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Supplemental Information

A microRNA checkpoint for Ca^{2+} signaling and overload in acute pancreatitis

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Figure S1

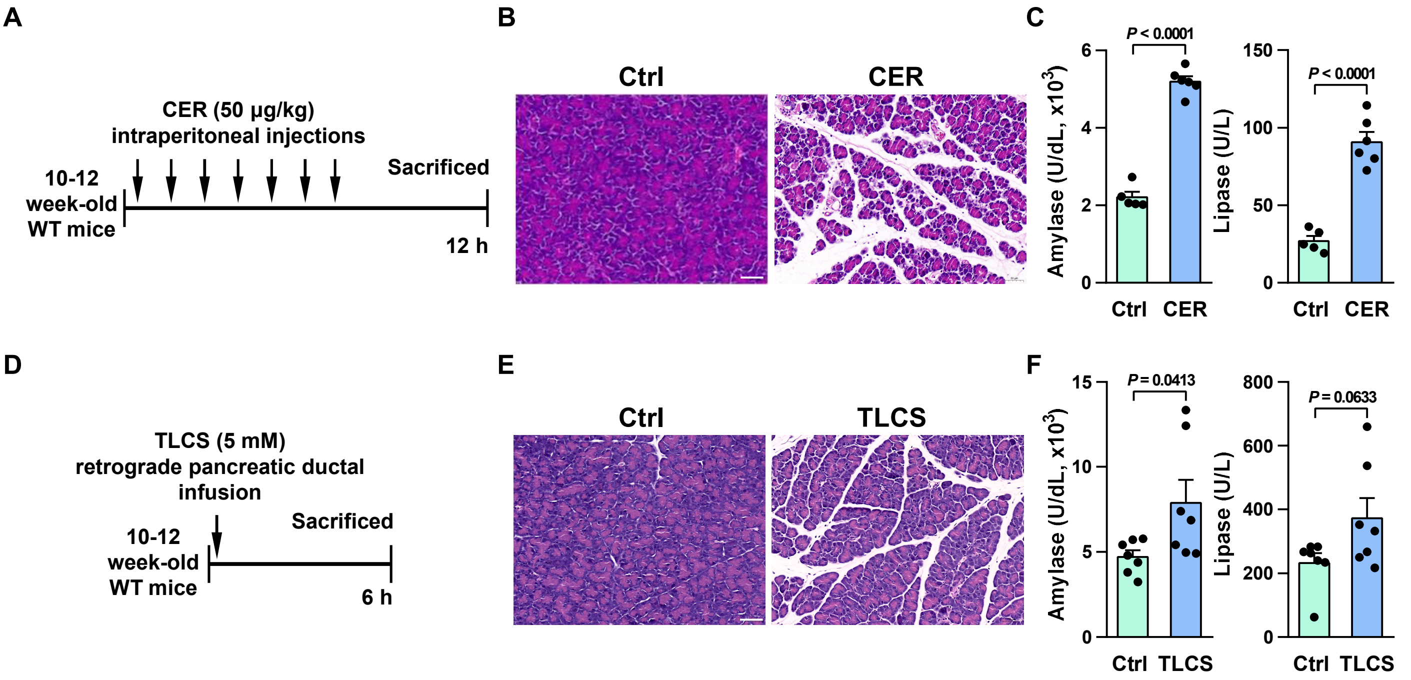

Figure S1. Characterisation of murine AP models.
(A-C) Schematic for CER-AP mouse model (A), representative images (*scale bar*, 50 μm, magnification ×200) of H&E stained pancreata (B), and levels of amylase/lipase (C) in CER-AP (50 μg/kg/h × 7 cerulein) at 12 h. (D-F) Schematic for TLCS-AP mouse model (D), representative images (*scale bar*, 50 μm, magnification ×200) of H&E stained pancreata (E), and levels of amylase/lipase (F) in TLCS (5 mM) at 6 h.

Data are from 5-7 mice per group, shown as mean ± SEM.

Figure S2

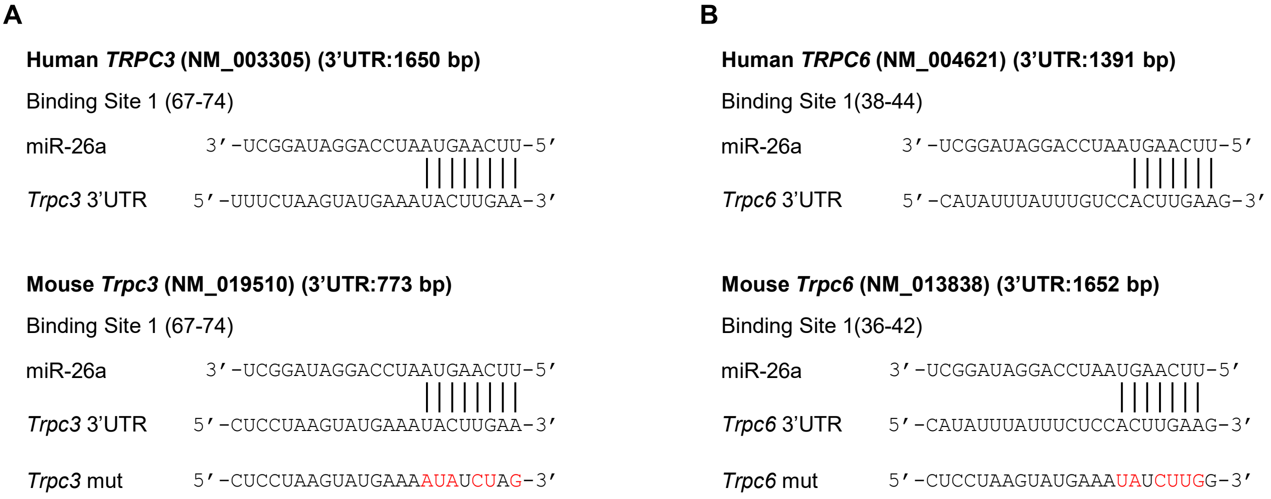

Figure S2. The base sequence of TRPC gene mRNA and miR-26a sites.
(A) The base sequence of miR-26a, human (mRNA) *TRPC3*, mouse (mRNA) *Trpc3,* and mouse mutant (mRNA) *Trpc3* sites. (B) The base sequence of miR-26a, human (mRNA) *TRPC6*, mouse (mRNA) *Trpc6,* and mouse mutant (mRNA) *Trpc6* sites.

Figure S3

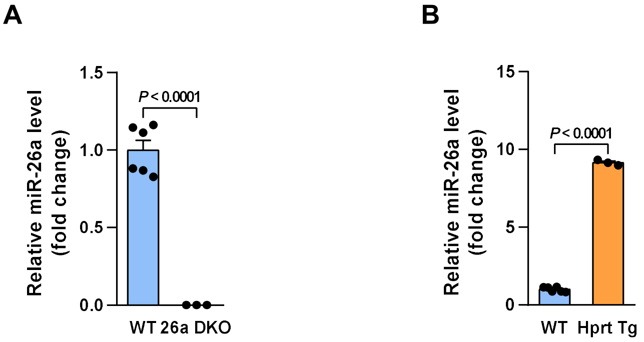

Figure S3. Expression of miR-26a in 26a DKO and Hprt Tg PACs.
(A and B) Expression of miR-26a in PACs of 26a DKO (A) and Hprt Tg (B) mice. Data are shown as mean ± SEM.

Figure S4

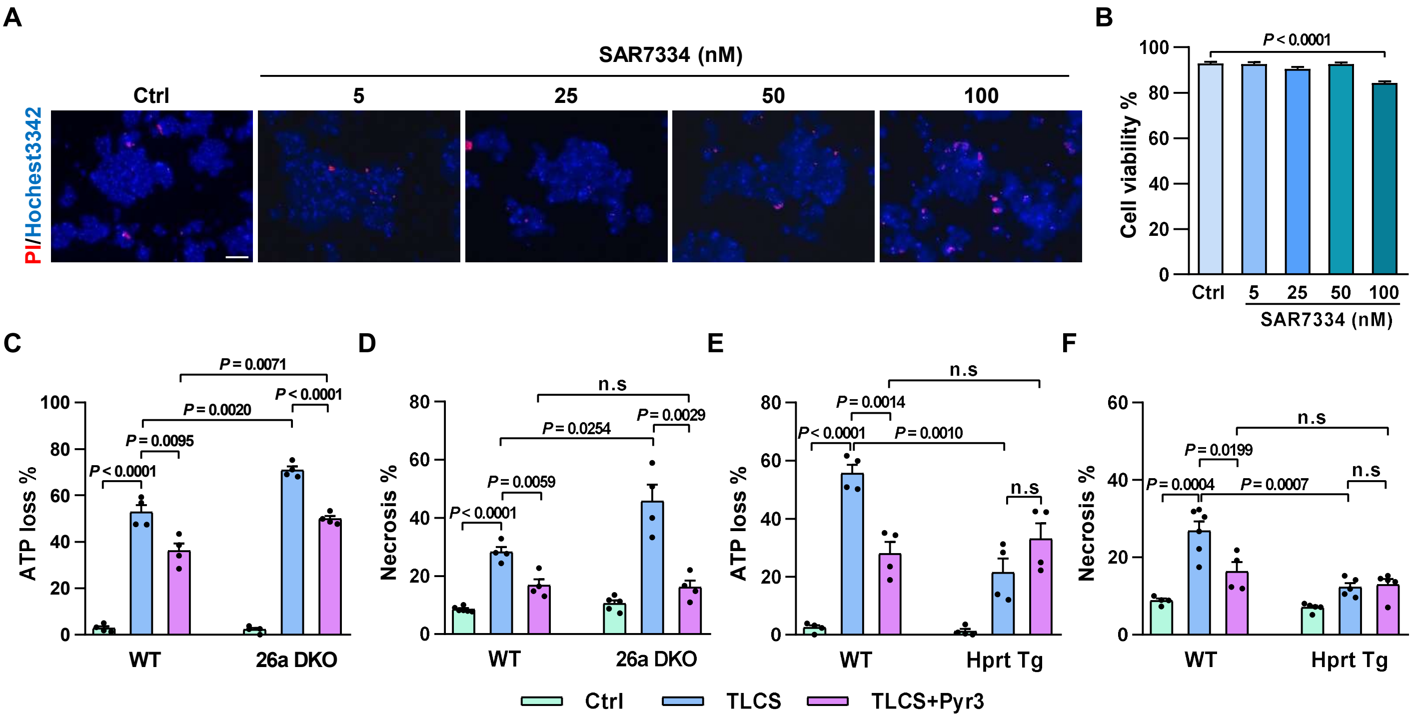

Figure S4. Chemical inhibition of Trpc3 and Trpc6 recapitulates the effect of miR-26a on ATP loss, and necrosis in PACs.

(A and B) Representative images of cell death (A), and percentage of cell viability (B) in PACs treated with different concentrations of SAR7334 (*scale bar*, 50 µm, magnification ×200). (C-F) ATP loss (C, E) and necrotic cell death pathway activation (D, F) determined in 26a DKO (C, D), Hprt Tg (E, F) PACs pre-treated with HEPES (Ctrl), TLCS, or TLCS plus Pyr3 in comparison with respective WT littermate PACs.

All experiments were from 3 or more independent repeats which yielded a sum of 30-40 cells per group. Data are shown as mean ± SEM.

Figure S5

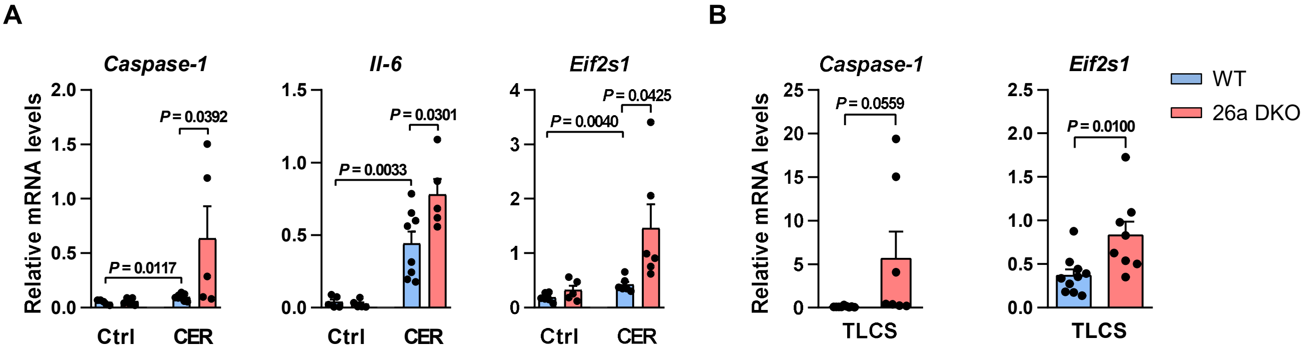

Figure S5. MiR-26a knockdown affects mRNA levels indicative of inflammation and ER stress.
(A) Expression of (mRNA) *Caspase-1*, *Il-6,* and *Eif2s1* in WT and DKO mice with CER-AP. (B) Expression of (mRNA) *Caspase-1*, *Il-6,* and *Eif2s1* in WT and DKO mice with TLCS-AP.
Data are from 5-9 mice per group, shown as mean ± SEM.

Figure S6

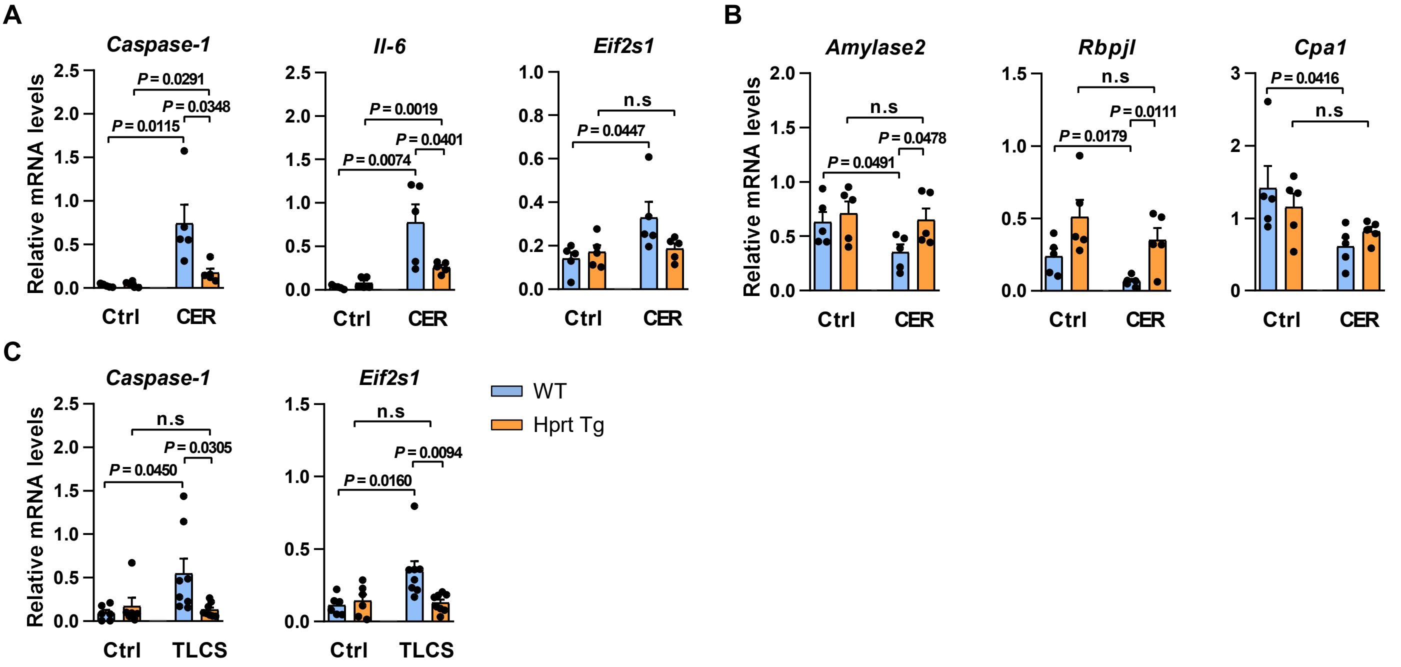

Figure S6. MiR-26a overexpression affects mRNA levels of inflammation, ER stress and cell function genes.

(A) Expression of (mRNA) *Caspase-1*, *Il-6,* and *Eif2s1* in WT and Hprt Tg mice with CER-AP. (B) Expression of (mRNA) *Amylase2*, *Rbpjl,* and *Cpa1* in WT and Hprt Tg mice with CER-AP. (C) Expression of (mRNA) *Caspase-1* and *Eif2s1* in WT and Hprt Tg mice with TLCS-AP.

Data are from 5-7 mice per group, shown as mean ± SEM.

Figure S7

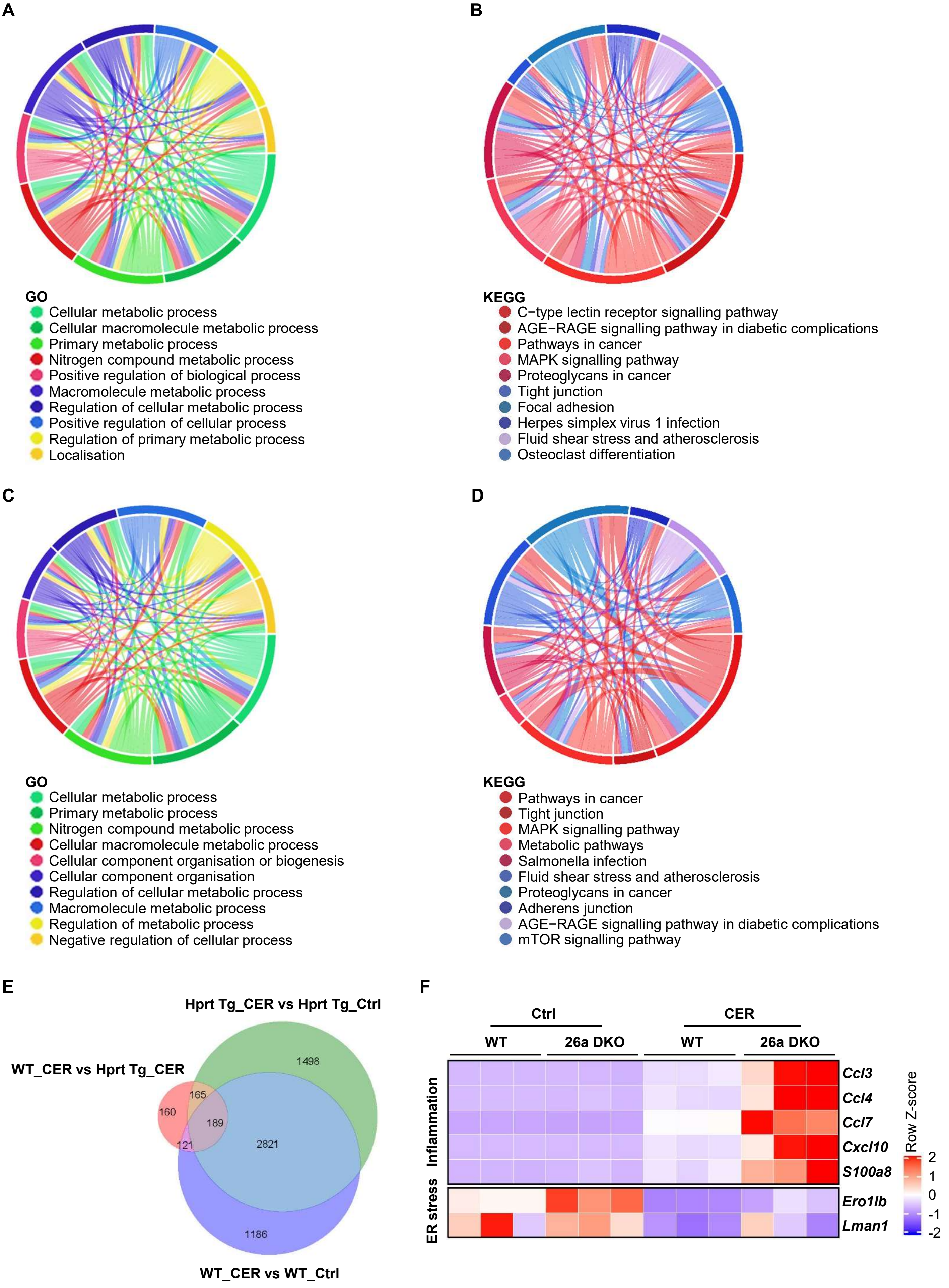
A
GO
Cellular metabolic process
Cellular macromolecule metabolic process
Primary metabolic process
Nitrogen compound metabolic process
Positive regulation of biological process
Macromolecule metabolic process
Regulation of cellular metabolic process
Positive regulation of cellular process
Regulation of primary metabolic process
Localisation
B
KEGG
C−type lectin receptor signalling pathway
AGE−RAGE signalling pathway in diabetic complications
Pathways in cancer
MAPK signalling pathway
Proteoglycans in cancer
Tight junction
Focal adhesion
Herpes simplex virus 1 infection
Fluid shear stress and atherosclerosis
Osteoclast differentiation
C
GO
Cellular metabolic process
Primary metabolic process
Nitrogen compound metabolic process
Cellular macromolecule metabolic process
Cellular component organisation or biogenesis
Cellular component organisation
Regulation of cellular metabolic process
Macromolecule metabolic process
Regulation of metabolic process
Negative regulation of cellular process
D
KEGG
Pathways in cancer
Tight junction
MAPK signalling pathway
Metabolic pathways
Salmonella infection
Fluid shear stress and atherosclerosis
Proteoglycans in cancer
Adherens junction
AGE−RAGE signalling pathway in diabetic complications
mTOR signalling pathway
E
Hprt Tg_CER vs Hprt Tg_Ctrl
WT_CER vs Hprt Tg_CER
1498
165
160
189
121
2821
1186
WT_CER vs WT_Ctrl
F
Ctrl
CER
WT
26a DKO
WT
26a DKO
Inflammation
ER stress
Ccl3
Ccl4
Ccl7
Cxcl10
S100a8
Ero1lb
Lman1
Row Z-score
2
1
0
-1
-2

Figure S7. MiR-26a ameliorates inflammation, autophagy, and ER stress in AP.
(A and B) Chord diagram of top 10 GO-biological processes (A) and KEGG pathway analysis (B) of WT CER-AP (WT_CER) versus WT control (WT_Ctrl). (C and D) Chord diagram of top 10 GO-biological processes (C) and KEGG pathway analysis (D) of Hprt Tg CER-AP (Hprt Tg_CER) versus Hprt Tg control (Hprt Tg_Ctrl). (E) Venn diagram of differentially expressed genes compared between WT CER-AP versus WT control (WT_CER vs WT_Ctrl)、Hprt Tg CER-AP versus Hprt Tg control (Hprt Tg_CER vs Hprt Tg_Ctrl) and WT CER-AP versus Hprt Tg CER-AP (WT_CER vs Hprt Tg_CER). (F) Heat map of expression of five inflammation-related genes and two ER stress-related genes in 26a DKO pancreata with CER-AP (7 injections) measured by qRT-PCR.

Figure S8

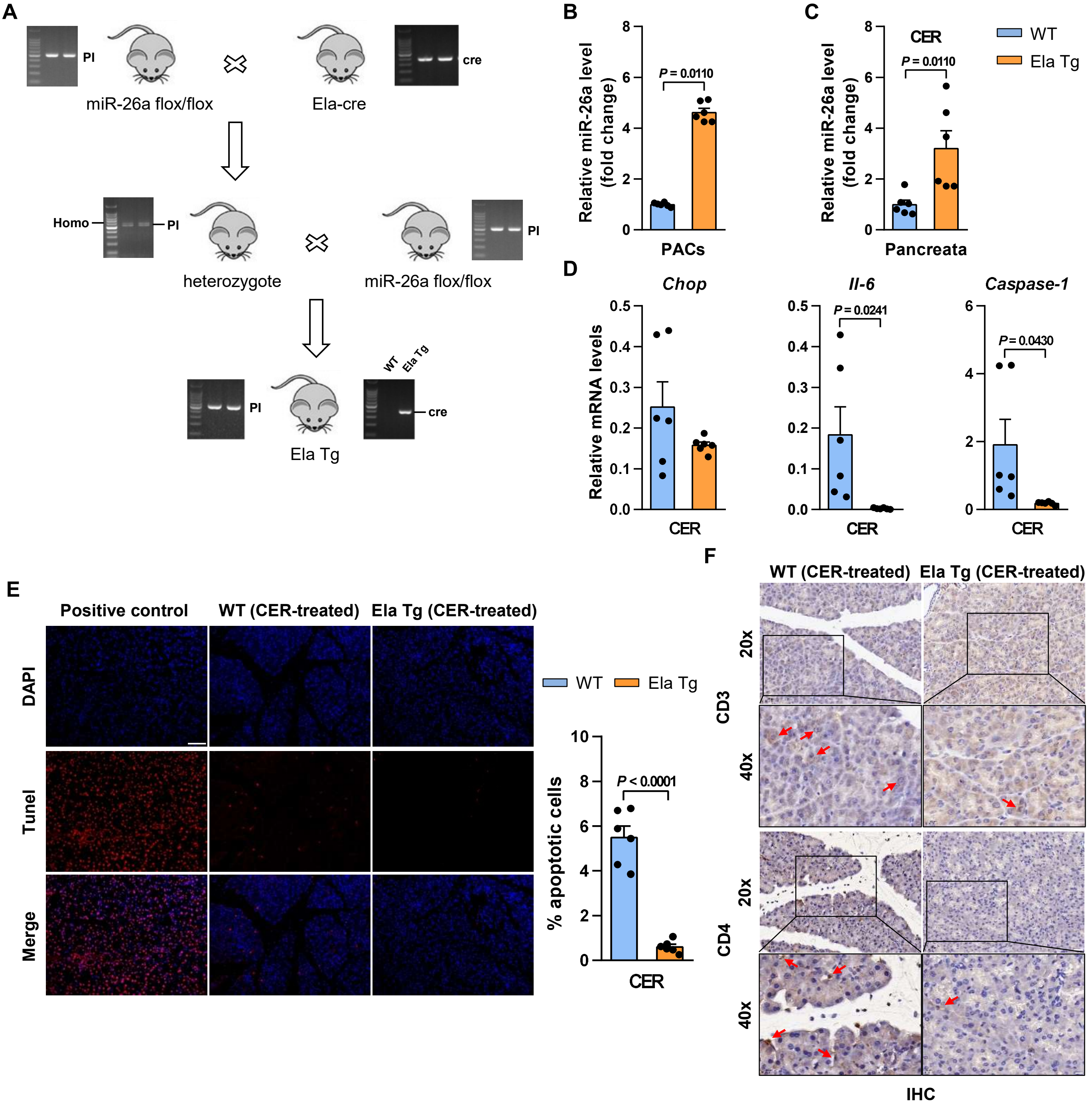
A
PI
miR-26a flox/flox
Ela-cre
cre
Homo
PI
heterozygote
miR-26a flox/flox
PI
PI
Ela Tg
WT
Ela Tg
cre
B
Relative miR-26a level (fold change)
P = 0.0110
PACs
C
CER
P = 0.0110
Relative miR-26a level (fold change)
Pancreata
WT
Ela Tg
D
Chop
Il-6
Caspase-1
Relative mRNA levels
P = 0.0241
P = 0.0430
CER
CER
CER
E
Positive control
WT (CER-treated)
Ela Tg (CER-treated)
DAPI
Tunel
Merge
WT
Ela Tg
% apoptotic cells
P < 0.0001
CER
F
WT (CER-treated)
Ela Tg (CER-treated)
CD3
CD4
20x
40x
20x
40x
IHC

Fig. S8. PAC specific miR-26a overexpression affects mRNA levels of oxidation, ER stress, and inflammation.
(A) Schematic showing the generation of PAC-specific miR-26a overexpression (Ela Tg) mice. (B) Levels of miR-26a in PACs of PAC-specific miR-26a overexpression (Ela Tg) and WT mice induced with tamoxifen. (C) Levels of miR-26a in the pancreata of Ela Tg mice on CER-AP. (D) Expression of (mRNA) *Chop, Il-6 and Caspase-1* in WT and Ela Tg mice with CER-AP (50 µg/kg/h × 7 caerulein) at 12 h. (E) Representative images of TUNEL images in the pancreata from WT and Ela Tg mice with CER-AP. *Scale bars*, 50 µm, magnification ×200. The percentage of TUNEL positive staining cells was counted per five fields. (F) Representative immunohistochemical staining (*scale bar*, 50 µm, magnification ×200) of CD3 and CD4 in WT and Ela Tg mice with CER-AP. Black outlines: higher magnifications of the indicated pancreata area in the low magnification images by black squares; High power view showing positive staining (red arrow). *scale bars*: 20 µm, magnification ×400.
Data are from 6 mice per group, shown as mean ± SEM.

Figure S9

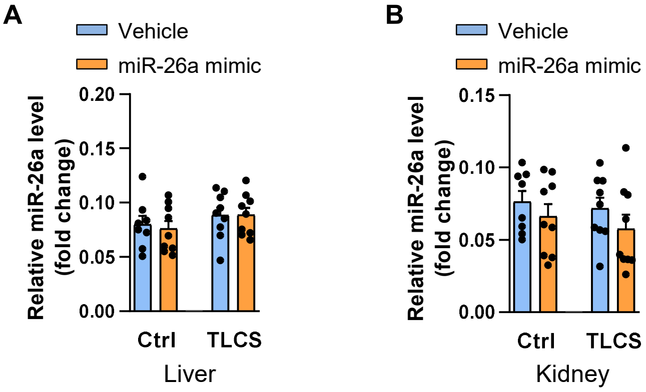

Figure S9. Expression of miR-26a in the liver and kidney of TLCS-AP WT mice with pancreatic injection of miR-26a mimic.

(A and B) Expression of miR-26a in the liver (A) and kidney (B) of TLCS-AP mice with or without administration of miR-26a mimic.

Data are from 8-9 mice per group, shown as mean ± SEM.

Figure S10

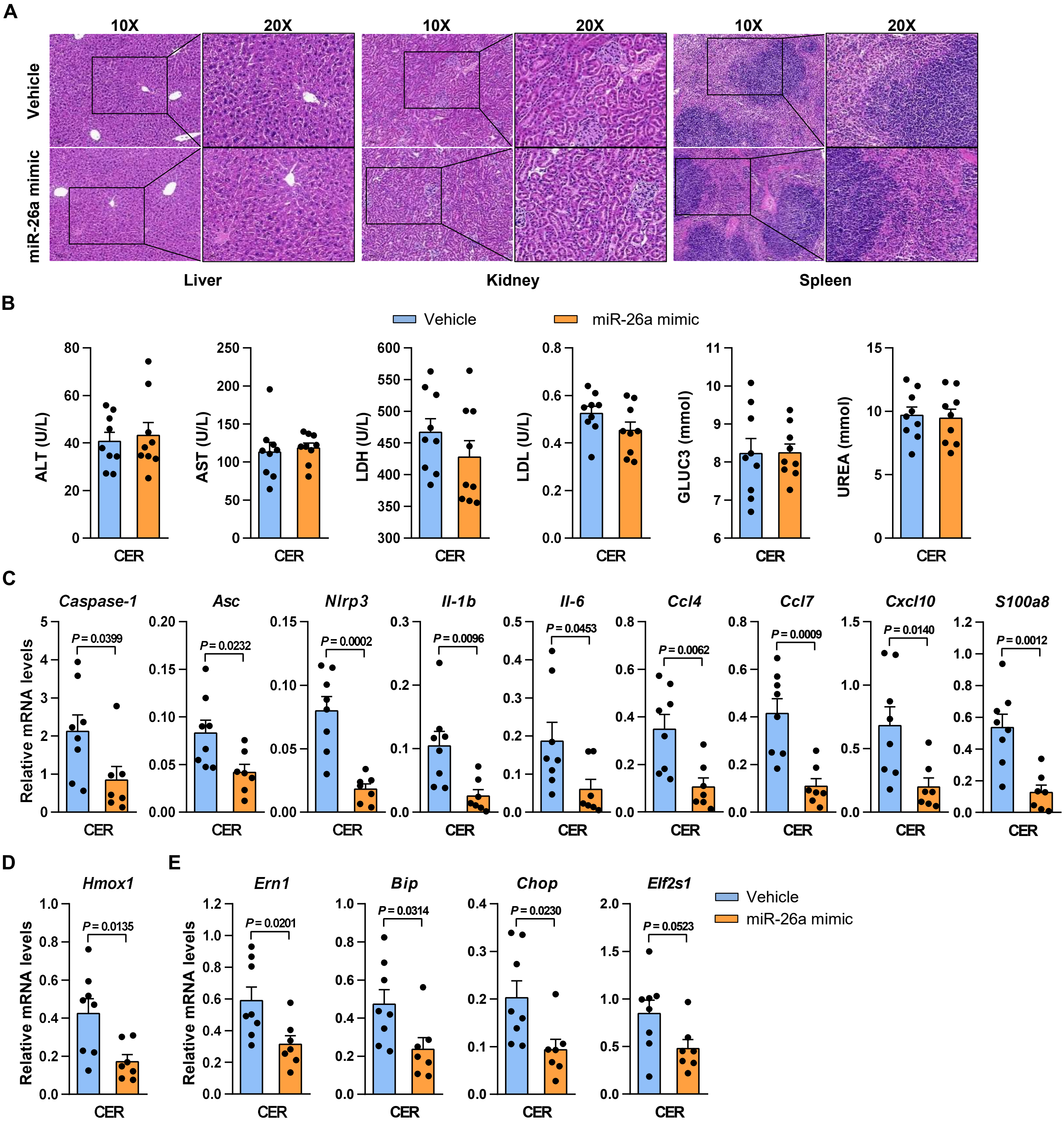
A
10X
20X
10X
20X
10X
20X
Vehicle
miR-26a mimic
Liver
Kidney
Spleen
B
Vehicle
miR-26a mimic
ALT (U/L)
AST (U/L)
LDH (U/L)
LDL (U/L)
GLUC3 (mmol)
UREA (mmol)
CER
C
Caspase-1
Asc
Nlrp3
Il-1b
Il-6
Ccl4
Ccl7
Cxcl10
S100a8
Relative mRNA levels
P = 0.0399
P = 0.0232
P = 0.0002
P = 0.0096
P = 0.0453
P = 0.0062
P = 0.0009
P = 0.0140
P = 0.0012
CER
D
Hmox1
Relative mRNA levels
P = 0.0135
E
Ern1
Bip
Chop
Elf2s1
Relative mRNA levels
P = 0.0201
P = 0.0314
P = 0.0230
P = 0.0523
CER
Vehicle
miR-26a mimic

Figure S10. Systemic administration of miR-26a mimic protects AP from inflammation, ER stress and oxidative stress.

(A) Representative H&E staining in the liver, kidney and spleen of CER-AP mice injected with miR-26a mimic (*scale bar*, 100 μm, magnification ×100) . Black outlines: higher magnifications of the indicated tissue area in the low magnification images by black squares; *scale bars*: 50 μm, magnification ×200. (B) Clinical chemistry and hematological parameters (measures of ALT, AST, LDH, LDL,GLUT3 and UREA) from the serum of CER-AP WT mice injected with miR-26a mimic. (C) Expression of inflammation-related genes in the pancreata of CER-AP WT mice injected with miR-26a mimic. (D) Expression of oxidative stress-related genes in the pancreata of CER-AP WT mice injected with miR-26a mimic. (E) Expression of ER stress-related genes in the pancreata of CER-AP WT mice injected with miR-26a mimic.

Data are from 7-8 mice per group, shown as mean ± SEM.

Table S1. TargetScan prediction of conserved miRNAs that target Ca^{2+} channels and Ca^{2+} regulator mRNAs.

Name	**Human**	**Mouse**
TRPC3	miR-19 **miR-26a** miR-130 miR-137/310/454 miR-218 miR-221/222	**miR-26a** miR-137 miR-218
TRPC6	**miR-26a** miR-29 miR-135	**miR-26a** miR-135
ORAI1	miR-7 miR-17/20/93/519 miR-183	miR-7 miR-183
STIM1	miR-223	None
SARAF (TMEM66)	miR-199 miR-217	miR-199

Table S2. Characteristics of patients from whom pancreatic tissue samples were obtained

Sample ID	Type	Gender	Age	BMI	Smoker	Alcohol abuse	Indication for surgery	Lesion region	Sampling location	Discharge diagnosis
AP-1	Pancreatitis	Male	51	17.3	Y	N	Infected pancreatic necrosis	Pancreatic body and tail	Pancreatic tail	Severe acute pancreatitis
AP-2	Pancreatitis	Male	55	19.8	Y	Y	Infected pancreatic necrosis	Pancreatic head and tail	Pancreatic tail	Severe acute pancreatitis
AP-3	Pancreatitis	Male	34	27.0	Y	Y	Pseudocyst	Pancreatic body and tail	Pancreatic tail	Pancreatic pseudocyst
AP-4	Pancreatitis	Male	49	21.9	N	N	Infected pancreatic necrosis	Pancreatic body	Pancreatic tail	Severe acute pancreatitis
AP-5	Pancreatitis	Male	41	20.7	Y	Y	Pseudocyst	Pancreatic head	Pancreatic head	Pancreatic pseudocyst
AP-6	Pancreatitis	Male	32	20.6	N	Y	Infected pancreatic necrosis	Pancreatic body and tail	Pancreatic tail	Severe acute pancreatitis
AP-7	Pancreatitis	Male	39	20.1	N	N	Portal hypertension	Pancreatic body and tail	Pancreatic tail	Pancreatic portal hypertension
AP-8	Pancreatitis	Male	55	21.5	Y	N	Pseudocyst	Pancreatic body and tail	Pancreatic tail	Pancreatic pseudocyst
AP-9	Pancreatitis	Male	42	20.8	Y	N	Pseudocyst	Pancreatic body and tail	Pancreatic tail	Pancreatic pseudocyst
AP-10	Pancreatitis	Female	62	N/A	N	N	Duodenal perforation	Pancreatic head	Pancreatic head	Duodenal perforation
NC-1	Normal	Male	64	24.4	Y	Y	Space-occupying lesion	Pancreatic body and tail	Upstream of lesion	Pancreatic adenocarcinoma
NC-2	Normal	Female	57	23.9	N	N	Space-occupying lesion	Duodenum	Upstream of lesion	Gastrointestinal stromal tumor
NC-3	Normal	Male	45	26.4	N	N	Space-occupying lesion	Pancreatic head	Upstream of lesion	Pancreatic adenocarcinoma
NC-4	Normal	Male	54	22.0	Y	Y	Space-occupying lesion	Pancreatic tail	Upstream of lesion	Pancreatic lesion without confirmative adenocarcinoma
NC-5	Normal	Female	65	23.9	N	N	Space-occupying lesion	Pancreatic tail	Upstream of lesion	Pancreatic adenocarcinoma
NC-6	Normal	Female	28	19.6	N	N	Space-occupying lesion	Pancreatic tail	Upstream of lesion	Solid pseudopapillary neoplasm of pancreas
NC-7	Normal	Male	67	23.3	Y	Y	Space-occupying lesion	Pancreatic head	Upstream of lesion	Pancreatic adenocarcinoma

BMI, body mass index; AP, acute pancreatitis; NC, normal control; Y, yes; N, no; N/A, not avaible.

Table S3. Characteristics of patients with infected or sterile pancreatic necrosis from whom pancreatic tissue samples were obtained for miR-26a analysis

Sample ID	Comorbidity	Worst MCTSI	Necroma/Pseudocyst	% Necrosis	Indication for surgery	Pancreatic infection	Extrapancreatic infection	Pancreatic pathology report
AP-1	Y	10	Y	> 50%	Infected pancreatic necrosis	Y	N	Necrosis with suppurative inflammation
AP-2	N	10	Y	> 50%	Infected pancreatic necrosis	Y	N	Necrosis with suppurative inflammation
AP-3	Y	6	Y	0	Pseudocyst	N	N	Consistent with necrotising pancreatitis and pseudocyst formation
AP-4	Y	10	Y	> 50%	Infected pancreatic necrosis	Y	N	Necrosis with suppurative inflammation
AP-5	N	8	Y	≤ 30%	Pseudocyst	N	N	Necrotic tissue with chronic inflammatory cell infiltration
AP-6	Y	8	Y	≤ 30%	Infected pancreatic necrosis	Y	N	Necrosis with suppurative inflammation
AP-7	N	4	N	0	Portal hypertension	N	N	Focal necrosis, calcification, chronic inflammation and fibrosis
AP-8	N	6	Y	0	Pseudocyst	N	N	Consistent with acute necrotising pancreatitis and pseudocyst formation
AP-9	Y	8	Y	≤ 30%	Pseudocyst	N	N	Necrosis with foam cell aggregation
AP-10	N	4	N	0	Duodenal perforation	N	Y	Focal necrosis and calcification

MCTSI, modified computed tomography severity index; Y, yes; N, no.

Table S4. Characteristics, complications, and outcomes of patients with AP from whom plasma samples are taken for miR-26a analysis.

Patient variables	**Total n = 85***
Characteristics	
Age (years)†	45 (36-52)
Male	59 (69.4)
Body mass index†	26.6 (23.1-28.7)
Smokers	32 (37.6)
Alcohol history	33 (38.8)
Diabetes mellitus	19 (22.4)
Charlson comorbidity index score†	1 (0-1)
Time from onset of pain to admission (h)†	24 (13-34)
Aetiology	
Hyperlipidaemia‡	44 (51.8)
Biliary	24 (28.2)
Alcohol excess§	6 (7.1)
Other	11 (12.9)
Complications	
Persistent organ failure	44 (51.8)
Respiratory	44 (51.8)
Circulatory	2 (2.4)
Renal	2 (2.4)
Multiple system	3 (3.5)
Acute necrotic collection	25 (29.4)
Acute peripancreatic fluid collection	39 (45.9)
Infection	29 (34.1)
Outcomes	
Need for HDU/ICU	5 (5.9)
Necrosectomy	3 (3.5)
Mortality	1 (1.2)
Length of hospital (days)†	11 (8-17)
Revised Atlanta Classification	
Mild	20 (23.5)
Moderately severe	23 (27.1)
Severe	42 (49.4)

*Values in parentheses are percentages unless indicated otherwise
†Values are medians (IQRs)
‡Serum triglyceride levels of ≥ 11.3 mmol/l on admission
§Drinking history > 35 standard drinks per week for > 5 years
HDU, high dependant unit; ICU, intensive care unit.

Table S5. Genes locations highlighted in SOM.

Table S6. Different genes expressed in caerulein-treated WT and WT control mice.

Table S7. Different genes expressed in caerulein-treated Hprt Tg and Hprt Tg control mice.

Table S8. Different genes expressed in caerulein-treated Hprt Tg and WT mice.

Table S9. Differentially expressed genes indicative of chemotaxis and immune responses in pancreata of WT mice with or without CER-AP versus Hprt Tg mice with or without CER-AP

Gene_name	WT3_NC_fpkm	WT4_NC_fpkm	WT5_NC_fpkm	TG1_NC_fpkm	TG4_NC_fpkm	TG5_NC_fpkm	WT1_CER_fpkm	WT2_CER_fpkm	WT3_CER_fpkm	TG1_CER_fpkm	TG2_CER_fpkm	TG3_CER_fpkm
Acod1	0	0	0.063498515	0	0.1594212	0.242492262	3.365555265	0.088129668	1.075709843	0.135283448	0.014925305	0.102527569
Arg1	0.162489623	0.046075586	1.719390438	0.033108324	1.266872618	0.32116892	0.159767393	0.242092883	1.185586007	0.063707089	0.263570975	0.144845502
Bbc3	1.704458008	1.111627737	1.097830724	0.83350673	1.107420038	0.935818626	5.999731986	4.788710546	3.222151186	2.338925975	1.843176814	2.785525386
Ccl3	0	0	0	0	0.136475785	0	4.647020267	0.804748888	1.175595905	0.092649735	1.022169074	0.983033265
Ccl4	0	0	0	0.22353135	0	0	4.314687909	1.75124332	1.45536398	0.322589531	0.474534249	1.629877664
Ccl7	0.45196864	0.384480917	0.311903753	0.184183135	2.022942571	0.397039453	37.77371905	16.73847547	24.65806295	9.568947873	13.73394535	16.11564432
Ccrl2	0.73157857	0.948327067	1.378355269	0.795007574	1.187045159	1.346541424	6.001202755	5.220026277	3.373721929	1.994144673	1.687719962	3.188236447
Cebpb	1.384078834	3.071501479	3.543757536	1.667567654	3.614430507	3.594738185	45.82060856	77.5158047	55.80266113	19.29960503	28.16442801	41.12623494
Csf3	0	0	0	0	0	0	2.116120821	0.654392408	0.934708289	0.100452508	0.692658803	0.418715918
Cxcl1	0	0.109500165	0.044415094	0.039341518	0.027877454	0	11.65656085	2.67122981	2.561440606	0.984113128	1.774758091	2.811212995
Cxcl10	0	0.182338197	0	0.098266446	0.02321058	0	6.164524132	0.239512852	0.666449425	0.283626674	0.208609639	0.453789208
Cxcl13	0	0	5.503609529	1.860169585	3.227118288	3.456832628	1.79528536	0.335020461	30.48671156	0.12342556	0.340426744	1.075719258
Cxcl3	0	0	0.023807405	0	0.014942889	0.090917268	0.264579919	0.044056436	0.085811555	0	0.033575536	0.030752409
Enpp2	0.156613117	0.444092425	0.720525195	0.931799659	4.504338544	2.325092304	4.34865889	0.400007126	4.97597734	0.4543829	0.501303269	1.200621079
Fos	0.192403742	0.785635752	2.018224158	0.282265353	1.022291831	0.067608121	31.20719105	11.07333786	5.053862802	2.021670782	3.878288521	6.265881734
Gadd45a	0.102615329	0.232780964	0.047209922	0.125451268	0.829686124	0.180288323	15.86088081	5.984407444	2.246161245	0.724180579	2.574429004	3.323509046
Gbp5	0.068183457	0.061869161	0.125475821	0.077799822	0.189013925	0	3.518320169	0.359905965	1.031166057	0.267325963	0.129769423	0.364678067
Gprc5b	0.254122541	0.266064117	0.557586904	0.223048561	1.625683049	0.635370317	1.952792335	0.765554315	1.996803388	0.383205706	0.820185816	0.975814446
Ifi47	0.365979459	0.622663192	0.37042512	0.447424256	0.866590885	0.225050567	2.821209199	0.903593399	2.451843988	0.401769411	0.474918021	0.869971094
Ikbke	0.260941975	0.409806008	0.517141818	0.613484245	0.65497178	0.396742268	0.63945225	0.529761785	0.632424883	0.236093469	0.334273544	0.256464449
Il1b	0.094920525	0.269156804	0.436697966	0.077362712	0.24668696	0.083384531	6.271795953	2.060718411	4.218418669	0.260507539	1.375452575	2.087132279
Itga2b	0.033189116	0.094111116	0.091615294	0.054099997	0.134173664	0.11662215	0.234958252	0.141281089	0.418277052	0.026024825	0.071780483	0.138064445
Itgb2	2.431700872	3.935386429	5.129856092	3.552918023	4.3501433	3.542913651	4.19876248	3.559866827	6.550210838	1.25568926	3.578830955	2.11478229
Itgb7	0	0.222360444	0.481029904	0.319561064	0.584973646	0.200920597	1.285060478	0.445081335	2.665759204	0.230587462	0.862127656	0.368928988
Junb	1.416011268	1.338414667	2.967762178	1.282318046	2.08990038	2.487837824	195.6320001	148.7179268	70.70469403	36.20965839	37.3796258	88.54464473
Lpl	2.634524687	6.338871351	4.649532995	5.554576989	15.99335216	3.710536035	3.016740181	2.485635679	6.800923659	1.774581079	1.546833105	2.304819369
Mmp28	0.070087806	0.158992883	0.150477056	0.285616981	0.728598914	0.143662894	0.459424048	0.775718517	0.526883836	0.146555904	0.181900712	0.416514943
Mmp9	0.076722283	0.522129214	0.564758194	0.291809788	1.01911432	0.3369899	0.603495483	0.239503184	0.865137602	0.320857629	0.221243716	0.182376817
Padi2	6.2468233	6.081977314	7.97398464	6.886531368	3.493023268	5.582788143	6.859346756	6.88619755	3.688489801	2.435026498	1.522854524	3.154413145
Rac2	0.175004938	0.231580675	0.268379962	1.117296566	1.549745657	0.743057481	0.940665927	0.744969765	4.043524562	0.45742634	0.89577324	0.589340232
Rarres2	0.715602833	1.004919627	1.881286945	0.944285298	7.045459652	1.017787318	1.769087023	1.334531807	2.328116608	0.694733477	0.766472864	0.992286213
Ripor2	0.108651525	0.035210566	0.035704983	0.177107673	0.19273021	0.04772338	0.177034657	0.09910998	0.427268258	0.018256653	0.137636091	0.106077615
S100a8	0	0	0	0	0.301269313	0.229127235	4.923966605	1.33235803	8.131374401	0.102261811	2.03078778	1.472526362
Saa3	0.034730131	0.236353964	1.118472975	0.084917896	1.564496398	1.311898492	10.90013348	1.981068805	16.86289923	0.626363402	2.05810566	2.435435005
Selplg	0.08474412	0.216270516	0.331397738	0.293541872	0.513892669	0.186112244	0.766584298	0.378780156	1.3631262	0.199353081	0.540682457	0.302168331
Serpine1	0.070051641	0.079455422	0.06445689	0.057093921	0.134856104	0.041025361	19.52463069	5.725427076	7.759782214	1.208462328	4.151256462	3.760576871
Sesn2	2.031517749	1.595236221	2.420462881	1.401010881	1.203343328	1.53294362	31.98021845	37.49626128	25.79292372	3.145131884	9.147927867	12.89315313
Trem2	0	0.041510879	0.252562582	0.059656567	0.327613627	0.080375203	0.244696716	0.062316786	0.279170355	0.028697815	0.102898905	0.043498555
Trpm2	0	0	0.020052565	0.011841295	0.041953789	0	0.097140217	0.061846622	0.134918163	0.011392519	0.034564558	0.025902221
Trpv4	0.177638313	0.251855753	0.326902069	0.434339621	0.397540971	0.5266666	0.541453107	0.434803297	0.76588708	0.208939245	0.124862115	0.263915422
Vcam1	0.081629511	0.092587513	0.131442641	0.207906837	0.542148903	0.080672419	1.958391603	0.634159362	1.197968012	0.568077618	0.4855015	0.81255006
Vegfa	15.03868957	13.4399634	10.80577269	14.32269955	10.35645781	9.629920907	42.31666667	31.055654	23.69127077	15.50236549	12.87305658	17.83660521

Table S10. Differentially expressed genes indicative of ER stress in pancreata of WT mice with or without CER-AP versus Hprt Tg mice with or without CER-AP

Gene_name	WT3_NC_fpkm	WT4_NC_fpkm	WT5_NC_fpkm	TG1_NC_fpkm	TG4_NC_fpkm	TG5_NC_fpkm	WT1_CER_fpkm	WT2_CER_fpkm	WT3_CER_fpkm	TG1_CER_fpkm	TG2_CER_fpkm	TG3_CER_fpkm
Alox15	0	0.041832276	0.237550169	0	0.702900347	0.518384029	2.030751644	0.188397814	1.369963649	0	0.095719011	0.197259033
Bbc3	1.704458008	1.111627737	1.097830724	0.83350673	1.107420038	0.935818626	5.999731986	4.788710546	3.222151186	2.338925975	1.843176814	2.785525386
Bhlha15	93.20068101	137.7370425	94.36141899	67.36840809	36.78663	90.68002134	54.34172832	59.61043803	34.93092233	21.38840602	16.95264777	28.6478755
Cebpb	1.384078834	3.071501479	3.543757536	1.667567654	3.614430507	3.594738185	45.82060856	77.5158047	55.80266113	19.29960503	28.16442801	41.12623494
Chac1	44.94927523	28.28224719	30.93048727	13.33814435	3.67200731	12.62789195	788.1606402	949.6980755	546.6116404	43.18009648	55.02872499	178.4760846
Ddit3	5.230686109	5.393506391	4.083699577	2.971283624	2.227511082	2.970494821	5.859965802	2.339080394	1.647161072	1.160041744	1.005580458	1.789725561
Ern1	6.987610482	4.534315697	5.869118072	5.902671728	5.871047018	6.605329152	16.29767378	16.09352542	16.21124649	9.742811663	8.243675395	12.48402932
Ero1lb	73.03931775	57.64682534	51.1586383	50.65893043	27.1368345	42.9623036	28.68881582	26.09413088	13.83312198	7.371119861	9.67987814	8.359339494
Herpud1	297.473438	412.6497067	228.4174261	111.8337023	52.47186833	165.7279351	215.8962193	298.079178	128.6878932	66.07208799	46.46540513	109.3471162
Lman1	27.52895094	21.55288116	22.238723	20.92952171	14.08059272	22.98030725	9.583372091	8.293206549	6.330186335	5.047914788	3.847124878	4.631079633
Nhlrc1	0.157814682	0.268499751	0.25411862	0.289401966	0.432926892	0.346587404	0.993092945	2.082559623	1.727213791	1.051861242	0.529041561	0.867515531
Nrbf2	3.016890675	3.145922088	3.313222771	3.608949705	3.091249913	2.949458807	23.08010072	21.4178941	14.00787831	10.72176601	6.966851615	11.16203316
Ppp1r15a	2.095490969	2.446696748	2.268390932	2.235313504	0.783074544	2.788299795	49.47347203	36.20547987	10.40421722	4.37368577	6.838091846	16.3903428
Rnf5	10.74118865	10.59098446	9.714865988	6.764724885	4.229552998	8.953266437	2.97634911	6.338957613	3.926685858	2.10564171	1.082341266	2.139832645
Sesn2	2.031517749	1.595236221	2.420462881	1.401010881	1.203343328	1.53294362	31.98021845	37.49626128	25.79292372	3.145131884	9.147927867	12.89315313
Trib3	2.001795695	2.31882703	2.390577142	0.867827596	0.66413934	0.97279337	47.77425497	60.04827917	36.27451916	14.52791439	18.0177863	36.27072229

Table S11. Primers for qRT-PCR analysis.

5s rRNA	F	TCTACGGCCATACCACCCTGAA
	R	CCAAGTACTAACCAAGGCCCGA
mAmylase 2	F	TGGCGTCAA ATCAGGAACATG
	R	AAAGTGGCTGACAAAGCCCAG
mAsc	F	GCTACTATCTGGAGTCGTATGGC
	R	GACCCTGGCAATGAGTGCTT
mBip	F	ACTTGGGGACCACCTATTCCT
	R	ATCGCCAATCAGACGCTCC
mCaspase-1	F	ACAAGGCACGGGACCTATG
	R	TCCCAGTCAGTCCTGGAAATG
mCcl3	F	TGTACCATGACACTCTGCAAC
	R	CAACGATGAATTGGCGTGGAA
mCcl4	F	TGTCTGCCCTCTCTCTCCTC
	R	TTGGAGCAAAGACTGCTGGT
mCcl7	F	CCAATGCATCCACATGCTGC
	R	CTCGACCCACTTCTGATGGG
mChop	F	CTGGAAGCCTGGTATGAGGAT
	R	CAGGGTCAAGAGTAGTGAAGGT
mCpa1	F	GCCACGGTAAGTTTCTGAGCA
	R	ACACCCACAAAACGAATCGC
mCxcl10	F	AAGTGCTGCCGTCATTTTCT
	R	CCTATGGCCCTCATTCTCAC
mEif2s1	F	ACAAACTGATCCGAATTGGCAG
	R	TGCTTCCTCTGGAGAAACTCT
mEnpp2	F	GGCTGTTTCGGGTCATACCA
	R	TGGGAGGTCCTTCATCCCAT

mErn1	F	CAATCGTACGGCAGTTGGAG
	R	CTCCCGGTAGTGGTGTTTCT
mEro1lb	F	ACCCTGAGCTTCCTCTCAAGT
	R	AAAGGACATGGTCGTTTCAGATT
mIl-1β	F	AAATACCTGTGGCCTTGGGC
	R	CTTGGGATCCACACTCTCCAG
mIl-6	F	CCAGAGATACAAAGAAATGATGG
	R	ACTCCAGAAGACCAGAGGAAAT
mLman1	F	GATGGGACCGTGCCCTTTT
	R	GCTTTTTAATGACGGCGCTATTC
mNlrp3	F	ATCAACAGGCGAGACCTCTG
	R	GTCCTCCTGGCATACCATAGA
mRbpjl	F	ACTCCGGTGCCTCTCATCAG
	R	CTACGCACACCAAGGAACGA
mS100a8	F	CAGCTGACACTTAGCCTCACA
	R	TTCTCCAGTTCAGACGGCAT
mTrpc1	F	ATCATCGGCCAAAACGATCAT
	R	GCAGCTAAAATAACAGGTGCGA
mTrpc3	F	GCATACTTGTCGCTGTCCAG
	R	TCCAGCACACCCACTACGAA
mTrpc6	F	AGCCAGGACTATTTGCTGATGG
	R	AACCTTCTTCCCTTCTCACGA

Table S12. Luciferase genes 3'UTR primers.

mTRPC3-3'UTR	F	CCGCTCGAGGGCAGCCACCTGCAGTCAA
	R	GGACTAGTCAGCGTTTGGATGAGAACGTATGC
mTRPC3-3'UTR-mut	F	GTATGAAATATCTAGAAAACTATGGTGTAGAGCTCTAG
	R	TTAGGAGTATTATTGCCC
mTRPC6-3'UTR	F	CCGCTCGAGAGCAGAGCCCCTCAGAAGTG
	R	GGACTAGTCAGCAATTGTTAGCCTCAGCAATGC
mTRPC6-3'UTR-mut	F	TAGGCCATATTATTTTCTGACTTATTTTTTTAAG
	R	GATAGGAGAAATAAATATGCACTTC