

Supplementary Material

Supplementary Figure Legends

Supplementary Figure S1. Comparative analysis of severe damage mediated by alcoholic chronic pancreatitis (ACP) as compared to the impact of alcohol or CP alone in *Ptfla^{CreERTM/+}* mice. (A) Dot plot depicting initial and final body weight measurements in mice treated with vehicle, alcohol (A), caerulein (CP), or ACP with 3 and 21 days of recovery periods (n=7 mice per group). (B) Blood alcohol concentration levels (mg/dL) shown in ctrl, A, and ACP-induced *Ptfla^{CreERTM/+}* mice, (n=7-9 mice per group). (C and D) Relative pancreas weight measurements of *Ptfla^{CreERTM/+}* mice in ctrl, A, CP, and ACP-induced groups (C) with 3 and 21 days of recovery periods (D), (n=5-7 mice per group). (E) Measurements of serum amylase activity in ctrl, A, CP and ACP-induced mice, (3-day recovery), (n=6 mice per group). (F) Representative images depicting H&E with histological images (*left*) and quantification (*right*) of CK19⁺ ducts, PanINs (Alcian Blue), and α SMA, collagen (Sirius red) and immune cells (CD45⁺) in pancreata of control, A, CP and ACP-induced *Ptfla^{CreERTM/+}* mice, (3-day recovery), (n=4 mice per group). Scale bar, 50 μ m. ^{ns}nonsignificant; *p<0.05; **p< 0.01; ***p<0.001; ****p<0.0001 by ANOVA and unpaired t test.

Supplementary Figure S2. Molecular profiling of *Ptfla^{CreERTM/+}* mice pancreata after experimental induction of ACP. (A) Quantitative (qPCR) analysis in pancreas tissue harvested from control and ACP-induced *Ptfla^{CreERTM/+}* mice, (n=3 mice per group). (B) Representative image of mouse kinase array membranes (*top*) and its quantification (*bottom*) in control and ACP induced pancreata. Scale bar, 50 μ m. ^{ns} nonsignificant; *p<0.05; **p< 0.01; ***p<0.001;****p<0.0001 by ANOVA and unpaired t test.

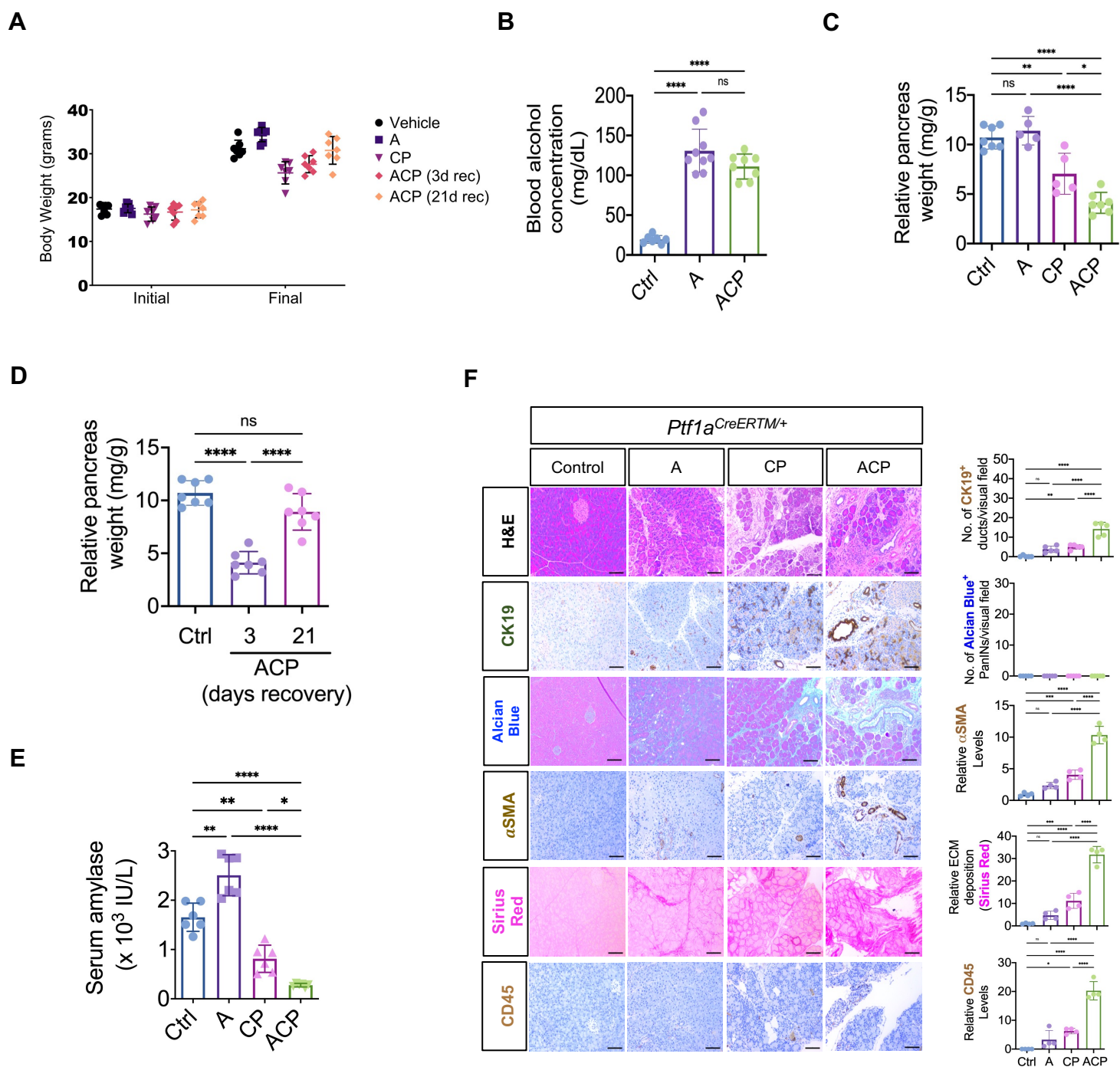
Supplementary Figure S3. Comparative analysis of pancreatic damage mediated by ACP as compared to the impact of alcohol or CP alone in *KC* mice. (A) Blood alcohol concentration measurement (mg/dL) in ctrl, alcohol alone (A), and ACP-induced *KC* mice with n = 6-7 mice per group. (B) Representative pancreas images displaying H&E, images (*left*) and quantification (*right*) of CK19⁺ ducts, PanINs (Alcian Blue), collagen (Sirius red), α SMA, and immune cells positivity (CD45⁺) in the pancreata of ctrl, A, CP, and ACP-induced *KC* experimental cohorts, (3-day recovery), (n=4-7 mice per group). (C) Comparative histological evaluation of mouse pancreas

using H&E based analysis (B), (n=3 mice per group). (D) Bubble plot outlining the expression of canonical lineage cell cluster annotations in *KC* scRNA seq dataset. Scale bar, 50 μ m. ^{ns} nonsignificant; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 by ANOVA.

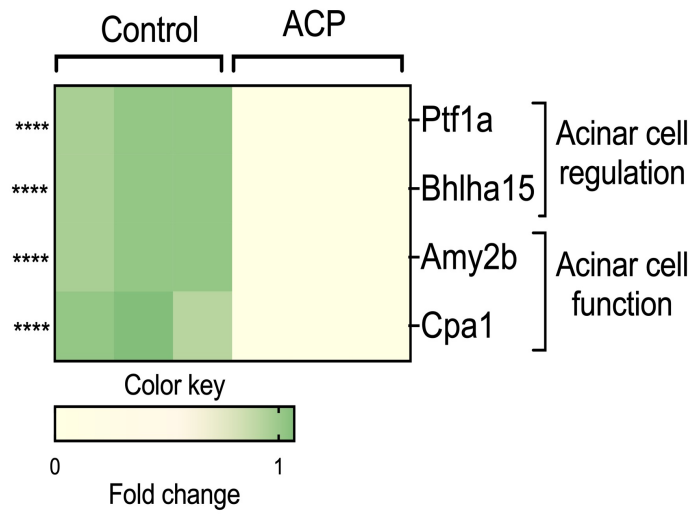
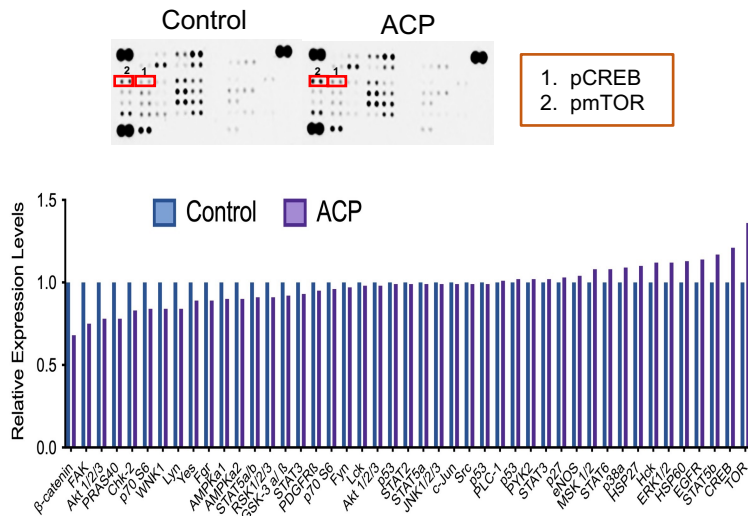
Supplementary Figure S4. Histological profiling of *Ptfla*^{CreERTM/+};*Creb*^{fl/fl} (*CC*^{-/-}) mice pancreata with ACP induction. (A) Mouse breeding strategy to generate a genetic knockout of acinar cell specific *Creb*, under a *Ptfla*^{CreERTM/+} promoter. (B) Representative images of the mouse pancreas with H&E staining, along with co-immunofluorescence of total CREB expression (tCREB, red) and DAPI (blue), in control *Ptfla*^{CreERTM/+} (C) and *CC*^{-/-} mice. (C) Comparative histological evaluation of mouse pancreas, accompanied by representative photomicrographs, showcasing H&E, CK19⁺ ducts, Sirius Red, α SMA, and CD45⁺ staining within the pancreata of control (C) and *CC*^{-/-} mice, in control or with ACP induction (3-day recovery)(*left*) and their quantification (*right*), (n=4 mice per group). Scale bar, 50 μ m. ^{ns} nonsignificant; ****p<0.0001 by ANOVA.

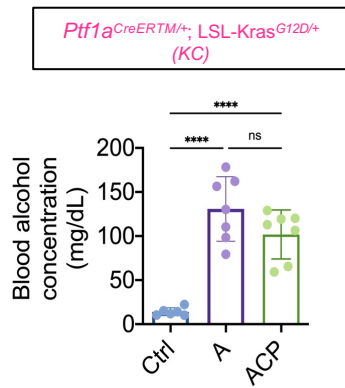
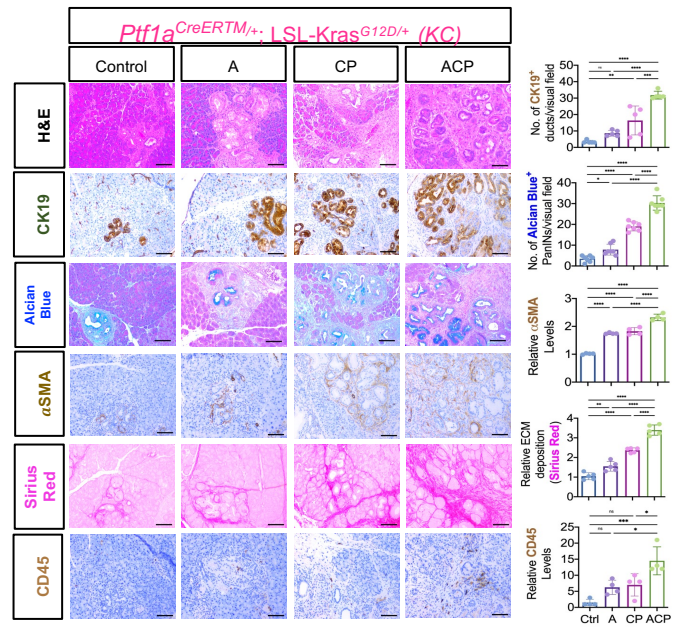
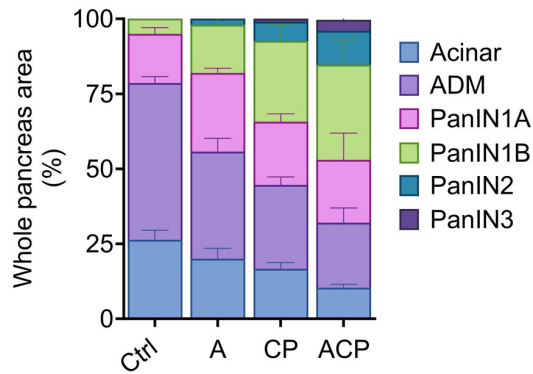
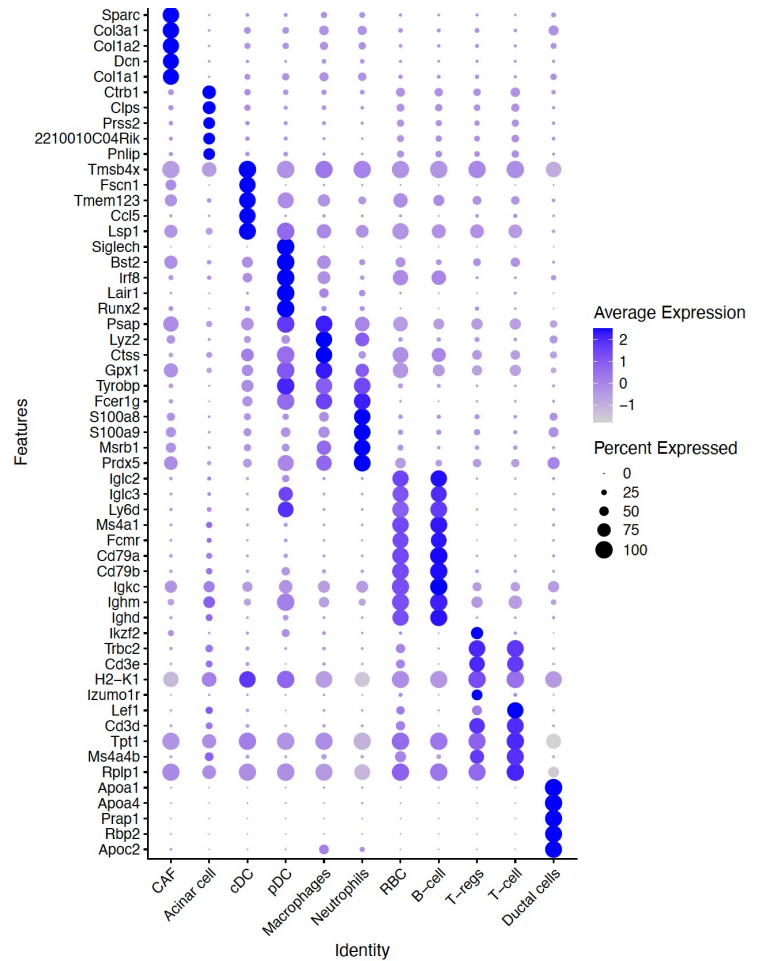
Supplementary Figure S5. Pancreas weight of *KC* and *Ptfla*^{CreERTM/+}; *LSL-Kras*^{G12D/+}; *Creb*^{fl/fl} (*KCC*^{-/-}) mice with ACP induction. (A) Schematic showing ACP induction and recovery phases in *KC* and *KCC*^{-/-} mice. (B) Comparison of relative pancreas weight measurements in all experimental cohorts (n=3-5 mice per group). (C) Representative photomicrographs of whole pancreas depicting significantly less tumor burden in *KCC*^{-/-} as compared to *KC* mice with ACP induction. Scale bar, 50 μ m. ^{ns} nonsignificant; ***p<0.001; ****p<0.0001 by ANOVA.

Supplementary Figure S6. Raw uncropped images of Western blot membranes for Figure 1F and 3B.

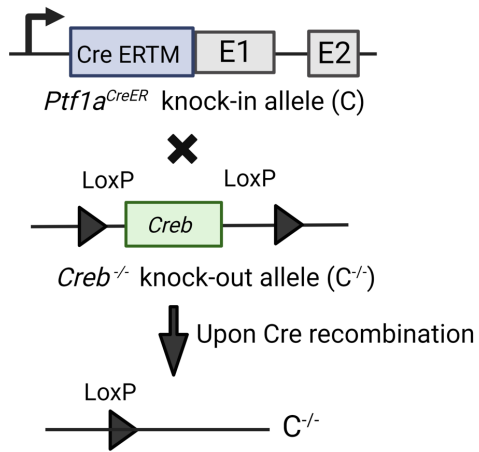


Supplementary Figure S1

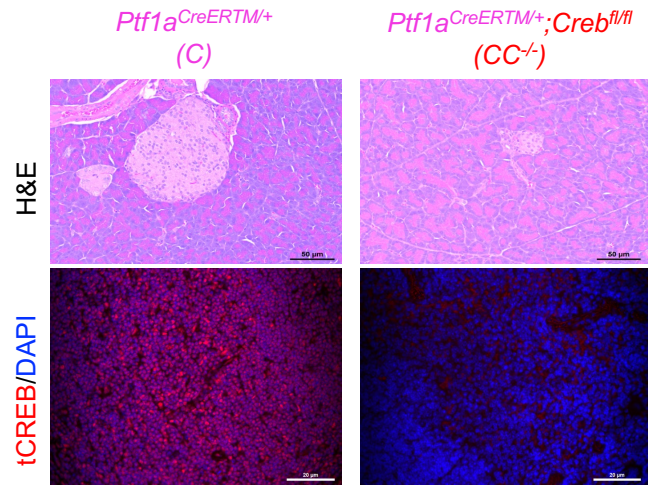
A**B****Supplementary Figure S2**

A**B****C****D**

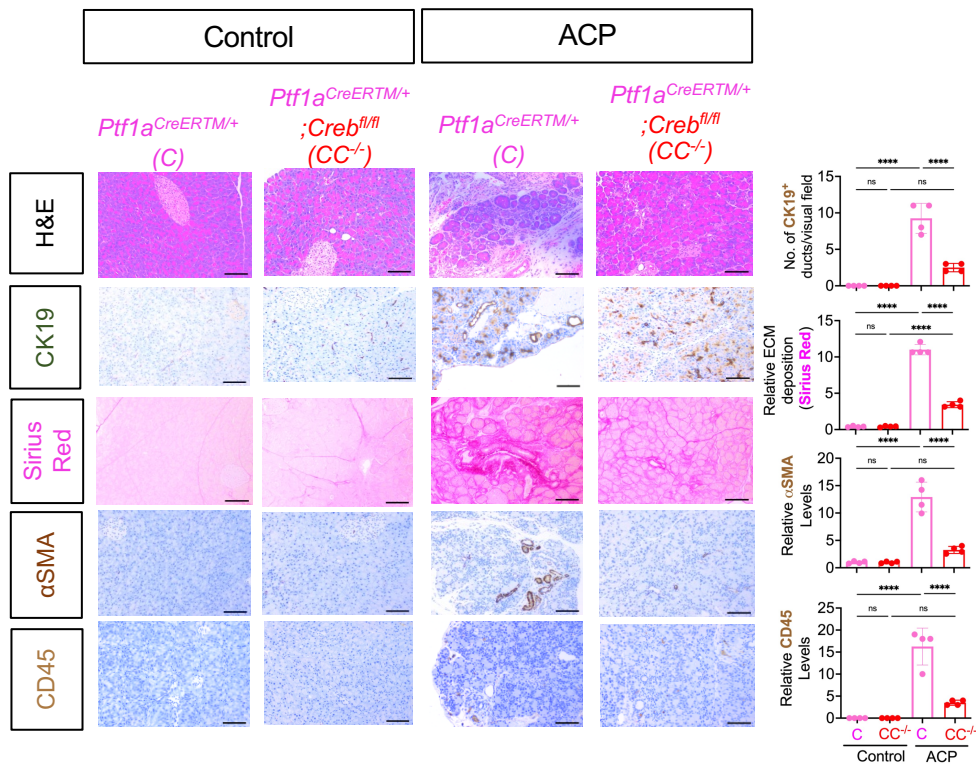
A



B



C



Supplementary Figure S4

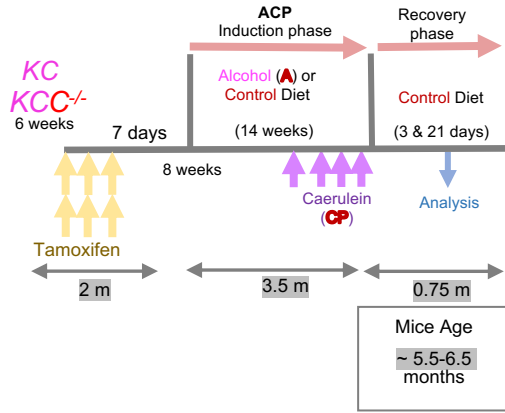
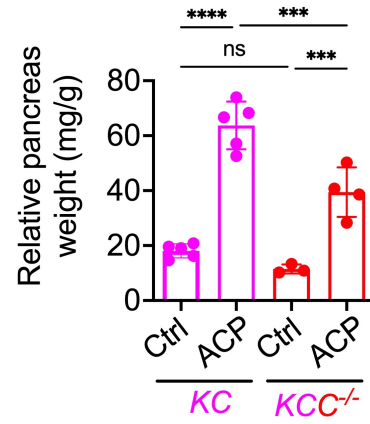
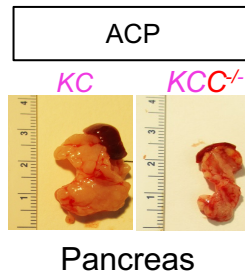
A**B****C****Supplementary Figure S5**

Figure- 1F

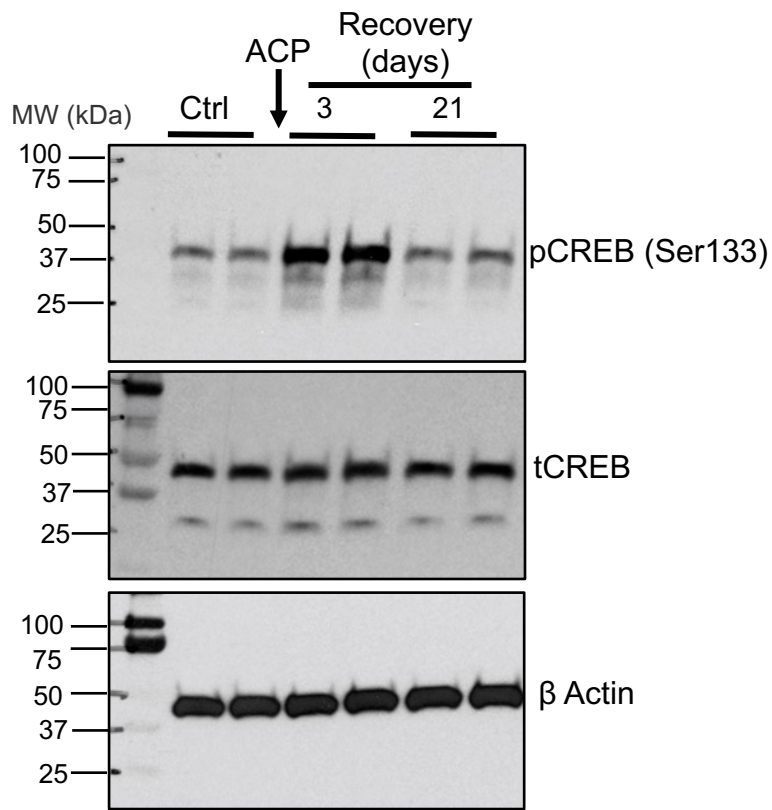
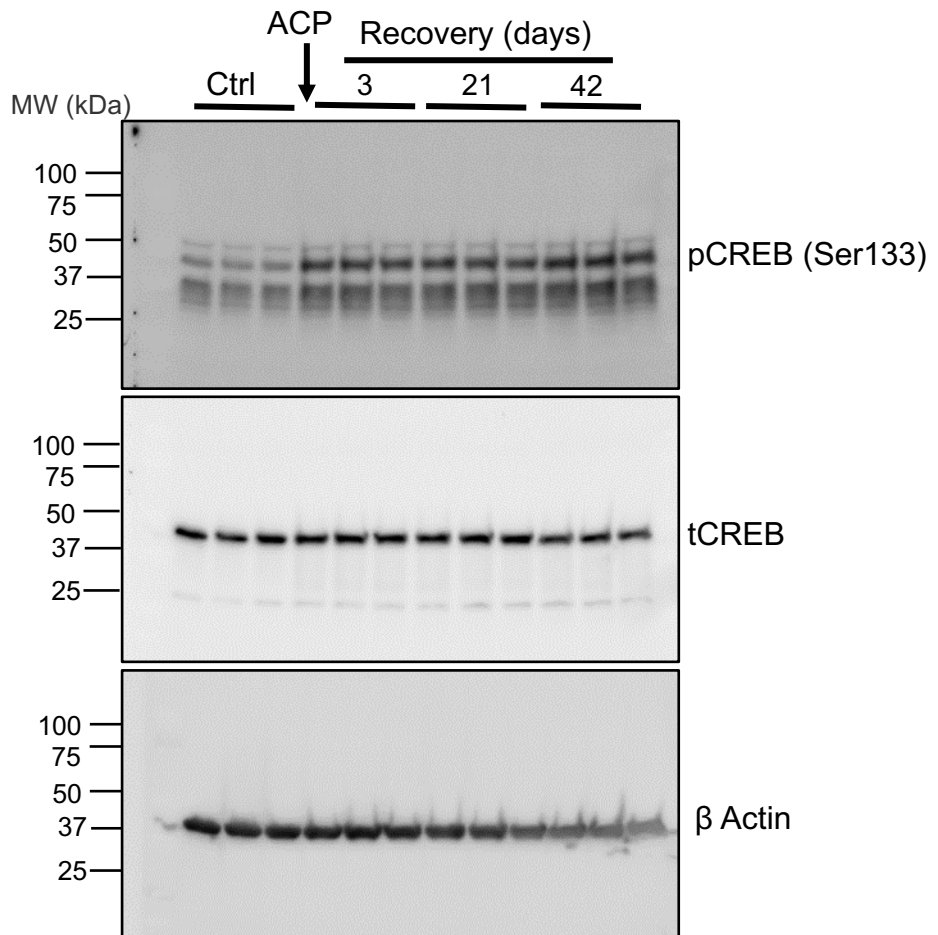


Figure- 3B



Supplementary Figure S6

Supplementary Tables

Supplementary Table S1. Sequence of probes used for mice genotyping analysis.

Gene	Forward primer	Reverse primer
<i>Cre</i>	GAA GGC ATT TGT GTA GGG TCA	GGC TGA GTG AGG GTT GTG AG
<i>Creb^{fl}</i>	CTCTTCTTGCATCAAGCTTGGT	AGATCCCTCTAGGCATTTCTTCCT
<i>Creb^{WT}</i>	CCAGTTACCTTCTAGGGAGCAGCTTACA	CAGGCCTGAGGTCTGGCTTCA
<i>Kras^{G12D}</i>	GGCCTGCTGAAAATGACTGAGTATA	CTGTATCGTCAAGGCGCTCTT
<i>Rosa^{EYFP}</i>	AGG GCG AGG AGC TGT TCA	TGA AGT CGA TGC CCT TCA G

Supplementary Table S2. List of treatment groups from ACP induction and recovery periods.

Groups	Induction period	Recovery period	Group Abbreviation
1	Control diet (14 weeks)	Continued control diet	Ctrl
2	Alcohol diet (14 weeks)	Control diet (3 or 21 days)	A
3	Control diet + Caerulein injections (for 4 weeks)	Continued control diet	CP
4	Alcohol diet + Caerulein injections (for 4 weeks)	Control diet (3 or 21 days)	ACP (3- or 21-days recovery) = ACP
5	Alcohol diet + Caerulein injections (for 4 weeks)	Control diet (3 days)	ACP (3-days recovery) = ACP + 3d
6	Alcohol diet + Caerulein injections (for 4 weeks)	Control diet (21 days)	ACP (21-days recovery) = ACP + 21d

Supplementary Table S3. Primary antibodies for Western blot, immunohistochemistry, and immunofluorescence analysis.

Primary antibodies	Supplier	Species	Catalogue Number
Phospho-CREB (Ser 133)	Cell signaling	Rabbit	9198
Total-CREB	Cell signaling	Rabbit	9197
Actin	Cell signaling	Mouse	3700
CK19	EMD Millipore	Rat	MABT913
GFP	Aves labs	Chicken	GFP-1010
α -amylase	Cell signaling	Rabbit	3796
CD45	Cell signaling	Rabbit	70257
α -SMA	Cell signaling	Rabbit	19245

Supplementary Table S4. Mouse Primers used in the study (Qiagen Catalogue#330001).

Primers	Company	Gene Globe-ID
Amy2b	Qiagen	PPM66197A-200
Ptf1a	Qiagen	PPM29825A-200
Alb	Qiagen	PPM60179A-200
Bhlh1a15	Qiagen	PPM41737A-200
Krt19	Qiagen	PPM02968A-200
Sox9	Qiagen	PPM05134D-200
Aldh1a3	Qiagen	PPM31491A-200
Spp1	Qiagen	PPM03648C-200
Tspan8	Qiagen	PPM26276B-200
Hes1	Qiagen	PPM05647A-200
Prss1	Qiagen	PPM67018A-200
Cpa1	Qiagen	PPM26764A-200