counting, zymogen granule area and number, and stained surface area were performed by a blinded scorer after de-identifying and randomizing samples by shuffling files. P*≤0.05, P**≤0.01, P***≤0.001.

**Study approval**

Animal care guidelines were followed as approved by the University of Michigan Animal Care and Use Committee, as well as the recommendations in the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health[12].

**B. Supplemental Figure Legends**

**Figure S1: Characterization of LMNA-KO pancreata**. (A) Transgenic mice expressing CreERT2 driven by the *Cela1* promotor were bred with $Lmna^{fl/fl}$ mice. Tamoxifen was administered to promote recombination of the *loxP* sites and excision of exons 10 and 11 of the floxed *Lmna* gene. (B) Representative LMNA immunostaining in control and KO-pancreata at 4-, 6- and 21 days- post-tamoxifen injection. White: LMNA; blue: DAPI. LMNA is efficiently deleted in -/- mice ($Lmna^{fl/fl}$ Cre+), but not in +/+ mice ($Lmna^{fl/fl}$ Cre-). Scale bar = 20 μm. (C) Representative hematoxylin and eosin stained sections for control and KO mice 3 and 4 days post-tamoxifen administration. No obvious phenotype was observed at the 3-day time point. Decreased eosin staining and smaller acini were noted 4 days after tamoxifen administration (insets). Scale bar = 50μm. (D) Immunoblotting of 4-day lysates from pancreata of control and KO mice (each lane corresponds to an animal), using supernatant soluble (amylase/Grp78) and pellet (chop) fractions. Protein loading was confirmed by Coomassie staining (lower 2 rows). The link between ER stress and lamins was recently reported in several contexts: (i) LMNA mislocalization to the ER triggers ER stress and cellular dysfunction[13], (ii) an anti-viral drug causes an ER stress-like transcriptional response while impairing lamin A maturation[14], and (iii) a *LMNA* mutation that causes familial dilated cardiomyopathy increases the unfolded protein response[15]. Although none of these studies report findings in the absence of LMNA, they all have altered lamins and ER stress response in common. (E) RT-qPCR was used to quantify changes in expression of acinar and ductal cell markers six days after tamoxifen injection. Decreased amylase transcription

and increased transcription of keratins 8, 18, and 19 was observed. N = 6 mice/group. (F) Relative expression of several acinar cell markers was determined by microarray analysis and is shown with a heat map using CIMminer. Black indicates relative expression ~1, red indicates expression >1, and blue indicates expression <1. *p≤0.05, **p≤0.01, ***p≤0.001.

**Figure S2: Mice administered tamoxifen by oral gavage develop a similar phenotype to mice treated by the intraperitoneal route six days after administration.** (A) Mice were administered tamoxifen (75mg/kg mouse weight) by oral gavage. Representative hematoxylin and eosin stained sections of KO and control pancreata. Decreased eosin staining, smaller acini and apoptotic bodies were noted. Scale bar = 20μm. (B) Immunoblots of the indicated proteins from pancreas lysates of mice treated with tamoxifen by oral gavage are similar to those treated by IP. The last lane represents a pancreas lysate from a mouse treated by IP for comparison. Similarities include increased Grp78 (S - supernatant), chop and presence of insoluble Grp78 in males (P - pellet). Apoptosis was assessed by cCasp7, which was elevated in KO mice. Coomassie stained gels confirm equal loading (bottom two rows). (C) Immunoblots of pancreatic amylase and lipase in oral gavage group showing exocrine pancreas enzymes are reduced in KO-pancreata. (D) DBA staining of pancreata isolated from the oral gavage group shows increased ductal cell staining in the KO-pancreata. (E) TUNEL staining in the oral gavage group shows increased apoptosis in KO-pancreata. *p≤0.05, **p≤0.01.

**Figure S3: Characterization of ultrastructural abnormalities, inflammation and LC3 in KO-pancreata.** (A) Ultrastructural abnormalities observed in KO-pancreata six days post-tamoxifen administration. Left panel: control acinar cells contained more round and regular-shaped nuclei, classified as “normal” (as quantified in Figure 1D). Middle panel: $LMNA^{-/-}$ pancreatic acinar cells often contained nuclei wih irregular perimeters and apparent disruption of heterochromatin, classified as “abnormal” (as quantified in Figure 1D). Arrowheads indicate electron-dense material-containing vacuoles likely due to increased autophagy. Right panel: Swirling ER with lipid-like

deposits in the center. Image was captured from LMNA$^{-/-}$ pancreata and represents "abnormal" ER (as quantified in Figure 1D). Scale bar = 2μm. (B) Granule quantification at six days post-tamoxifen injection. Note the decreased number of granules and granule area. (C) Immunoblots of LC3B from three independent experiments show increased expression of LC3-II in KO-pancreata (observed six days post-tamoxifen administration) compared to controls (left). Relative quantification of LC3B immunoblots shows increased LC3-II:LC3-I ratio in KO-pancreata (right). (D) RT-qPCR analysis of genes associated to pancreatitis 21 days post-tamoxifen injection. N = 5-8 mice/group. (E) Granule quantification at 21 days post-tamoxifen injection. Representative electron micrographs display the increased number of granules observed in KO cells at 21 days. *p≤0.05, ***p≤0.001.

**Figure S4. Disruption of *Lmna* leads to alterations consistent with pancreatic fibrosis, preferentially in males.** (A) Male KO-pancreata have higher expression of ACTA at 21 days after tamoxifen injection. Immunoblots for ACTA from two representative experiments show expression in KO males is consistently higher than in control males. (B) Relative quantification of ACTA immunoblots from four independent experiments (8-10 mice/genotype/sex). KO male pancreata have increased ACTA expression compared to male controls. (C) Quantification of pancreatic hydroxyproline (21d). KO-pancreata have increased hydroxyproline content compared to controls. *p≤0.05.

**References***


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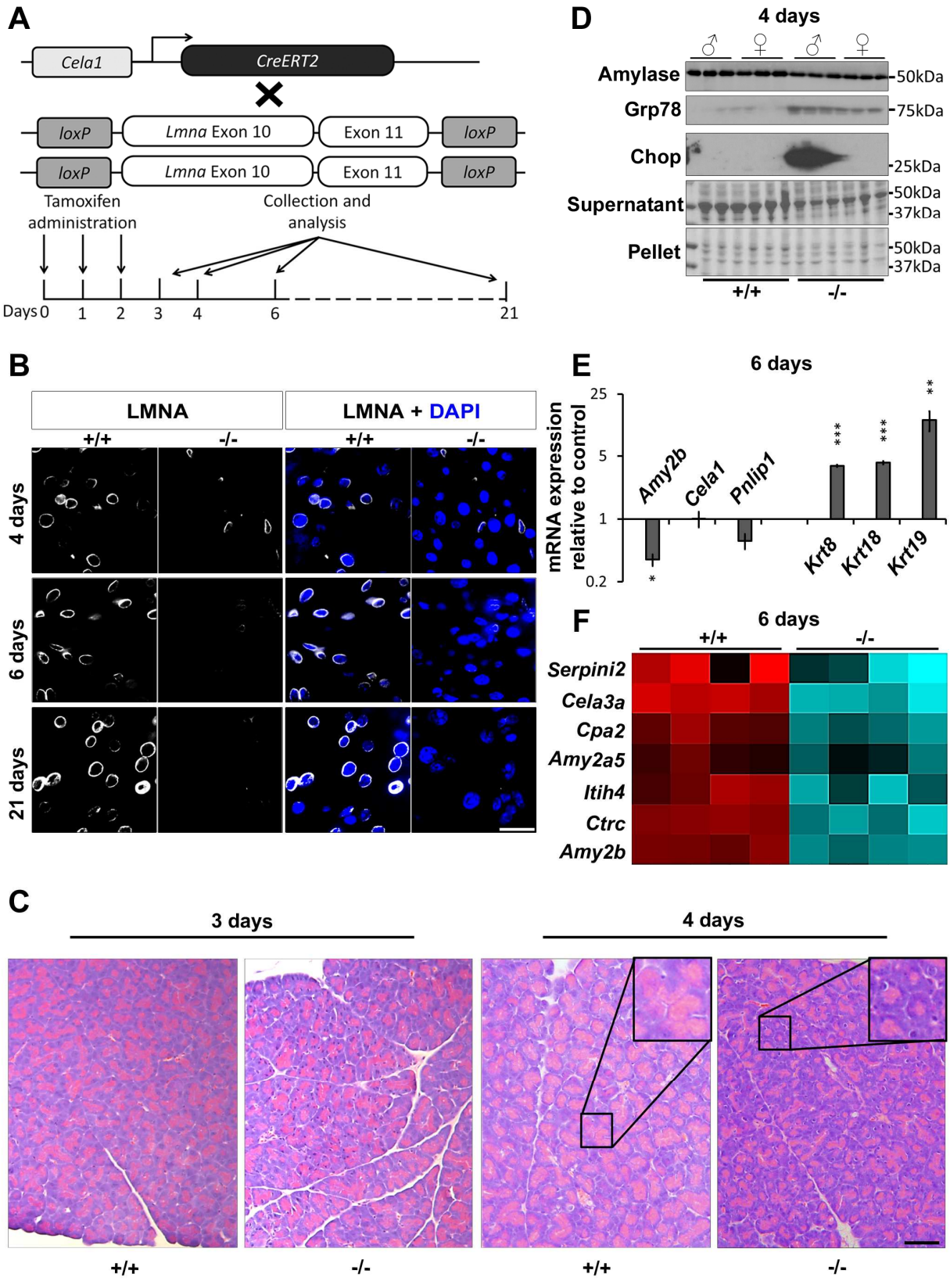
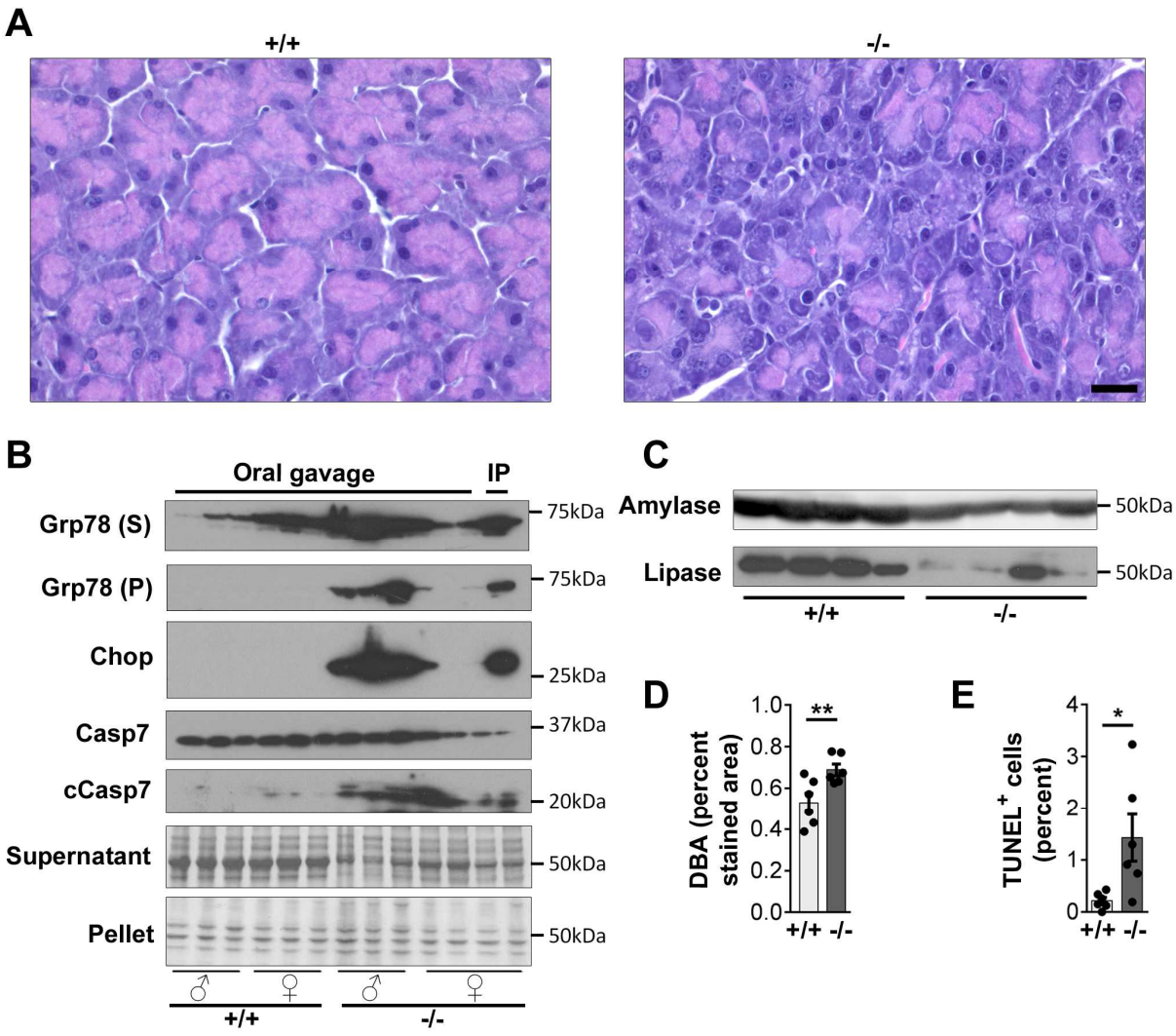
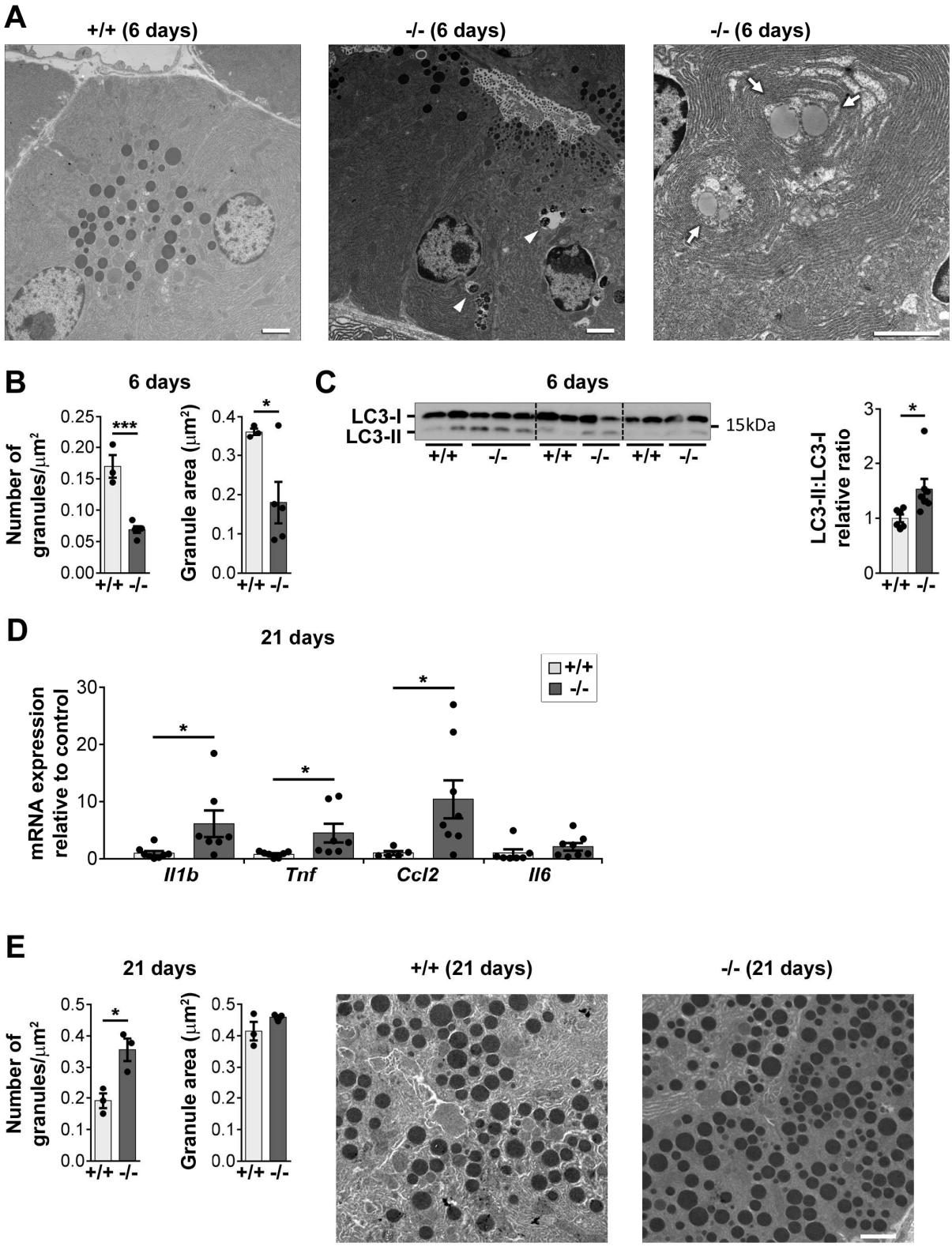
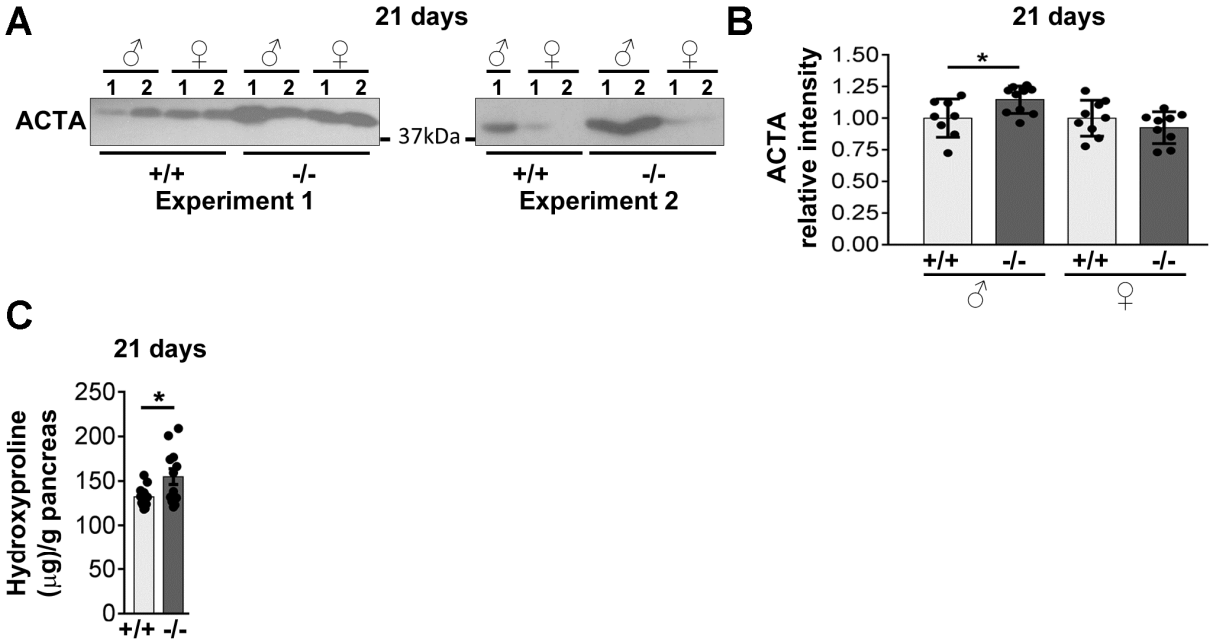
Table S1. Forward and reverse qPCR primers are listed 5' to 3' for the indicated target gene.

| Gene | Forward | Reverse |
|---|---|---|
| *Acta2* | TCAGCGCCTCCAGTTCCT | AAAAAAAACCACGAGTAACAAATCAA |
| *Amy2b* | CCTTCTGACAGAGCCCTTGTG | GGATGATCCTCCAGCACCAT |
| *Apaf* | GAACATAGACTCCCGCCTAAAG | TTTGTCTCCCAGACCCTTATTG |
| *Atf2* | ATGCAGAAGAAGTCTGGCATAC | GCTGGATCGCTTCTGTATGT |
| *Atf4* | ACTATCTGGAGGTGGCCAAG | CATCCAACGTGGTCAAGAGC |
| *Casp8* | AAGCGCAGACCACAAGAACAAAGA | TTCACGCCAGTCAGGATGCTAAGA |
| *Ccl2* | AACTACAGCTTCTTTGGGACA | CATCCACGTGTTGGCTCA |
| *Ccne1* | GACGTTCTACTTGGCACAGGA | ACACAATGGTCAGAGGGCTTA |
| *Cdkn1a* | CCCGAGAACGGTGGAACTT | TGCAGCAGGGCAGAGGAAG |
| *Cela1* | CTGAAGCCCGGAGGAACTC | TGGTGCCATGATCCTCCATA |
| *Col1a1* | TCTGACTGGAAGAGCGGAGAG | GGCACAGACGGCTGAGTAGG |
| *Ddit3* | CAGCGACAGAGCCAGAATAA | GACCAGGTTCTGCTTTCAGG |
| *E2f1* | TCACTAAATCTGACCACCAAACG | TTGGACTTCTTGGCAATGAGC |
| *Hes5* | AAAATGCTGCACACTGCAGG | CGAGTCCTTCAATGATGCTCAG |
| *Hspa5* | GAGACTGCTGAGGCGTATTT | TGACATTCAGTCCAGCAATAGT |
| *Il1b* | GTCCGTCAACTTCAAAGAACAG | GCAAGTGTCTGAAGCAGCTAT |
| *Il6* | AGTTGCCTTCTTGGGACTGA | TCCACGATTTCCCAGAGAAC |
| *Krt18* | CAAGTCTGCCGAAATCAGGGAC | TCCAAGTTGATGTTCTGGTTTT |
| *Krt19* | GAAGATCACCATGCAGAACC | GAATCCACCTCCACACTGAC |
| *Krt8* | GGACATCGAGATCACCACCT | TGAAGCCAGGGCTAGTGAGT |
| *Map3k5* | TCCCTGGAGTATGACTACGAATA | CCTGCATAGACGATCCCATAAG |
| *Mcm3* | GCTTTGCCATTGGGTAGTTC | CGCAGGCGTGAGTATTCTTC |
| *Pcna* | TGAAGAAGGTGCTGGAGGCT | TTGGACATGCTGGTGAGGTT |
| *Pnlip* | AGAGGACCTTTGGAGCCATTGGAA | ATTGCGTCCACAAACTGAGCATCG |
| *Pola1* | GCTACAGAGGATGAGGAACAAG | TTTCTCCGCTCTACCAGTTTC |
| *Ppm1d* | ACCTGACTGATAGCCCTACTT | GCATCTTCTTCCGGTGACTT |
| *Rb1* | CTGGACTCTGTTTCAGCATACA | CCTTGCAGATGCCATACATAGA |
| *Rbl1* | GCAGTCACCACGCCTGTAGC | TTCCCATAGGATTCCGCATAC |
| *Rn18s* | AAACGGCTACCACATCCAAG | CCTCCAATGGATCCTCGTTA |
| *Tnf* | CGTCAGCCGATTTGCTATCT | CGGACTCCGCAAAGTCTAAG |
| *Xbp1* | ACACGCTTGGGAATGGACAC | CCATGGGAAGATGTTCTGGG |


A
Cela1
CreERT2
loxP
Lmna Exon 10
Exon 11
loxP
loxP
Lmna Exon 10
Exon 11
loxP
Tamoxifen administration
Collection and analysis
Days 0 1 2 3 4 6 21
D
4 days
♂ ♀ ♂ ♀
Amylase
Grp78
Chop
Supernatant
Pellet
50kDa
75kDa
25kDa
50kDa
37kDa
50kDa
37kDa
+/+ -/-
B
LMNA
LMNA + DAPI
+/+ -/- +/+ -/-
4 days
6 days
21 days
E
6 days
mRNA expression relative to control
25
5
1
0.2
Amy2b
Cela1
Pnlip1
Krt8
Krt18
Krt19
F
6 days
+/+ -/-
Serpini2
Cela3a
Cpa2
Amy2a5
Itih4
Ctrc
Amy2b
C
3 days
4 days
+/+ -/- +/+ -/-


A
+/+
-/-
B
Oral gavage
IP
Grp78 (S)
Grp78 (P)
Chop
Casp7
cCasp7
Supernatant
Pellet
75kDa
75kDa
25kDa
37kDa
20kDa
50kDa
50kDa
+/+
-/-
C
Amylase
Lipase
50kDa
50kDa
+/+
-/-
D
DBA (percent stained area)
1.0
0.8
0.6
0.4
0.2
0.0
**
+/+ -/-
E
TUNEL+ cells (percent)
4
3
2
1
0
*
+/+ -/-


A
+/+ (6 days)
-/- (6 days)
-/- (6 days)
B
6 days
Number of granules/μm²
Granule area (μm²)
***
*
+/+ -/-
C
6 days
LC3-I
LC3-II
15kDa
+/+ -/- +/+ -/- +/+ -/-
LC3-II:LC3-I relative ratio
D
21 days
mRNA expression relative to control
+/+
-/-
Il1b
Tnf
Ccl2
Il6
E
21 days
+/+ (21 days)
-/- (21 days)


A
21 days
♂ ♀ ♂ ♀
1 2 1 2 1 2 1 2
ACTA
37kDa
+/+ -/-
Experiment 1
Experiment 2
B
21 days
ACTA relative intensity
1.50
1.25
1.00
0.75
0.50
0.25
0.00
*
+/+ -/- +/+ -/-
♂ ♀
C
21 days
Hydroxyproline (μg)/g pancreas
250
200
150
100
50
0
*
+/+ -/-