{p+/-}Kras^{pG12D}$ PDEC lines and gray bars represent $Sin3B^{p-/-}Kras^{pG12D}$ PDEC lines. $Sin3B^{p-/-}Kras^{pG12D}$ mRNA levels are relative to $Sin3B^{p+/-}Kras^{pG12D}$ levels. (C) Quantitative PCR for *Il-6* mRNA expression in acinar 3D cultures obtained from $Sin3B^{p+/-}Kras^{pG12D}$ and $Sin3B^{p-/-}Kras^{pG12D}$ mice one day (d1), 3 days (d3) and 5 days (d5) after plating in 3D culture. Black bars represent $Sin3B^{p+/-}Kras^{pG12D}$ cells and gray bars represent $Sin3B^{p-/-}Kras^{pG12D}$ cells. $Sin3B^{p-/-}Kras^{pG12D}$ mRNA levels are relative to $Sin3B^{p+/-}Kras^{pG12D}$ levels.



Supplementary Figure 6: IL-1 α expression correlates with senescence in the pancreas

(A) Kaplan Meier Survival curve of *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} mice (black, n=23) and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} mice (red, n=14). (B) H&E staining on *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} pancreata. Scale bar represent 50 μ m. (C) Immunohistochemistry for CK19 on *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} pancreata. Scale bar represent 50 μ m. (D) Cryogenic sections stained for Senescence-associated β -galactosidase (SA- β -GAL) on *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} pancreata. Scale bar represent 50 μ m. (E) Quantitative PCR for *p15^{INK4B}* and *Dec1* mRNA expression in pancreas obtained from *Sin3B*^{+/+}*Kras*^{pG12D} (black bars, n=3), *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} (gray bars, n=3) and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} (dark gray bars, n=2) mice. *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} values are relative to *Sin3B*^{+/+}*Kras*^{pG12D} value. *Dec1* (ND: not detected). *p15^{INK4B}* (* p <0.05). (F) Immunohistochemistry for CD45 and F4/80 on *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} pancreata. Scale bar represent 50 μ m. (G) Quantitative PCR for *Il-6* and *Il-1 α* mRNA expression in pancreas obtained from *Sin3B*^{+/+}*Kras*^{pG12D} (black bars, n=3), *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} (grey bars, n=3) and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} (dark gray bars, n=2) mice. *Sin3B*^{+/+}*Kras*^{pG12D}*Ink4a*^{p-/-} and *Sin3B*^{-/-}*Kras*^{pG12D}*Ink4a*^{p-/-} values are relative to *Sin3B*^{+/+}*Kras*^{pG12D} values. ND: not detected.



Supplementary Figure 7: Related to Figure 6. SIN3B levels correlates with an inflammatory response in both human pancreatic tissue and cancer cells

Quantitative PCR for *SIN3B* (* $p < 0.005$) and *IL-1 α* (* $p < 0.05$) mRNA expression in BxPc3 cells infected with empty vector (black bars) or a shRNA against *SIN3B* (shSIN3B, gray bars). shSIN3B mRNA levels are relative to empty vector levels.

Supplementary Table 1: Information of animals used for survival curve

mouse number	genotype	date of birth	date of death	number of days of survival	status ^A
937	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	9/26/2012	5/29/2013	245	S
895	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	9/5/2012	5/29/2013	266	S
805	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	8/8/2012	5/29/2013	294	A
799	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	8/5/2012	5/15/2013	283	D
796	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	7/31/2012	5/29/2013	302	A
741	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	7/15/2012	5/29/2013	318	A
687	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	6/19/2012	5/29/2013	344	S
550	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	4/29/2012	10/23/2012	177	S
624	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	6/2/2012	5/29/2013	361	A
627	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	6/2/2012	5/29/2013	361	S
611	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	5/23/2012	5/15/2013	357	S
605	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	5/23/2012	2/8/2013	261	A
568	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	5/11/2012	11/18/2012	191	D
576	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	5/10/2012	11/29/2012	203	A
536	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	4/23/2012	4/26/2013	368	S
540	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	4/23/2012	4/26/2013	368	S
509	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	4/11/2012	4/19/2013	373	S
429	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	2/28/2012	12/26/2012	302	D
407	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	2/25/2012	12/18/2012	297	D
381	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	2/15/2012	2/19/2013	370	A
47	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	7/7/2011	5/5/2012	303	D
265	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	8/22/2011	6/20/2012	303	S
2	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	6/8/2011	4/10/2012	307	A
115	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	8/22/2011	7/10/2012	323	A
242	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	12/23/2011	12/26/2012	369	S
99	<i>Sin3B</i> ^{p-/-} <i>KRas</i> ^{pG12D}	9/29/2011	10/9/2012	376	A
941	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	9/26/2012	5/29/2013	245	S
894	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	9/5/2012	5/29/2013	266	D
942	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	9/26/2012	5/29/2013	245	S
855	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	8/22/2012	2/12/2013	174	S
857	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	8/22/2012	3/5/2013	195	S
821	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	8/12/2012	5/29/2013	290	A
822	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	8/12/2012	5/15/2013	276	A
788	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	8/1/2012	5/29/2013	301	A
791	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	8/1/2012	5/29/2013	301	A
778	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	7/24/2012	5/29/2013	309	S
664	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	6/1/2012	10/16/2012	137	S
671	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	6/16/2012	11/22/2012	159	S
379	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	2/15/2012	7/24/2012	160	S
690	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	6/19/2012	5/29/2013	344	S
426	<i>Sin3B</i> ^{p+/-} <i>KRas</i> ^{pG12D}	2/27/2012	8/15/2012	170	A

645	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	6/11/2012	5/29/2013	352	A
77	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	12/5/2011	5/25/2012	172	D
658	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	6/10/2012	5/29/2013	353	S
652	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	6/10/2012	5/29/2013	353	A
664	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	6/1/2012	5/29/2013	362	S
45	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	7/7/2011	1/10/2012	187	D
216	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	12/9/2011	6/20/2012	194	A
219	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	12/9/2011	6/20/2012	194	A
400	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	2/21/2012	9/7/2012	199	A
570	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	5/11/2012	5/15/2013	369	A
403	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	2/21/2012	9/21/2012	213	A
549	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	4/29/2012	12/21/2012	236	S
551	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	4/29/2012	4/26/2013	362	A
553	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	4/29/2012	4/26/2013	362	A
498	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	4/5/2012	4/19/2013	379	S
65	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	8/17/2011	4/13/2012	240	A
196	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	11/23/2011	8/4/2012	255	S
70	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	8/22/2011	5/25/2012	277	S
389	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	2/19/2012	12/14/2012	299	A
390	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	2/19/2012	1/29/2013	345	A
160	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	11/10/2011	9/7/2012	302	A
200	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	11/23/2011	9/21/2012	303	A
226	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	12/16/2011	11/28/2012	348	A
59	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	8/17/2011	8/15/2012	364	A
66	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	8/17/2011	8/15/2012	364	A
3	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	6/8/2011	7/10/2012	398	A
46	<i>Sin3B^{p+/-}-KRas^{pG12D}</i>	6/8/2011	7/10/2012	398	A

^A A: autopsy (see Supplementary Table 2-3); D: animal died; S: animal sacrificed

Supplementary Table 2: Description of 6 - 12 month old sacrificed animals

mouse number	genotyping	age at death in months	mouse description at autopsy	acini (%)	precursor lesions present	number of tumors per biopsy	number of lymph nodes per biopsy ^A	presence of duodenal tissue in biopsy ^A	presence of colonic tissue in biopsy ^A	description of invasive tumors
216	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	6	mice ill appearing with enlarged abdomen; pancreas was tough and granular	0	PanINs	1	4/neg	no	no	
219	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	6	mouse ill appearing, pancreas tough and granular; no visible pancreatic tumors	0	PanINs	0	0	no	no	
426	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	6	mouse ill appearing, pancreas was white and granular, tumor present in middle of the pancreas	0	PanINs	0	3/neg	no	no	
422	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	6	mouse healthy appearing, pancreas was tough and granular	0	PanINs	3	2/neg	yes/neg	no	
389	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	10	mouse ill appearing, pancreas was tough and granular and fused with the small intestine	0	PanINs	1 (invasive)	2/neg	no	yes/neg	ADENOCARCINOMA. TUBULAR, WELL TO MODERATLY DIFFERENTIATED, SCHIROUS STROMA
822	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	9	mouse ill appearing, pancreas was tough and granular	1	PanINs	2	1/neg	no	yes/neg	
65	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	8	mouse ill appearing, pancreas was tough and granular	0	PanINs	0	1/neg	no	no	
160	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	10	mouse ill appearing, pancreas was granular, pancreas fused with the small intestine and with the omentum, invaded the bile duct, multiple tumors present in the pancreas, metastasis visible in the liver	0	PanINs	1 (invasive)	0	yes/invaded	no	ADENOCARCINOMA. TUBULAR AND PAPILLARY, MODERATLY TO POORLY DIFFERENTIATED, SCHIROUS STROMA
400	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	7	mouse ill appearing, pancreas tough and granular, cyst present in pancreatic tail	1	PanINs and large retention cyst	4	2/neg	yes/neg	no	
403	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	7	mouse ill appearing, pancreas granular and started to fuse with small intestine	0	PanINs	2	5/ neg	yes/neg	no	
200	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	11	mouse ill appearing, pancreas was tough and granular, pancreas fused with small intestine	0	PanINs	3	1/neg	yes/neg	no	
2	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	10	mouse ill appearing, pancreas was tough and granular, visible tumor in the pancreas.	40	PanINs	1 (invasive) and 2 (small)	1/neg	yes/neg	no	ADENOCARCINOMA. TUBULAR AND MICROPAPILLARY, WELL TO MODERATLY DIFFERENTIATED, CELLULAR AND SCHIROUS STROMA
115	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	9	mouse ill appearing, pancreas was tough and granular	10	PanINs	2	4/ neg	no	no	BURKITT'S LYMPHOMA
576	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	7	mouse ill appearing, pancreas was tough and granular, intestinal occlusion present	60	PanINs	1 (invasive)	2/neg	yes/neg	yes/neg	TUBULAR AND MICROPAPILLARY, WELL TO MODERATLY DIFFERENTIATED, CELLULAR STROMA
605	<i>Sin3B</i> ^{pp/+} <i>KRas</i> ^{G12D}	9	mouse was ill appearing with ascites, pancreas was tough and granular, visible cyst at the tail of the pancreas, spleen appeared enlarged	30	Papillary Mucinous Neoplasm and PanINs	invasive papillary	2/metastatic carcinoma in one of two lymph nodes	no	no	LVI TUBULAR AND MICROPAPILLARY, WELL TO MODERATLY DIFFERENTIATED, CELLULAR STROMA

^Aneg: negative for pancreatic cancerous tissue

Supplementary Table 3: Description of 12 month old sacrificed animals

mouse number	genotyping	age at death in months	mouse description at autopsy	acini (%)	precursor lesions present	number of tumors per biopsy	number of lymph nodes per biopsy ^A	presence of duodenal tissue in biopsy ^A	presence of colonic tissue in biopsy ^A	description of invasive tumors
46	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas white, tough granular, no visible metastasis	0	PanINs	0	1/neg	no	no	
59	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse ill appearing with scruffy hair, large tumor at head of the pancreas, granular and white, metastasis grossly evident in liver	0	PanINs	1 (invasive)	3/ neg	yes/invaded	no	TUBULAR AND MICROPAPILLARY, WELL TO MODERATLY POORLY DIFFERENTIATED, TUMOR NECROSIS CELLULAR STROMA
66	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas white, tough and granular, no visible metastasis	0	PanINs	1	0	no	no	
74	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, cysts visibly present in pancreas	30	PanINs	1	6/neg	no	no	
226	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse ill appearing with scruffy hair, large tumor at the head of the pancreas, granular and white, tough, pancreas fused with small intestine, metastasis visible in liver	5	PanINs	1 (invasive)	1/neg	no	yes/invaded	TUBULAR , WELL TO MODERATLY POORLY DIFFERENTIATED, TUMOR NECROSIS CELLULAR STROMA
478	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas tough, granular, with cysts,	25	PanINs	1 (invasive) and 3 (small)	5/neg	yes/neg	no	TUBULAR, WELL TO MODERATLY DIFFERENTIATED, SCLEROTIC STROMA
551	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas white, tough and granular, pancreas appeared large	3	PanINs	3	1/neg	yes/neg	no	
553	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, head of the pancreas appears tough, granular and white	10	PanINs	0	1/neg	no	no	
570	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas tough, white, and granular	5	PanINs	3	2/neg	yes/neg	yes/neg	
645	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing	5	PanINs	0	0	no	no	
652	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas appeared tough and granular, pancreas started to fuse with intestine	60	PanINs	1	0	no	no	
788	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, cyst visible at the tail of the pancreas	2	PanINs	1	2/neg	no	no	
791	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas granular	40	PanINs	4	1/neg	yes/neg	no	
821	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas granular and tough	30	PanINs	5	1/neg	yes/neg	yes/neg	
390	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas tough and granular, pancreas started to fuse with the intestine	1	PanINs	3	1/neg	no	yes/neg	
99	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse ill appearing, ascites present in abdomen, pancreas tough and granular, pancreas fused with small intestine, metastasis visible in liver	2	PanINs	1 (invasive)	4/neg	no	no	TUBULAR AND MICROPAPILLARY, WELL TO MODERATLY DIFFERENTIATED, CELLULAR AND SCLEROTIC STROMA
624	<i>Sin3B^{+/+}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas appeared enlarged and was tough and granular, pancreas fused with small intestine, no visible metastasis	10	PanINs	1 (invasive) and 2 (small)	1/neg	no	no	TUBULAR AND MICROPAPILLARY, WELL TO MODERATLY DIFFERENTIATED, CELLULAR STROMA

805	<i>Sin3B^{ΔC}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas appeared enlarged and was tough and granular	10	Papillary Mucinous Neoplasm and PanINs	1 (invasive) and 1 (small)	5/neg	yes/invaded	no	TUBULAR AND MICROPAPILLARY, WELL TO MODERATLY DIFFERENTIATED, CELLULAR STROMA
381	<i>Sin3B^{ΔC}KRas^{G12D}</i>	12	mouse healthy appearing, head of the pancreas appears tough and granular, tail of the pancreas appeared normal	50	PanINs	1	2/neg	yes/neg	yes/neg	
796	<i>Sin3B^{ΔC}KRas^{G12D}</i>	12	mouse healthy appearing, pancreas pink and granular, small tumor visible on head of the pancreas	70	PanINs	1 (invasive)	1/neg	no	yes/neg	spleen/neg TUBULAR, WELL TO MODERATLY DIFFERENTIATED, CELLULAR STROMA
741	<i>Sin3B^{ΔC}KRas^{G12D}</i>	12	mouse healthy appearing, large tumor visible on head of the pancreas, pancreas fused with small intestine, visible lung metastasis	5	PanINs	1 (invasive)	1/neg	no	yes/neg	TUBULAR AND MICROPAPILLARY, WELL TO MODERATLY DIFFERENTIATED, CELLULAR STROMA

^Aneg: negative for pancreatic cancerous tissue