Supplementary Figure 1. (A-B) Macroscopic images of the pancreas of mice after repeated

cerulein or vehicle (control) injection (A) and of mice subjected to PDL surgery or sham

surgery (B). (C-D) Representative images of p-AKT and nuclear YAP staining of pancreatic

tissue in mice after repeated cerulein injection (C left) and quantification of the p-AKT and

nuclear YAP staining intensity (C right), and in mice subjected to PDL surgery (D left) and

quantification of the p-AKT and nuclear YAP staining intensity (D right). All data are

presented as the means ± SDs of results for 3 mice per group. Student's t-test was used to

evaluate differences between two groups. * $p < 0.05$ and ** $p < 0.005$. Scale bars: 100 μm

and 50 μm (insets).
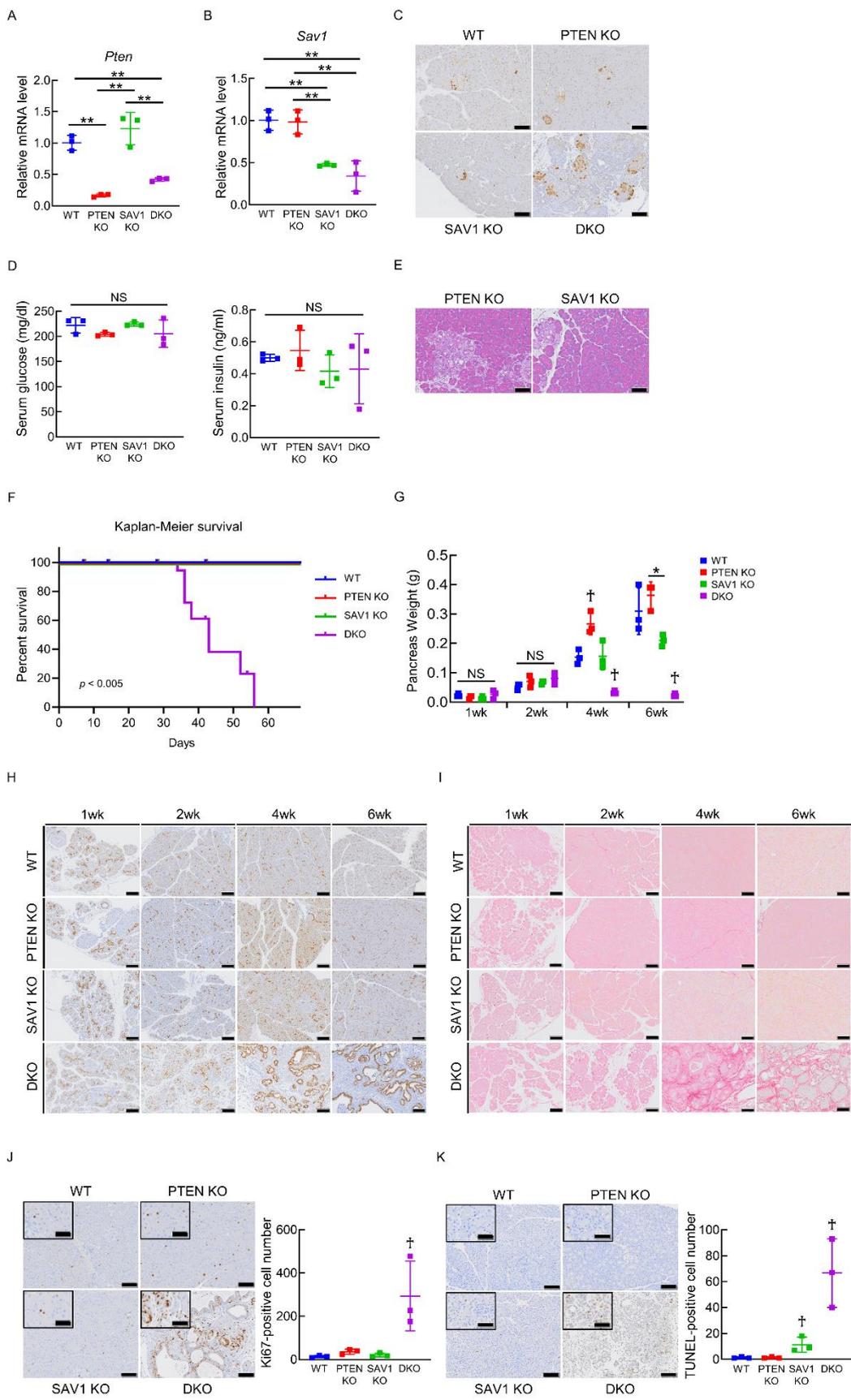
16   **Supplementary Figure 2.** Pancreatic phenotypes were examined in wild-type (WT) mice,

17   pancreas-specific *Pten* knockout (KO) (PTEN KO) mice, *Sav1* KO (SAV1 KO) mice, and *Pten*

18   and *Sav1* double KO (DKO) mice. **(A)** *Pten* mRNA levels in pancreatic tissue from mice at 6

19   weeks of age. **(B)** *Sav1* mRNA levels in pancreatic tissue from mice at 6 weeks of age. **(C)**

20   Representative Glucagon staining images of pancreatic tissue at 6 weeks of age. **(D)** Serum

21   glucose and insulin levels at 6 weeks of age. **(E)** Representative images of H&E staining of

22   pancreatic tissue from PTEN KO and SAV1 KO mice at 10 months of age (*n*=3). **(F)** Kaplan-

23   Meier survival curves (*n*=18-27). **(G)** Pancreas weight. **(H-I)** Representative images of SOX9

24   **(H)** and Sirius red staining **(I)** of pancreatic tissue. **(J)** Representative images of Ki67 staining

25   of pancreatic tissue **(left)** and quantification of the Ki67-positive cell number **(right)**. **(K)**

26   Representative images of TUNEL staining of pancreatic tissue **(left)** and quantification of the

27   TUNEL-positive cell number **(right)**. All data are presented as the means ± SDs of results for

28   3 mice per group. One-way analysis of variance (ANOVA) with Tukey's post hoc test was

29   used to compare differences among four groups **(A, B, D, G, J, and K)**. The survival data

30   were analyzed using the log-rank test **(F)**. * $p < 0.05$, ** $p < 0.005$, and [†] $p < 0.05$ versus all

31   groups. Scale bars: 100 μm and 50 μm (insets).

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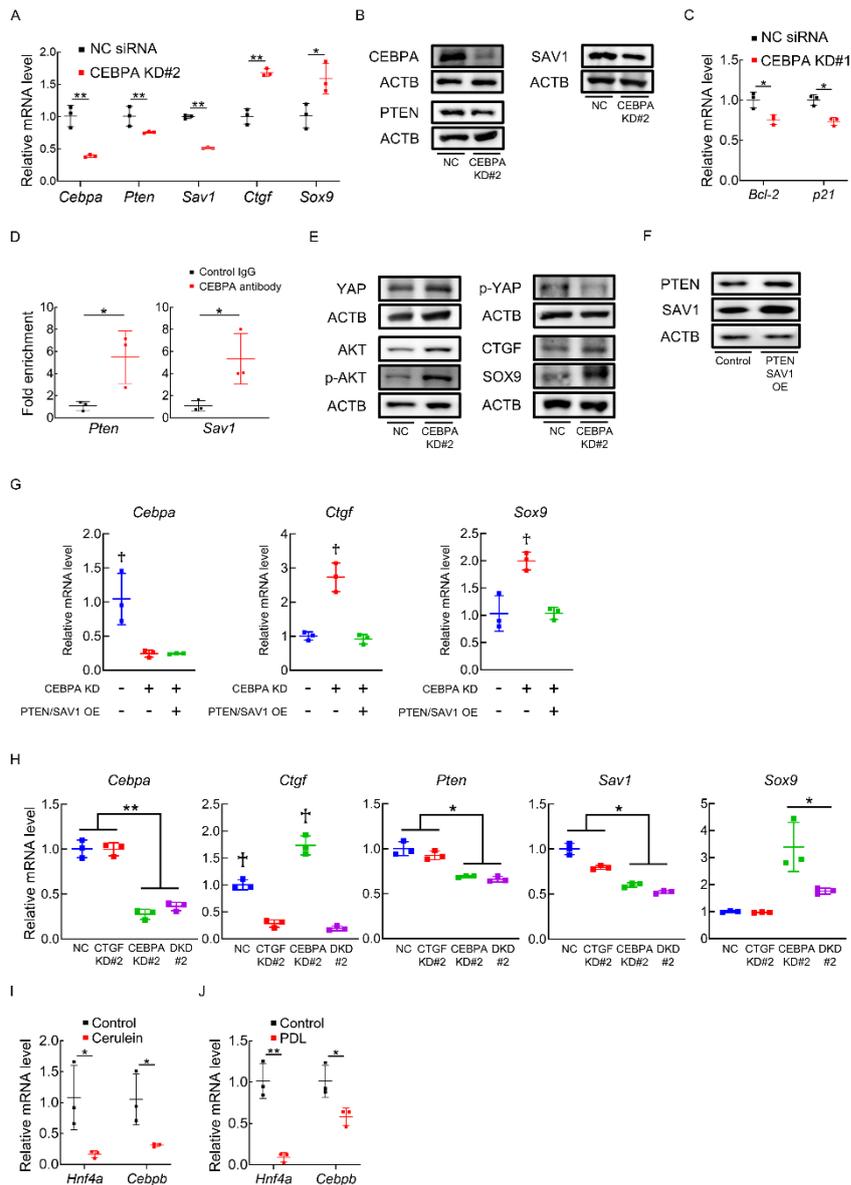
Supplementary Figure 3. (A) mRNA levels of *Cebpa*, *Pten*, *Sav1*, *Ctgf*, and *Sox9* in 266-6

cells 3 days after transfection with negative control (NC) siRNA or *Cebpa* siRNA (#2) (CEBPA

knockdown [KD] #2). **(B)** Protein levels of CEBPA, PTEN, SAV1, and ACTB in 266-6 cells 3

days after transfection with NC siRNA or *Cebpa* siRNA (#2) (CEBPA KD#2). **(C)** mRNA levels

of *Bcl-2* and *p21* in 266-6 cells 3 days after transfection with NC siRNA or *Cebpa* siRNA (#1)

(CEBPA KD#1). **(D)** Quantification of the chromatin immunoprecipitation assay to show direct

41 binding of CEBPA protein to murine *Pten* and *Sav1* promoter DNA using the antibody against

42 CEBPA compared with the immunoglobulin G control. **(E)** Protein levels of YAP, p-YAP, AKT,

43 p-AKT, CTGF, SOX9, and ACTB in 266-6 cells 3 days after transfection with NC siRNA or

44 *Cebpa* siRNA (#2) (CEBPA KD#2). **(F)** Protein levels of PTEN, SAV1, and ACTB in 266-6

45 cells transfected with the control vector or both *Pten* and *Sav1* cDNA expression vectors

46 (PTEN SAV1 overexpression [OE]). **(G)** mRNA levels of *Cebpa*, *Ctgf*, and *Sox9* in 266-6 cells

47 transfected with the control vector, *Cebpa* siRNA (CEBPA KD), or both *Pten* and *Sav1* cDNA

48 expression vectors (PTEN/SAV1 OE) and *Cebpa* siRNA (CEBPA KD). **(H)** mRNA levels of

49 *Cebpa*, *Ctgf*, *Pten*, *Sav1*, and *Sox9* in 266-6 cells 3 days after transfection with NC siRNA,

50 *Ctgf* siRNA (#2) (CTGF KD#2), *Cebpa* siRNA (#2) (CEBPA KD#2), or both *Cebpa* (#2) and

51 *Ctgf* (#2) siRNAs (double KD [DKD] #2). **(I-J)** *Hnf4a* and *Cebpb* mRNA levels in pancreatic

52 tissue in mice after repeated cerulein or vehicle (control) injection **(I)** and in mice subjected

53 to PDL surgery or sham surgery **(J)**. Blots run in parallel contemporaneously or run at

54 different times with loading control for each gel are shown. All data are presented as the

55 means ± SDs of results for 3 samples per group. Student's t-test was used to evaluate

56 differences between two groups **(A, C, D, I, and J)**. One-way analysis of variance (ANOVA)

57 with Tukey's post hoc test was used to compare differences among three or four groups **(G**

58 **and H)**. * $p < 0.05$, ** $p < 0.005$, and † $p < 0.05$ versus all groups.
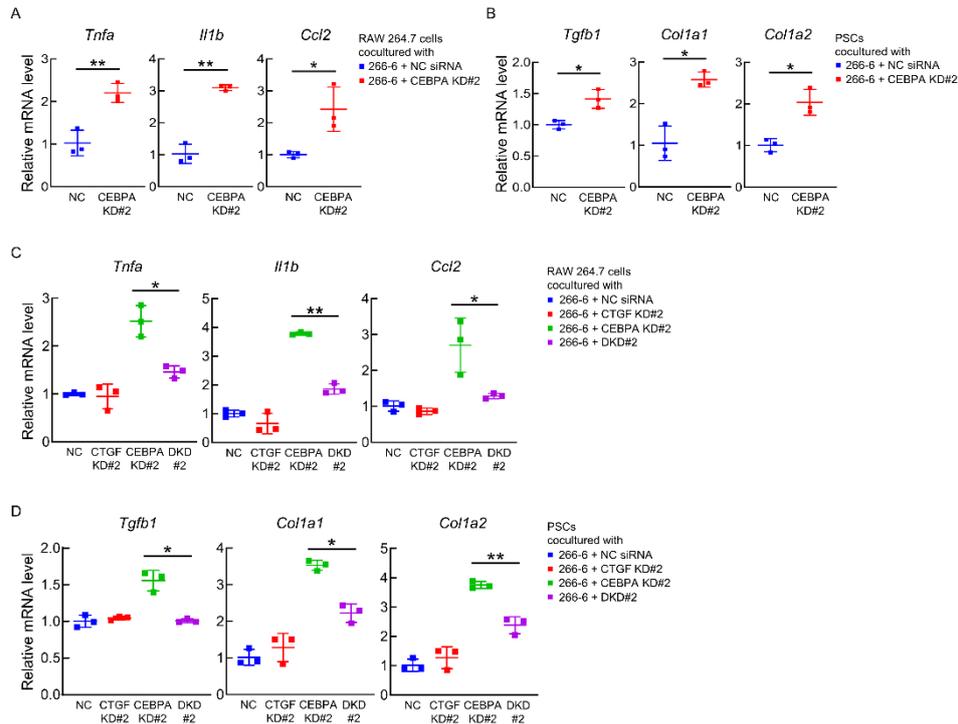
Supplementary Figure 4. (A) mRNA levels of *Tnfa*, *Il1b*, and *Ccl2* in RAW 264.7 cells 2 days

after coculture with 266-6 cells transfected with negative control (NC) siRNA or *Cebpa* siRNA

(#2) (CEBPA knockdown [KD] #2). **(B)** mRNA levels of *Tgfb1*, *Col1a1*, and *Col1a2* in PSCs

isolated from mouse pancreata 2 days after coculture with 266-6 cells transfected with NC

siRNA or *Cebpa* siRNA (#2) (CEBPA KD#2). **(C)** mRNA levels of *Tnfa*, *Il1b*, and *Ccl2* in RAW

264.7 cells 2 days after coculture with 266-6 cells transfected with NC siRNA, *Ctgf* siRNA

(#2) (CTGF KD#2), *Cebpa* siRNA (#2) (CEBPA KD#2) or both *Cebpa* (#2) and *Ctgf* (#2)

siRNAs (double KD [DKD] #2). **(D)** mRNA levels of *Tgfb1*, *Col1a1*, and *Col1a2* in PSCs

isolated from mouse pancreata 2 days after coculture with 266-6 cells transfected with NC

siRNA, *Ctgf* siRNA (#2) (CTGF KD#2), *Cebpa* siRNA (#2) (CEBPA KD#2) or both *Cebpa* (#2)

70   and *Ctgf* (#2) siRNAs (DKD#2). All data are presented as the means ± SDs of results for 3

71   samples per group. Student's t-test was used to evaluate differences between two groups **(A**

72   **and B)**. One-way analysis of variance (ANOVA) with Tukey's post hoc test was used to

73   compare differences among four groups **(C and D)**. * $p < 0.05$ and ** $p < 0.005$.

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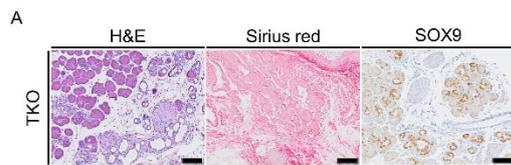
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89 **Supplementary Figure 5. (A)** Representative images of H&E, Sirius red, and SOX9 staining

90 of pancreatic tissue from *Pten*, *Sav1* and *Ctgf* triple knockout (TKO) mice at 10 months of

91 age (*n*=3). Scale bars: 100 µm.

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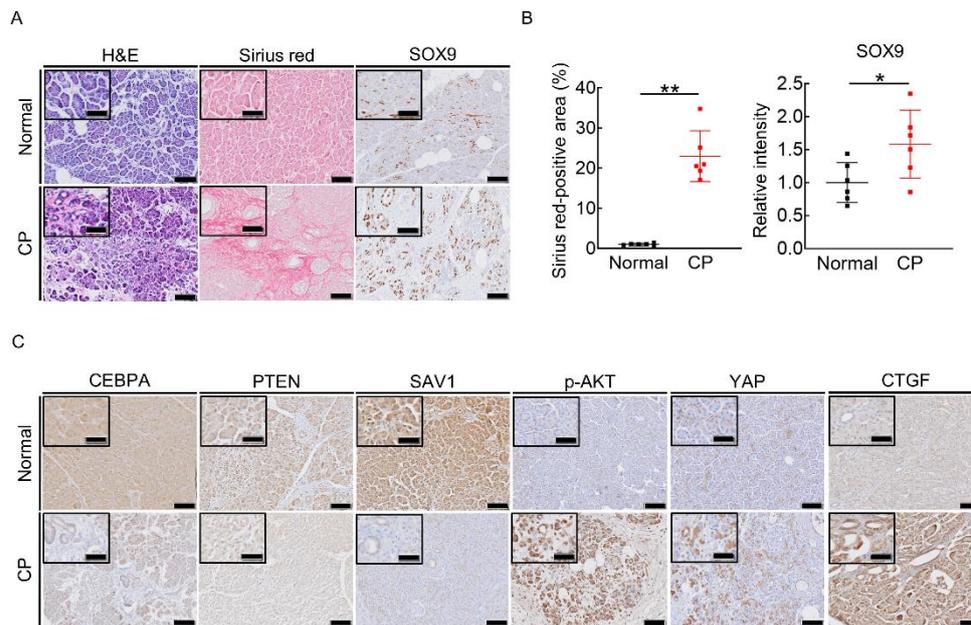
Supplementary Figure 6. (A-B) Representative images of H&E, Sirius red, and SOX9

staining of pancreatic tissue from the normal pancreatic regions obtained from pancreatic

neuroendocrine tumor patients or from the chronic pancreatic regions obtained from chronic

pancreatitis patients **(A)** and quantification of the Sirius red-positive area **(B left)** and SOX9

staining intensity **(B right)**. **(C)** Representative images of CEBPA, PTEN, SAV1, p-AKT,

nuclear YAP, and CTGF staining of pancreatic tissue from the normal pancreatic regions

obtained from pancreatic neuroendocrine tumor patients or from the chronic pancreatic

regions obtained from chronic pancreatitis patients. All data are presented as the means ±

SDs of results for 6 samples per group. Student's t-test was used to evaluate differences

between two groups. * $p < 0.05$ and ** $p < 0.005$. Scale bars: 100 μm and 50 μm (insets).

117 **Supplementary Table 1. List of antibodies**

Antibody	Host	Dilution	Cat. no.	Supplier
AKT	Rabbit	1:1000 (WB)	4685	Cell Signaling
p-AKT	Rabbit	1:2000 (WB)	4060	Cell Signaling
	Rabbit	1:50 (IHC)	38449	Abcam
ACTB	Mouse	1:10000 (WB)	A5316	Sigma-Aldrich
CEBPA	Rabbit	1:1000 (WB)	8178	Cell Signaling
	Rabbit	1:200 (IHC)	140479	Abcam
CTGF	Rabbit	1:1000 (WB) 1:100 (IHC)	227180	Abcam
Glucagon	Mouse	1:100 (IHC)	10988	Abcam
Ki67	Rabbit	1:200 (IHC)	12202	Cell Signaling
LATS1	Rabbit	1:1000 (WB)	3477	Cell Signaling
LATS2	Rabbit	1:1000 (WB)	PA5-38804	Invitrogen
p-LATS1/2	Rabbit	1:1000 (WB)	PA5-64591	Invitrogen
PTEN	Rabbit	1:1000 (WB)	9188	Cell Signaling
	Rabbit	1:100 (IHC)	170941	Abcam
SAV1	Rabbit	1:1000 (WB)	13301	Cell Signaling
	Mouse	1:150 (IHC)	NBP2-45687	Novus Biologicals
SOX9	Rabbit	1:1000 (WB)	82630	Cell Signaling
	Rabbit	1:1000 (IHC)	185966	Abcam
YAP	Rabbit	1:1000 (WB) 1:400 (IHC)	14074	Cell Signaling
p-YAP	Rabbit	1:1000 (WB)	13008	Cell Signaling

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125 **Supplementary Table 2. List of TaqMan PCR probes**

Gene name	TaqMan PCR probe	Supplier
Actb	Mm02619580_g1	Applied Biosystems
Bcl-2	Mm00477631_m1	Applied Biosystems
Ccl2	Mm00441242_m1	Applied Biosystems
Cd68	Mm03047343_m1	Applied Biosystems
Cebpa	Mm00514283_m1	Applied Biosystems
Cebpb	Mm00843434_s1	Applied Biosystems
Col1a1	Mm00801666_g1	Applied Biosystems
Col1a2	Mm01165187_m1	Applied Biosystems
Ctgf	Mm001192933_g1	Applied Biosystems
Hnf4a	Mm01247712_m1	Applied Biosystems
Il1b	Mm00434228_m1	Applied Biosystems
p21	Mm00432448_m1	Applied Biosystems
Pten	Mm00477208_m1	Applied Biosystems
Sav1	Mm00499038_m1	Applied Biosystems
Sox9	Mm00448840_m1	Applied Biosystems
Tgfb1	Mm01178820_m1	Applied Biosystems
Tnfa	Mm00443258_m1	Applied Biosystems

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137 **Supplementary Table 3. List of siRNAs**

Gene	siRNA ID	Sequences of siRNA (5'→3')		Supplier
Cebpa (#1)	s63855	sense	ACUCAAAACUCGCUCCUUUTT	Thermo Fisher Scientific
		antisense	AAAGGAGCGAGUUUUGAGUAT	
Cebpa (#2)	s63854	sense	AAAGCUGAGUUGUGAGUUATT	Thermo Fisher Scientific
		antisense	UAACUCACAACUCAGCUUUCT	
Ctgf (#1)	s66077	sense	AGAAUAUGAUGUUCAUCAATT	Thermo Fisher Scientific
		antisense	UUGAUGAACAUCAUAUUCUTT	
Ctgf (#2)	s66076	sense	GGCAAAAGUGCAUCCGGATT	Thermo Fisher Scientific
		antisense	UCCGGAUGCACUUUUUGCCCT	
Lats1	s201588	sense	CCAUAUGAGUCAGUAAGUATT	Thermo Fisher Scientific
		antisense	UACUUACUGACUCAUAUGGAG	
Lats2	s78350	sense	CCAUCGACUUUUCCCGUGATT	Thermo Fisher Scientific
		antisense	UCACGGGAAAAGUCGAUGGTG	
Pten	s72350	sense	GUAUAGAGCGUGCAGAUAATT	Thermo Fisher Scientific
		antisense	UUAUCUGCACGCUCUAUACTG	
Sav1	s204977	sense	AGAUUACAGAUAUUAUGAATT	Thermo Fisher Scientific
		antisense	UUCAUAAUAUCUGUAAUCUTC	

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