Science Advances
AAAS

Supplementary Materials for

Perinuclear damage from nuclear envelope deterioration elicits stress responses that contribute to *LMNA* cardiomyopathy

Kunal Sikder *et al.*

Corresponding author: Jason C. Choi, jason.choi2@jefferson.edu

Sci. Adv. **10**, eadh0798 (2024)
DOI: 10.1126/sciadv.adh0798

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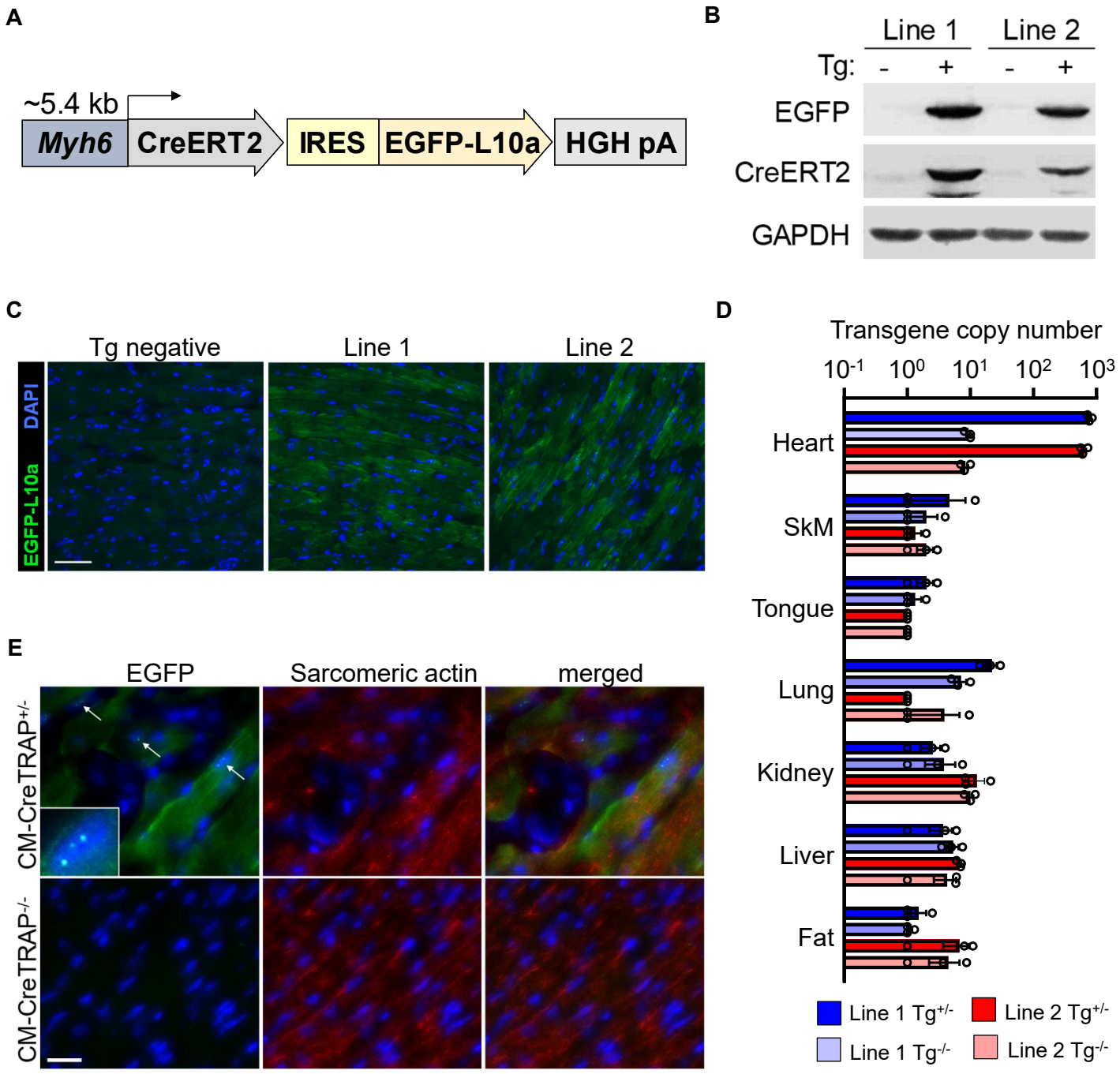
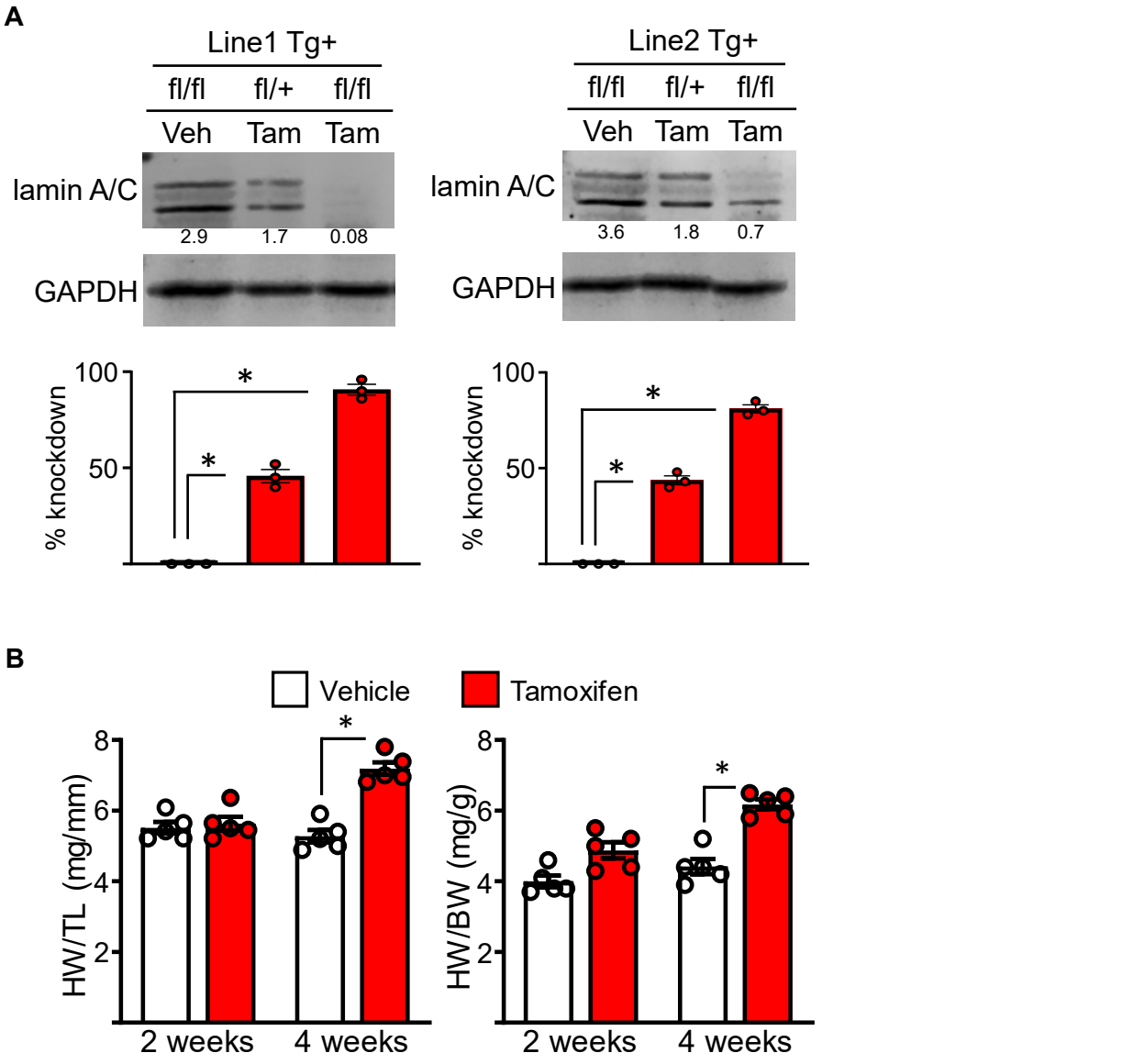
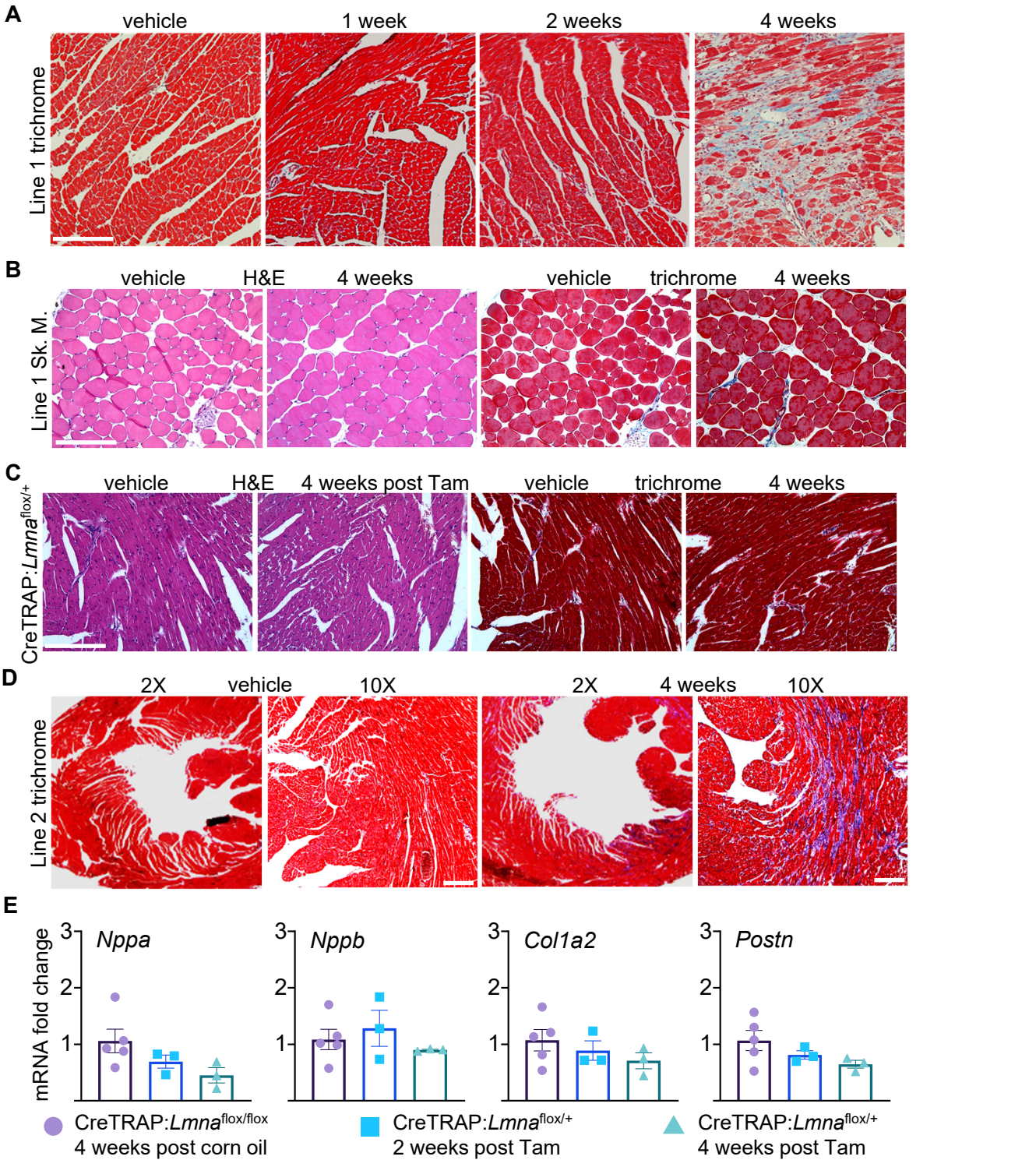


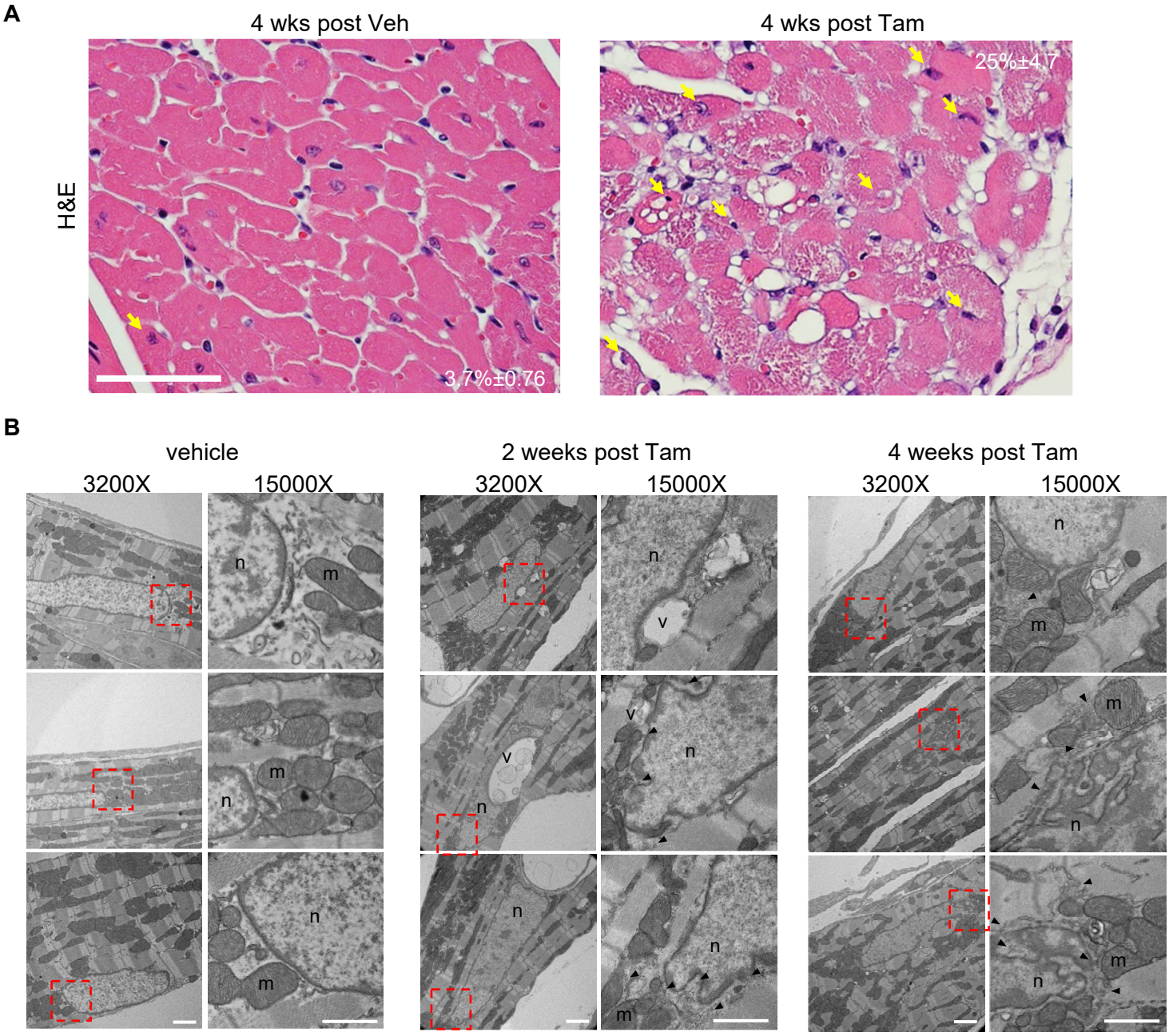
Supplementary Fig. 1. Generation and EGFP-L10a expression in CM-CreTRAP mice. (**A**) Schematic of the transgene vector. IRES and HGH pA denote internal ribosomal entry site and human growth hormone polyadenylation signal, respectively. (**B**) Immunoblot of GFP, CreERT2, and GAPDH on the heart extracts from 8-week-old lines 1 and 2 at F2. - and + signs denote transgenic (Tg) negative and positive, respectively. (**C**) Direct fluorescence micrograph images of heart sections from CM-CreTRAP transgenic (Tg) line 1 and line 2 showing robust green fluorescence signal but not in hearts from the Tg negative mice. DAPI counterstain shows the nucleus. Scale bar = 100μm. (**D**) qPCR of transgene (CreERT2) mRNA expression (as fold change over Tg-) in various tissues normalized to *Rpl13a* from 8-week-old line 1 and 2 mice. SkM denotes skeletal muscle (quadriceps). Error bars indicate SEM. n = 3. (**E**) EGFP and sarcomeric actin staining on 8-week-old Tg+ and Tg- hearts from line 1. White arrows and inset highlight enriched areas of EGFP-L10a in the nucleolus. Scale bar = 30μm. Representative images represent data from 2 independent experiments.



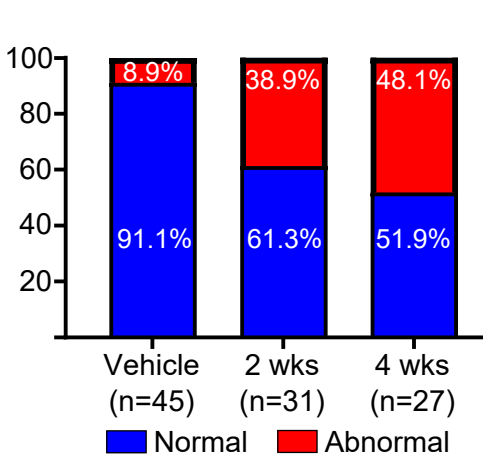
Supplementary Fig. 2. CM-specific depletion of lamin A/C. (**A**) Immunoblot of lamin A/C and GAPDH in CM extracts from Tg+ line 1 (left) and line 2 (right) mice with (+) or without (-) tamoxifen (Tam) administration. fl/fl and fl/+ denote homozygous and heterozygous *Lmna* flox, respectively. The numbers in line with blots denote quantitation of lamin A/C blot normalized to GAPDH in arbitrary units. The bottom shows % knockdown calculation with one-way ANOVA with Dunnett post hoc. n=3. (**B**) Assessment of heart weight (HW) of CM-CreTRAP:*Lmna*$^{flox/flox}$ mice at 2 and 4 weeks post last Tam dosing. The left panel shows the HW relative to tibia length (TL) and the right panel relative to body weight (BW). P values were derived using unpaired, two tailed Student's t test. For all data in this figure, * = $p < 0.0001$. Error bars = SEM. n=5.

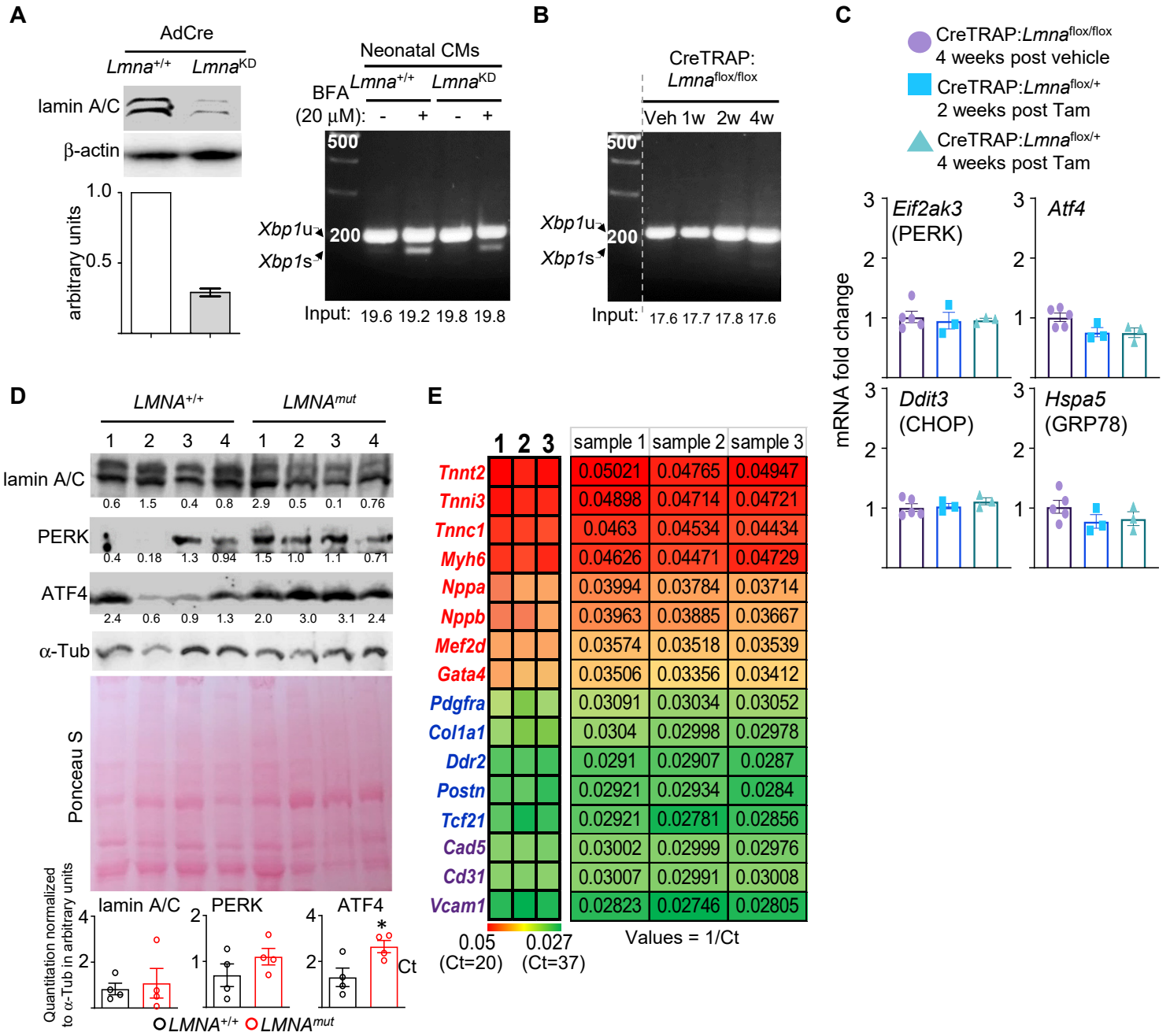


Supplementary Fig. 3. CM-specific depletion of lamin A/C causes cardiac remodeling. (**A**) A representative Masson's trichrome staining of hearts from line 1 CM-CreTRAP:*Lmna*$^{flox/flox}$ mice at 1, 2, and 4 weeks post tamoxifen and vehicle treatment from 3 mice per group (**B**) A representative hematoxylin and eosin (H&E) and Masson's trichrome staining of quadriceps from line 1 CM-CreTRAP:*Lmna*$^{flox/flox}$ mice at 4 weeks post tamoxifen and vehicle treatment. 3 mice per group. Sk.M. denotes skeletal muscle. (**C**) H&E and Masson's trichrome staining of hearts from line 1 CM-CreTRAP:*Lmna*$^{flox/+}$ mice at 4 weeks post tamoxifen treatment. Representative images are shown from n =5 mice per group. (**D**) Masson's trichrome staining of hearts from line 2 CM-CreTRAP:*Lmna*$^{flox/flox}$ mice at 4 weeks post tamoxifen and vehicle treatment. Representative images are shown from n =5 mice per group. Scale bars = 200µm. (**E**) qPCR of cardiac stress and profibrotic marker mRNAs in hearts from vehicle-treated CM-CreTRAP:*Lmna*$^{flox/flox}$ and Tam-treated CM-CreTRAP:*Lmna*$^{flox/+}$ mice. Data normalized to Rpl13a presented as fold change relative to vehicle (Veh). Error bars = SEM. n = 3 – 5 (biological replicates).

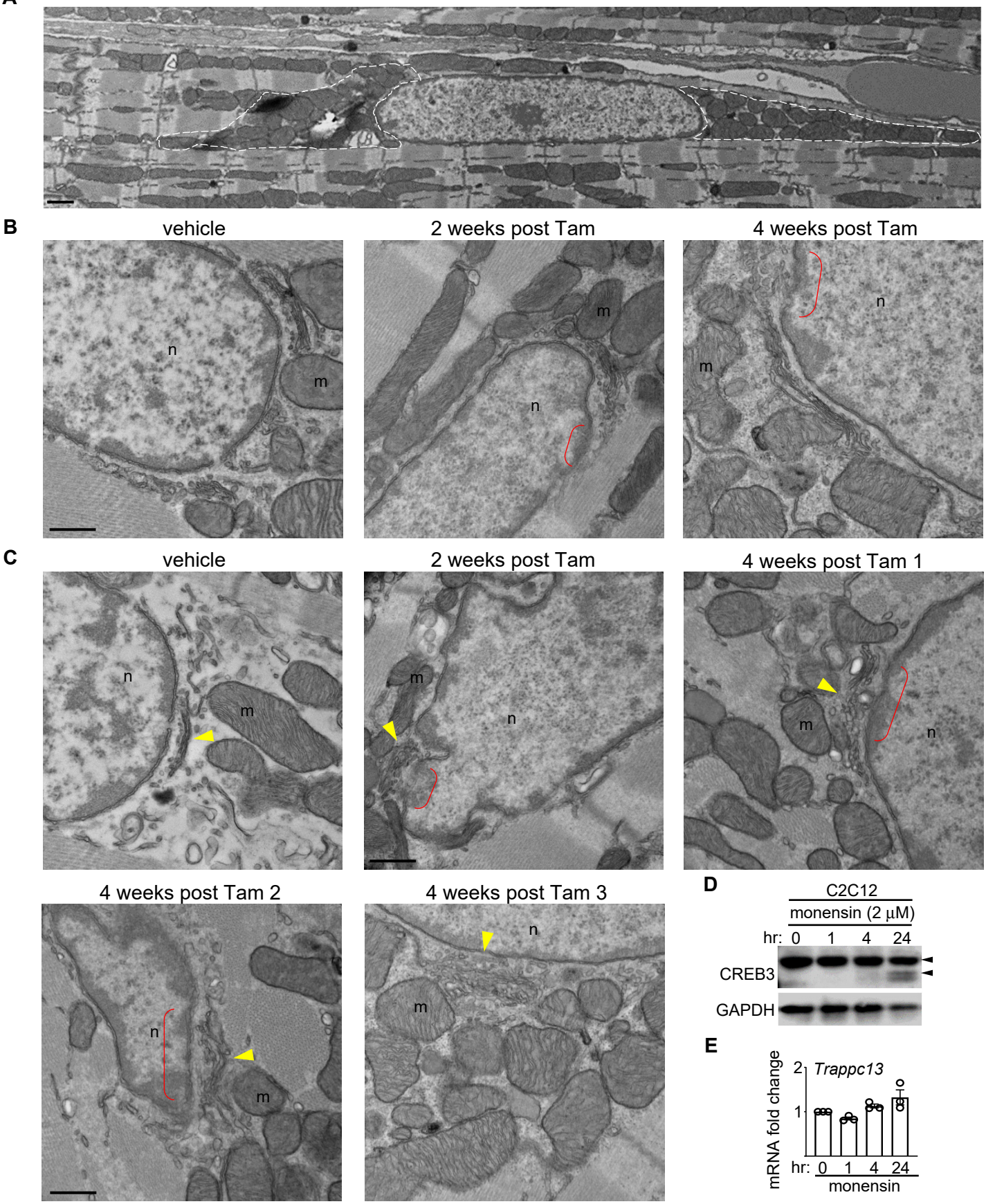


Supplementary Fig. 4. Perinuclear abnormalities in hearts of CM-specific *Lmna* deleted mice. (**A**) H&E staining of hearts from line 1 CM-CreTRAP:*Lmna*$^{flox/flox}$ mice at 4 weeks post tamoxifen and vehicle treatment. Yellow arrows denote abnormal nuclei. Numbers in line denote average number ± SEM of abnormal nuclei per field counted from at least 15 fields from 3 mice per group. Scale bar = 50µm. (**B**) Transmission electron microscopy images of hearts from line 1 CM-CreTRAP:*Lmna*$^{flox/flox}$ mice treated with vehicle, 2 weeks, and 4 weeks post tamoxifen treatment. Dotted box denotes the area shown in the higher magnification (15000X) image. Scale bar = 1 µm. Black arrowheads denote 100 nm vesicles. n = nucleus, m = mitochondria, v = vacuoles. (**C**) Quantitation of EM images showing % of normal and abnormal nuclei from their respective groups. N = total number of nuclei counted from 2 independent hearts per group.

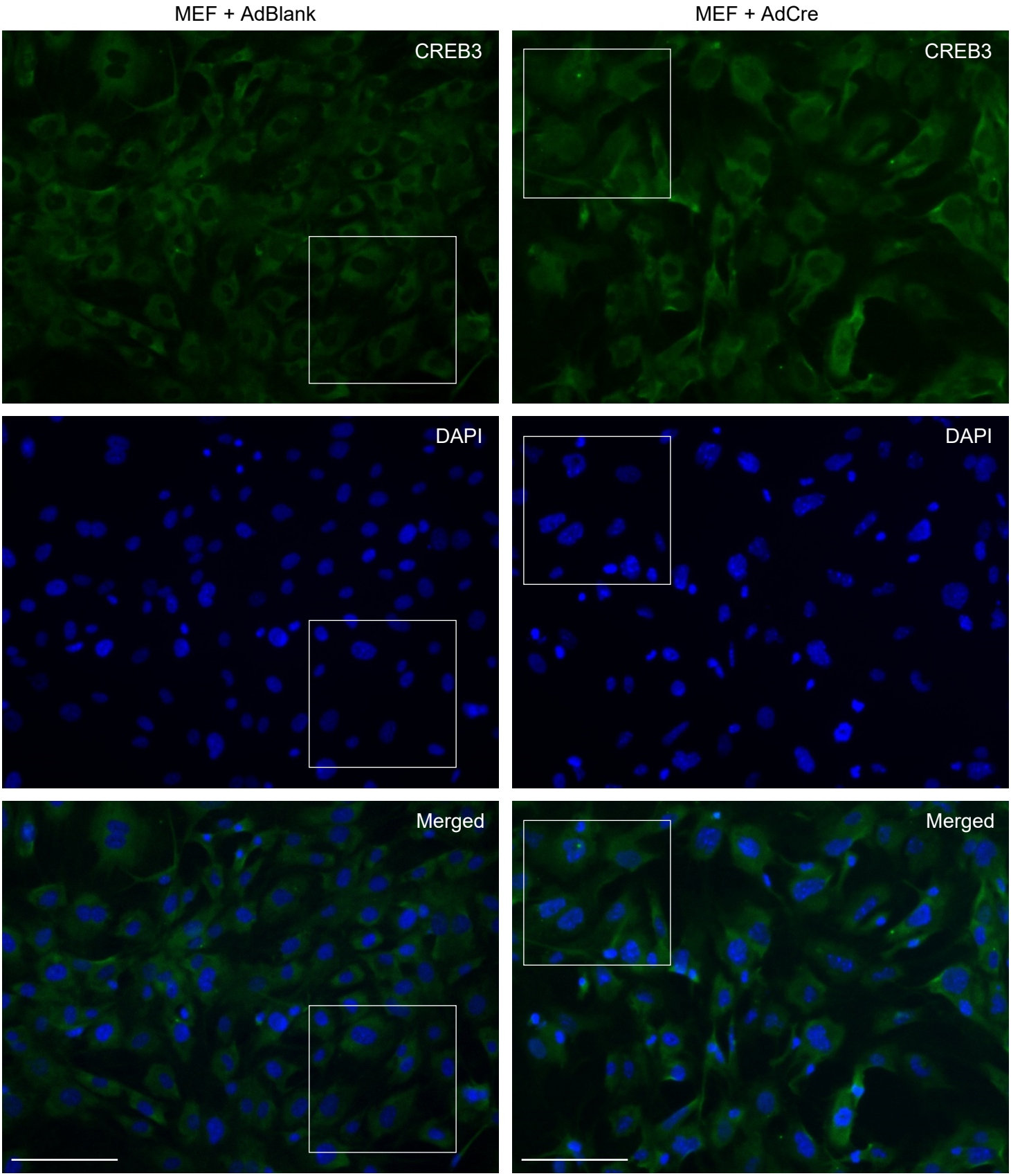




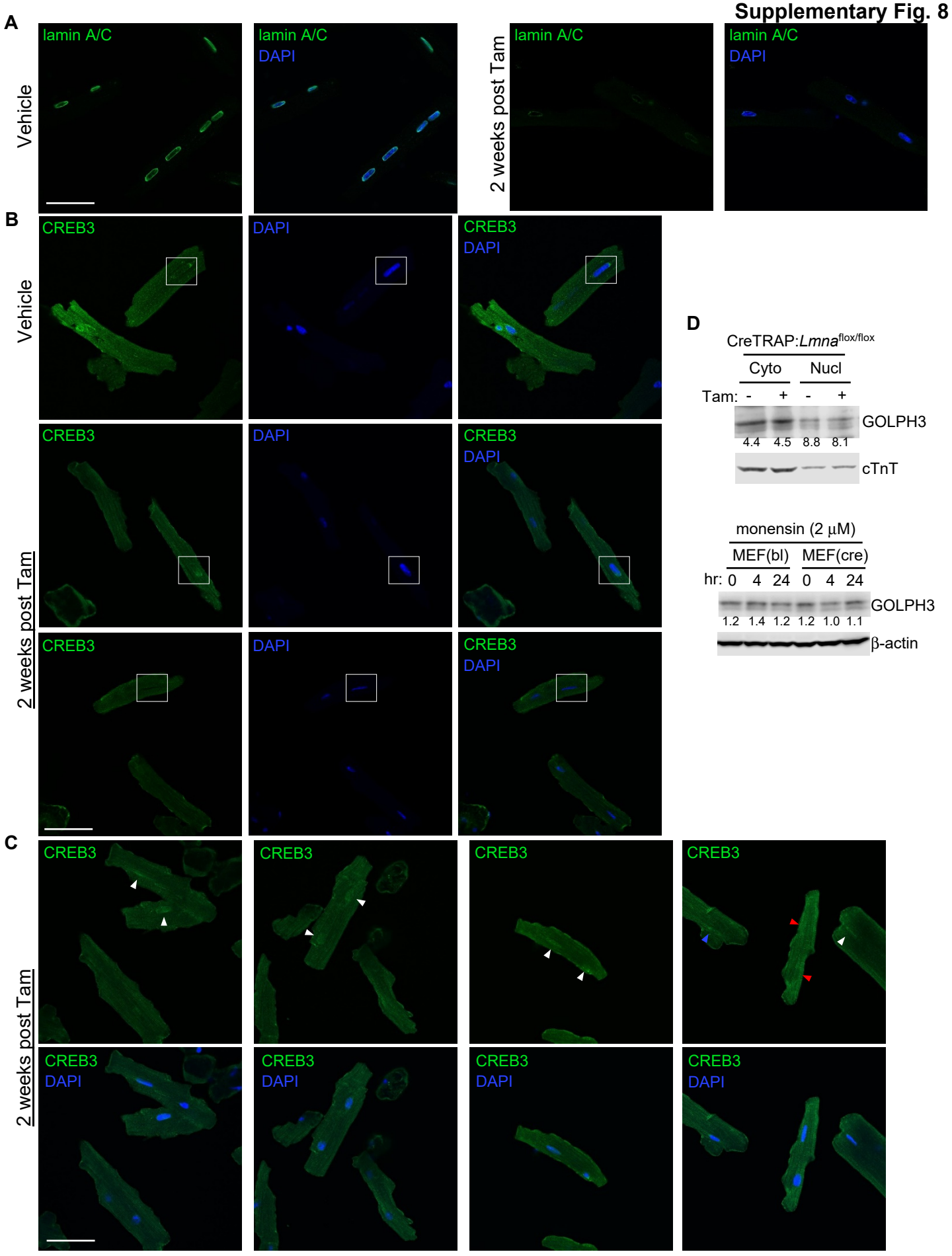
Supplementary Fig. 5. Cardiac perturbations in CM-specific *Lmna* deleted mice. (**A**) (Left panel) Immunoblot of lamin A/C and β-actin in AdCre-treated nCMs from *Lmna*$^{+/+}$ and *Lmna*$^{flox/flox}$ (*Lmna*^{KD}) mice. Quantitation of blots are shown on the bottom. (Right panel) RT-PCR analyses of *Xbp1* mRNA splicing in 24 hr brefeldin A (BFA)-treated *Lmna*$^{+/+}$ and *Lmna*-deleted neonatal CMs. *Xbp1*u and *Xbp1*s denote unspliced and spliced variants, respectively. Input denotes CT values for internal control *Rpl13a*. Representative images from 3 independent experiments are shown. (**B**) RT-PCR analyses of *Xbp1* mRNA splicing in the hearts from CM-CreTRAP:*Lmna*$^{flox/flox}$ mice treated with vehicle (Veh) or Tam, similar to those shown in Supplementary Fig. 4b. Input denotes CT values for internal control *Gapdh*. (**C**) qPCR of unfolded protein response marker mRNAs in hearts from vehicle-treated CM-CreTRAP:*Lmna*$^{flox/flox}$ and Tam-treated CM-CreTRAP:*Lmna*$^{flox/+}$ mice at 2 and 4 weeks post tamoxifen treatment. Data normalized to *Rpl13a* presented as fold change relative to vehicle (Veh). Error bars = SEM. n = 3 - 5. (**D**) Immunoblot of lamin A/C, PERK, and ATF4 on human hearts with quantitation (normalized to α-tubulin) on the bottom. Numbers on top of blots denote individual heart samples (biological replicates). Ponceau S stain was used to assess even loading. * denotes p = 0.03 using unpaired, two-tailed Student's t test. Error bars = SEM. (**E**) qPCR data on TRAP mRNA (n=3) in the hearts from CM-CreTRAP:*Lmna*$^{flox/flox}$ mice 2 weeks post vehicle or Tam treatment. Primers recognizing genes specifically expressed in CMs (red), cardiac fibroblasts (blue), and endothelial cells (purple) were used and presented as 1/cycle threshold (Ct) for each genes from 100ng TRAP mRNA. The actual values are shown on the right panel.



Supplementary Fig. 6. Golgi abnormalities in hearts of CM-specific *Lmna* deleted mice. (**A**) EM image of an adult CM showing perinuclear mitochondria highlighted by dashed lines. All scale bar in this figure = 500 nm. (**B**) Uncropped images of transmission electron microscopy images of hearts from line 1 CM-CreTRAP:*Lmna*$^{flox/flox}$ mice treated with vehicle, 2 weeks, and 4 weeks post tamoxifen treatment from Fig. 4A. Red brackets show area of nuclear envelope deterioration. n = nucleus, m = mitochondria. (**C**) Additional EM images showing abnormal golgi (yellow arrowheads) in hearts from CM-CreTRAP:*Lmna*$^{flox/flox}$ mice treated with vehicle, 2 weeks, and 4 weeks post tamoxifen. Red brackets show area of nuclear envelope deterioration. (**D**) Representative immunoblot of CREB3 and GAPDH in C2C12 cells treated with 2 μM monensin for 1, 4, and 24 hrs from 3 independent experiments. 0 hr denotes vehicle treatment (EtOH). Black arrowheads denote CREB3 and its fragments. (**E**) qPCR analysis of MEFs treated with 2 μM monensin for 0, 1, 4, and 24 hrs probed for *Trappc13*. n=3. Error bars denote SEM.



Supplementary Fig. 7. Uncropped images shown in Figure 4E. White boxes denote the region shown in Fig. 4E. Scale bar = 100 μm

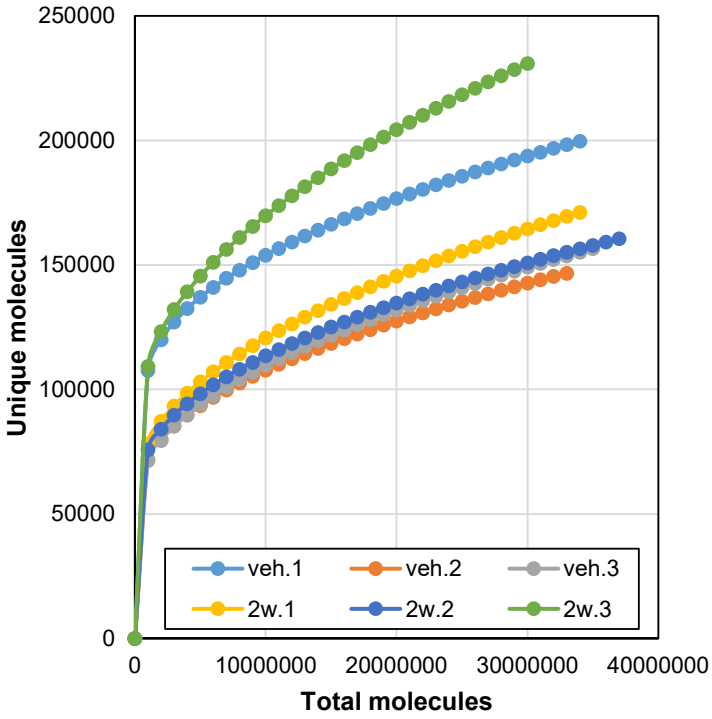


Supplementary Fig. 8. CREB3 localization to the nucleus in adult CMs with *Lmna* deletion. (**A**) Immunofluorescence images of adult CMs from hearts of CM-CreTRAP mice treated with Tam stained for lamin A/C and DAPI. (**B**) Uncropped images of adult CMs from hearts of vehicle or Tam-treated CM-CreTRAP mice stained for CREB3 and DAPI as shown in Fig. 4F. (**C**) Additional uncropped images of adult CMs from hearts of Tam-treated CM-CreTRAP mice stained for CREB3 and DAPI. Scale bar = 50μm. Blue, red, and white arrowheads denote perinuclear, undetected, and intranuclear CREB3, respectively. (**D**) Representative GOLPH3 immunoblot on nuclear/cytoplasmic extracts from primary CMs at 2 week post Tam (+) or vehicle (-) (top) and monensin-treated MEFs infected with AdBl (bl) or AdCre (cre) for 5 days (bottom). Numbers below blots denote GOLPH3 quantification normalized to internal controls in arbitrary units. n=2 experiments.

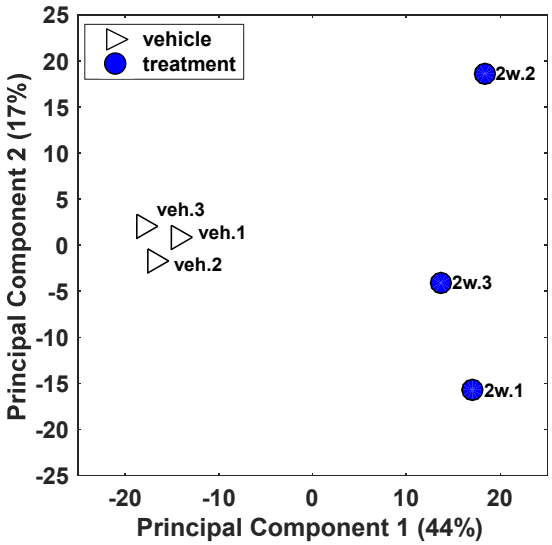
A

Number of reads

Sample	Total	Aligned	%
veh.1	37,873,693	36,782,447	97%
veh.2	36,609,358	35,504,303	97%
veh.3	40,852,376	38,734,857	95%
2w.1	37,500,006	36,235,769	97%
2w.2	41,127,589	39,725,364	97%
2w.3	33,520,115	32,338,371	96%



B



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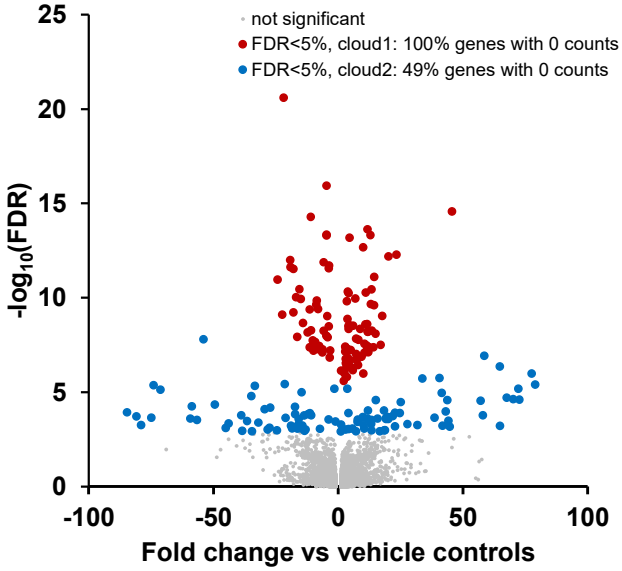
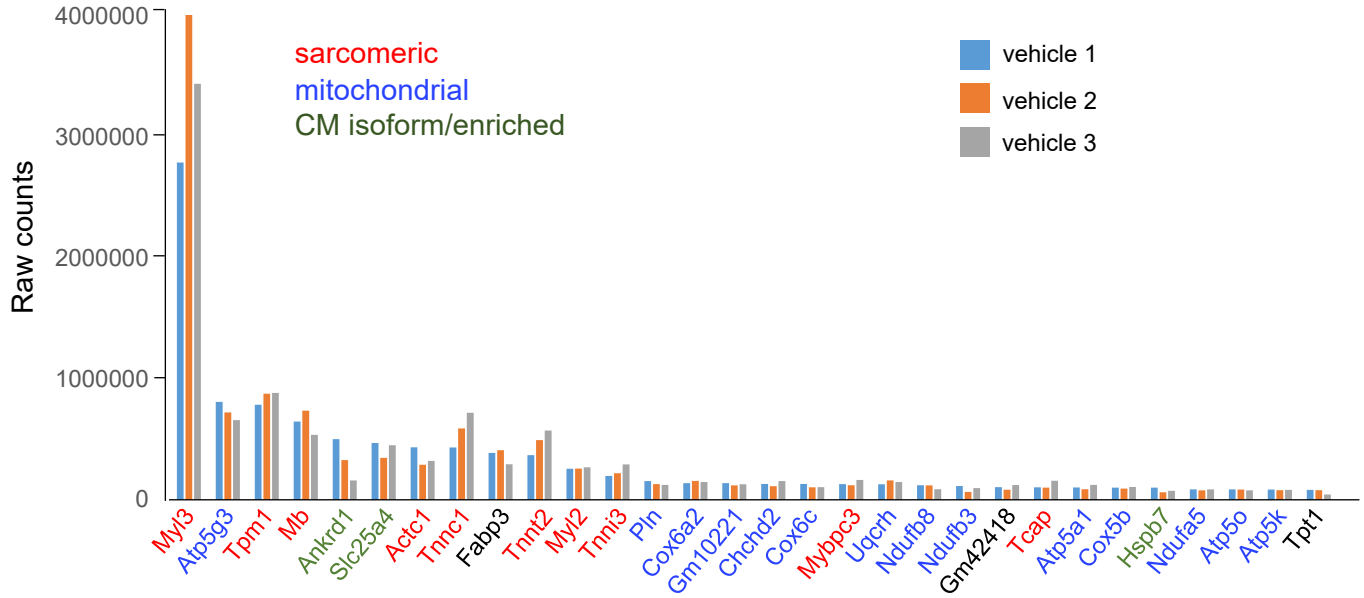
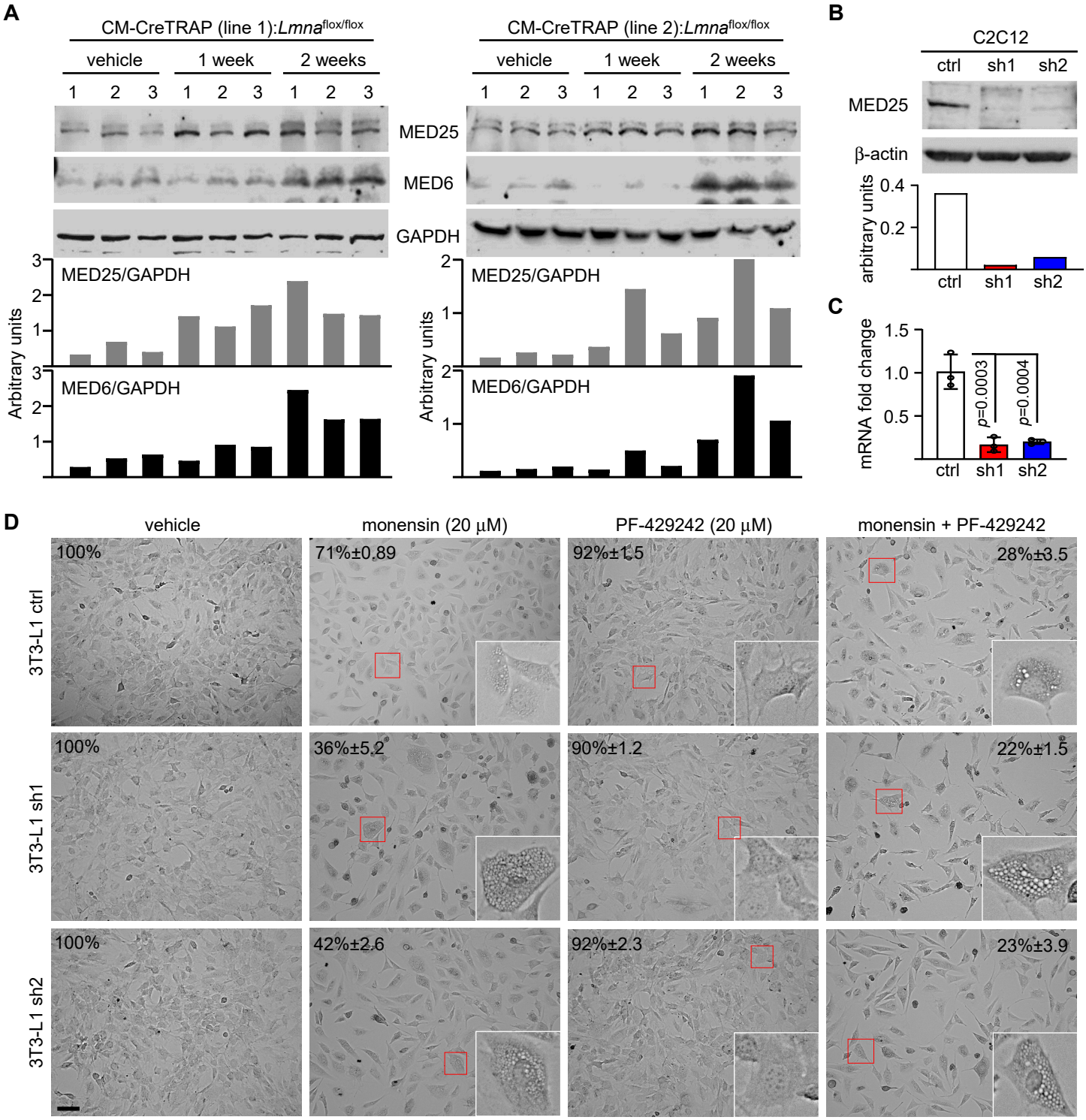


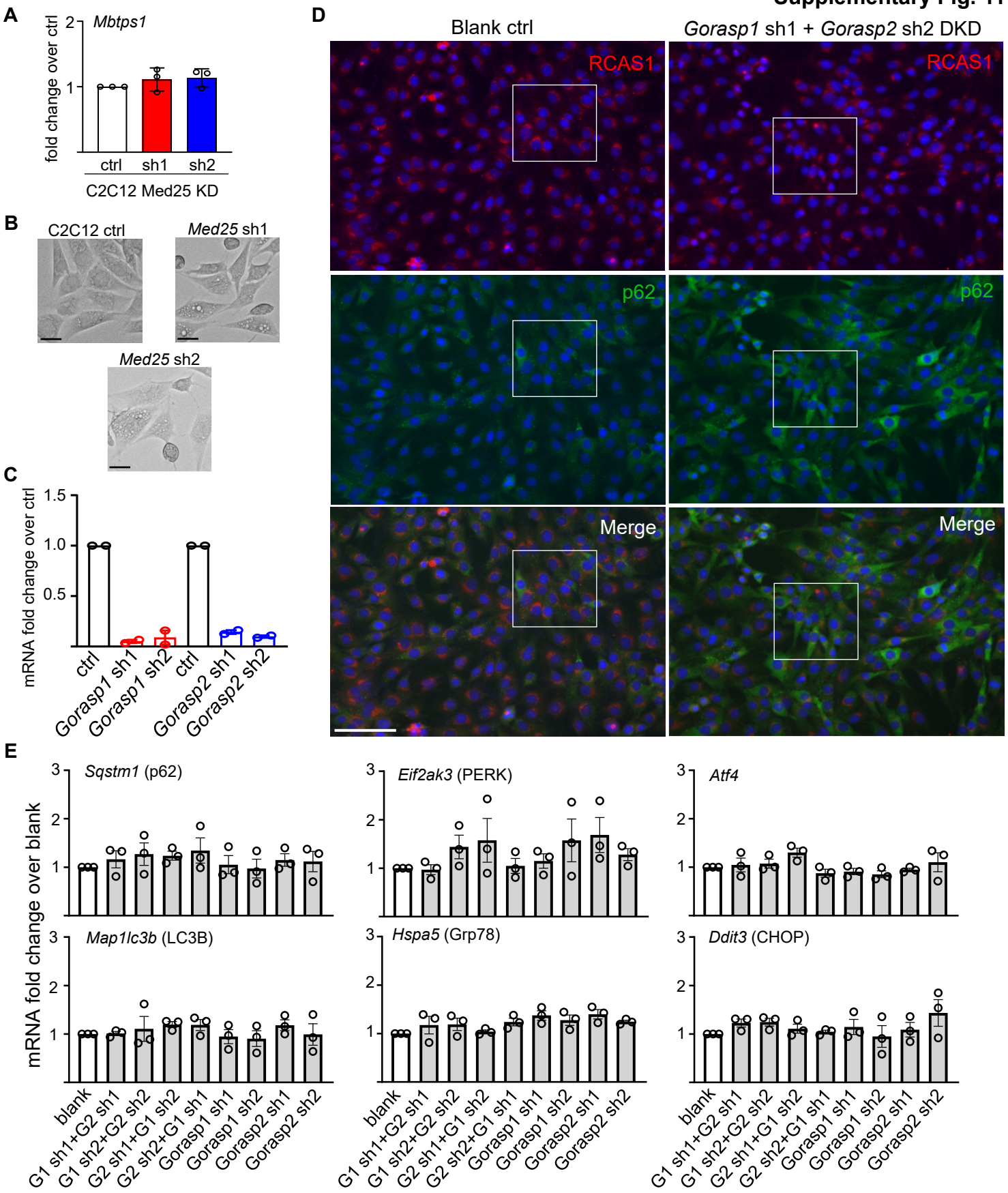
D



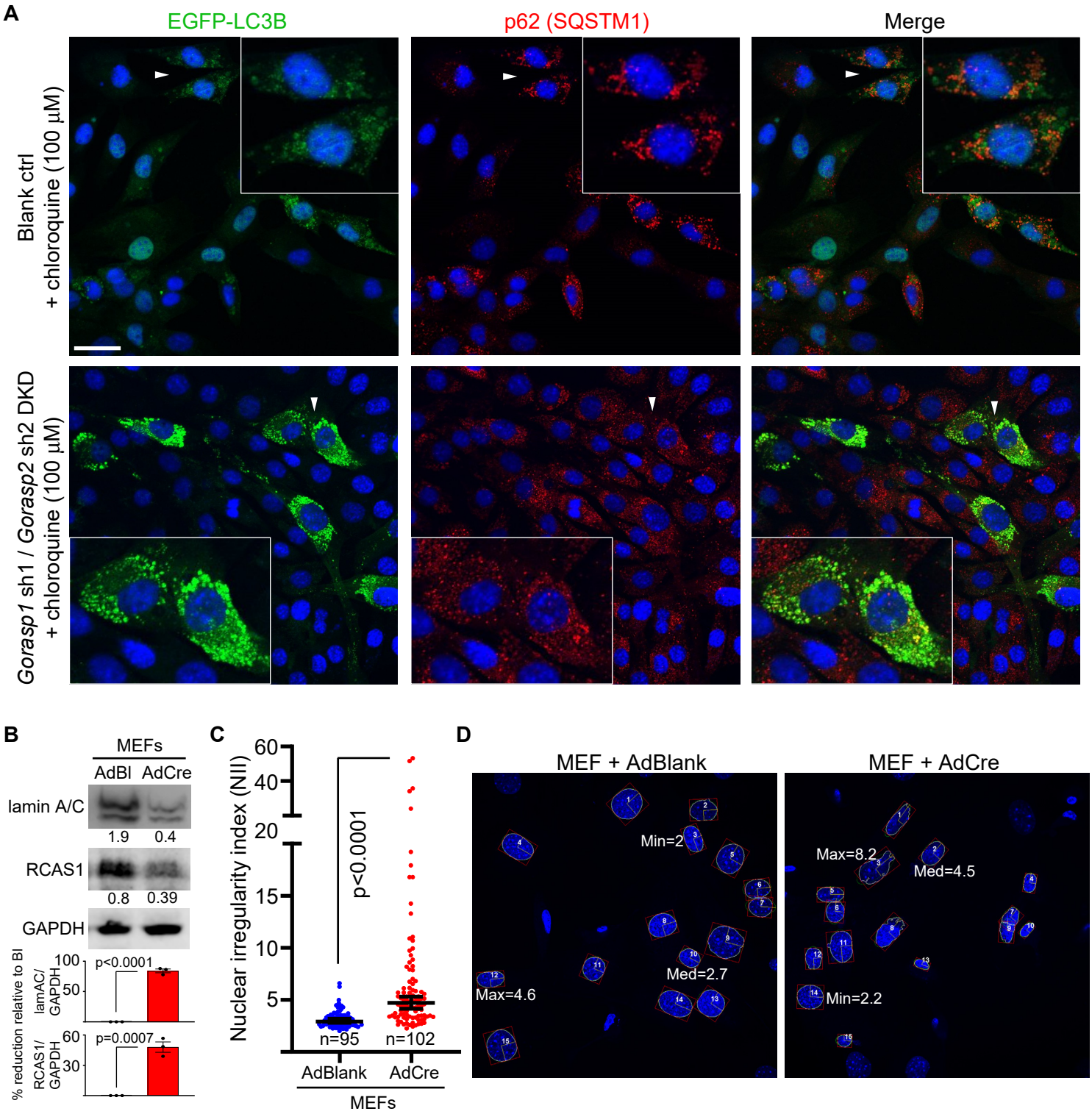
Supplementary Fig. 9. Quality control data for TRAP sequencing. (**A**) Top - Number of reads for TRAP sequencing. Bottom - unique molecule curve associated with the unique reads. Veh.1-3 and 2w.1-3 denote triplicates of TRAP sequencing samples from individual hearts. (**B**) Principle component analysis for the TRAP sequencing samples. (**C**) Volcano plot partitioned by genes with 100% zero counts. (**D**) Top 30 genes sorted based on raw counts from TRAP sequencing of hearts from vehicle treated mice (vehicle 1). Gene symbols with red fonts denote those encoding sarcomeric proteins, blue for mitochondrial, and green for CM-specific isoform or CM enriched. Those in black are genes that do not belong to the three categories.



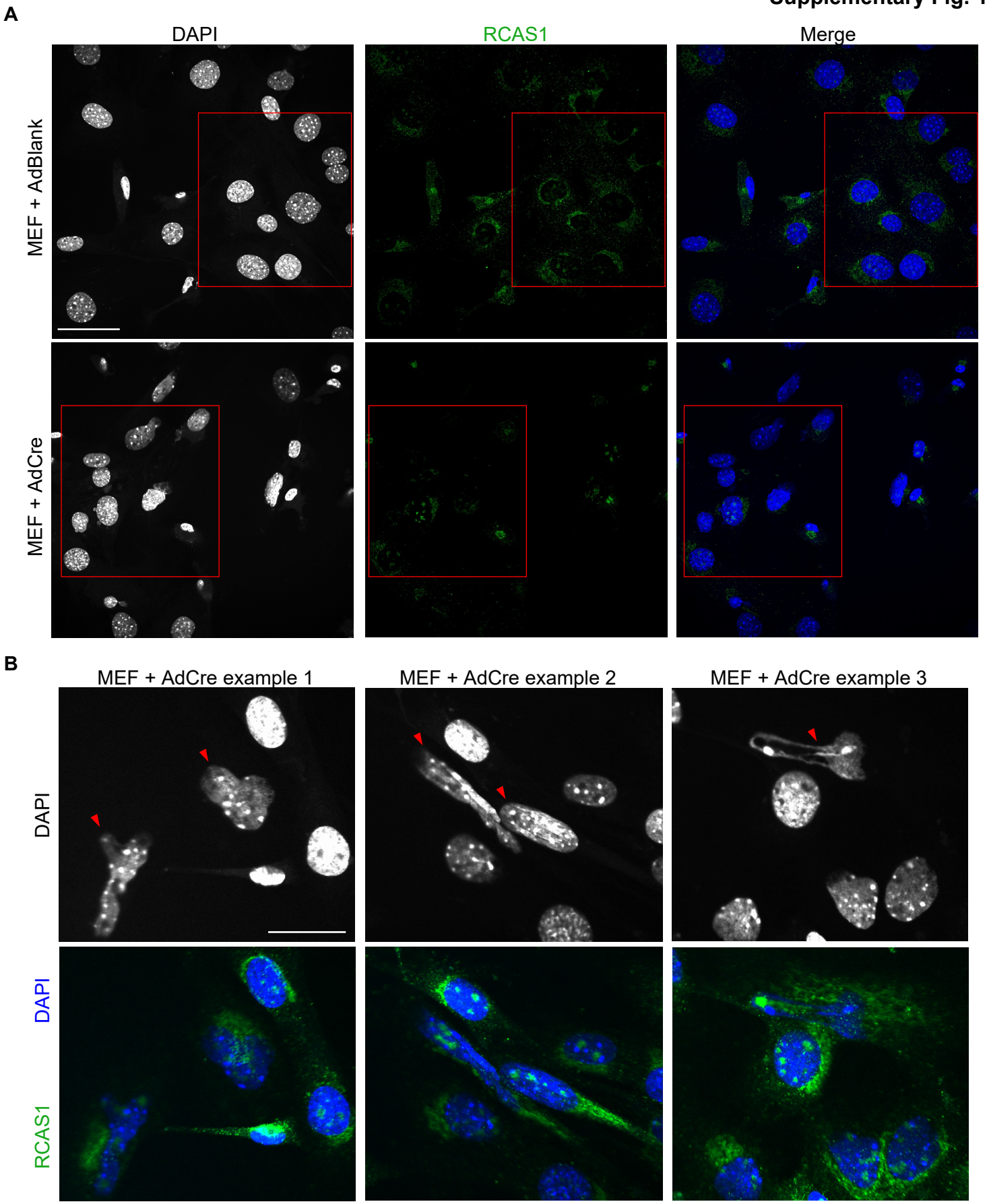
Supplementary Fig. 10. MED25 and its role in response to monensin-induced Golgi stress. (**A**) Immunoblot analysis of MED6, MED25, and GAPDH on the heart extracts from line 1 (left) and line 2 (right) CM-CreTRAP:*Lmna*$^{flox/flox}$ mice at 1 and 2 weeks post Tam treatment or vehicle alone (4W Tam). Numbers on top of blots denote individual heart samples. Bottom panel shows quantitation of blots normalized to GAPDH. (**B**) A representative immunoblot of MED25 and β-actin in nuclear extracts from C2C12 cells expressing two independent shRNAs (sh1 and sh2) that target *Med25* from 2 independent experiments. Bottom panel shows quantitation of MED25 levels normalized to β-actin. (**C**) qPCR analysis confirming *Med25* expression knockdown at the mRNA level. Error bars = SEM. n=3. p values were derived using one-way ANOVA with Dunnett post hoc. (**D**) 3T3-L1 with sh1/2-mediated *Med25* knockdown treated with monensin, site-1 protease inhibitor PF-429242, or in combination. The numbers in line denote % cell viability ± SEM from n=3 experiments. The insets (represented by red boxes) show magnified images showing the presence (or absence) of vacuolation. Ctrl denotes 3T3-L1 cells infected with lentivirus generated from empty vector. Scale bar = 20 μm.



Supplementary Fig. 11. Golgi disruption in C2C12 culture model. (**A**) qPCR analyses of *Mbtps1* in C2C12 with *Med25* KD from two short hairpin RNA (sh1 and sh2). Data presented as fold change relative to ctrl (set to 1). n=3. (**B**) Representative micrographs of control and Med25 KD C2C12 cells treated with 40 μM nigericin for 24 hr from n=3 experiments. Scale bar = 10 μm. (**C**) qPCR analyses of *Gorasp1* and *Gorasp2* knockdown in C2C12 using lentiviruses to deliver two independent shRNAs for each gene. Fold change values were derived using ctrl, which is C2C12 infected with lentivirus carrying blank shRNA, as reference. Error bars = SEM. n = 2 experiments. (**D**) Uncropped images shown in Fig. 6c. Boxes show the cropped borders. Scale bar = 100 μm. (**E**) qPCR analyses on C2C12 cells with *Gorasp1* and *Gorasp2* knockdown probed for genes involved in UPR (*Eif2ak3*, *Atf4, Ddit3,* and *Hspa5*) and autophagy (*Sqstm1* and *Map1lc3b*). Error bars = SEM. n = 3.

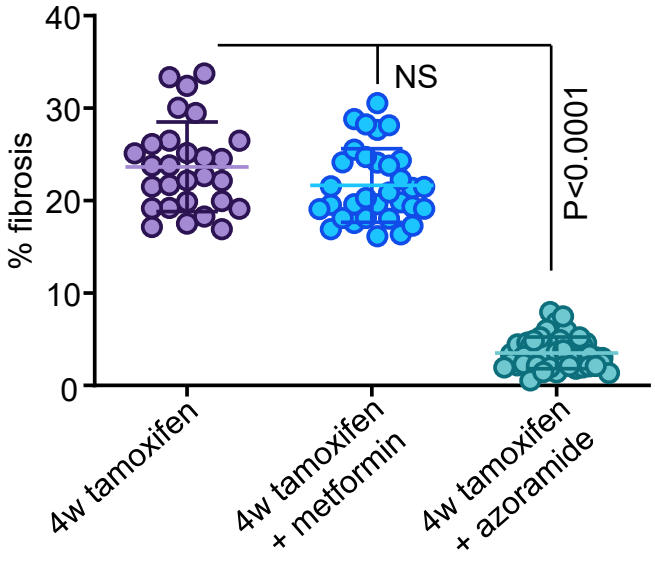


Supplementary Fig. 12. Autophagy and Golgi disruption in *in vitro* culture models. (**A**) A representative immunofluorescence images (from n=3 experiments) on blank control and *Gorasp1/Gorasp2* double KD (DKD) C2C12 cells transduced with retroviruses carrying expression constructs for EGFP-LC3B. After 1 week recovery, the cells were treated with chloroquine for 24 hr after which they were stained for p62. Insets show cells highlighted by white arrowheads with punctas co-localized with LC3B and p62. Scale bar = 20 µm. (**B**) A representative immunoblot of lamin A/C and RCAS1 on *Lmna*$^{flox/flox}$ MEFs 5 days after infection with AdBlank (AdBl) or AdCre from 3 independent experiments. Numbers in line denote quantitation of blots normalized to GAPDH in arbitrary units. % reduction calculated from the quantitation, relative to blank (Bl) controls, are shown below. P values were derived using unpaired, 2-tailed student's t-test. Error bars = SEM. (**C**) Nuclear irregularity index (NII) of nuclei of *Lmna*$^{flox/flox}$ MEFs 5 days after infection with AdBlank or AdCre pooled from 3 independent experiments. P value was derived using unpaired, two-tailed student's t test. Error bars = SEM. (**D**) A representative image of NII plugin for automated nuclear irregularity index as shown for Fig. 6F. Maximum/median/minimum NII for MEFs infected with either AdBlank or AdCre are shown.



Supplementary Fig. 13. Golgi disruption in *Lmna*$^{flox/flox}$ MEFs with *in vitro Lmna* deletion. (**A**) Uncropped images shown in Fig. 6F. Red boxes denote cropped images in Fig. 6F. (**B**) Additional images of *Lmna*$^{flox/flox}$ MEFs transduced with AdCre showing reduced RCAS1 signal and disrupted Golgi, particularly in severely misshapen nuclei (denoted by red arrowheads). The DAPI and RCAS1 signals have been saturated for better viewing. Scale bars = 20 μm.

A



B

	4W Tam					4W Tam + Metformin								4W Tam					4W Tam+ Azoramide							
	1	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Nppa	0.5	1.4	0.9	1.7	1.0	1.3	1.2	1.2	1.3	1.0	1.9	1.3	0.9	0.9	1.1	0.7	1.5	1.0	0.4	0.4	0.2	0.1	0.3	0.6	0.5	0.2
Nppb	1.1	0.7	1.8	0.8	0.9	2.5	2.4	2.0	2.3	1.9	2.4	2.1	2.3	1.1	1.0	0.5	1.3	0.7	2.1	1.2	1.1	0.7	1.4	1.2	1.3	0.6
Acta2	1.0	0.5	1.6	0.9	1.3	1.1	3.1	0.9	1.4	3.9	1.7	2.1	3.3	1.0	0.6	1.4	1.2	1.2	1.0	1.1	1.0	0.9	1.0	0.9	1.3	0.7
Col1a1	1.8	0.6	1.6	1.4	0.4	1.7	1.0	1.6	1.3	1.1	1.7	1.7	1.2	1.0	1.9	0.5	0.9	1.2	0.8	0.6	0.6	0.2	0.6	0.8	0.4	0.4
Col1a2	1.5	0.8	1.1	1.5	0.5	1.5	0.8	1.5	1.0	0.9	1.5	1.6	1.1	1.4	0.6	1.0	0.9	1.4	0.8	0.6	0.5	0.2	0.6	0.7	0.4	0.4
Col3a2	1.9	0.5	1.6	1.4	0.5	2.6	1.6	2.1	1.7	2.2	2.5	2.6	1.6	1.6	0.9	1.0	1.1	1.0	1.1	1.0	0.8	0.3	0.8	1.1	0.6	0.5
Ctgf	0.3	1.6	2.4	1.7	0.6	1.3	2.3	3.4	3.4	1.6	4.1	3.5	4.4	1.0	1.0	0.9	1.0	1.3	0.8	0.6	0.4	0.3	0.6	0.5	0.5	0.4
Fn1-eda	1.5	0.2	2.0	2.3	0.8	1.7	0.4	1.1	0.8	0.9	2.5	0.8	0.1	1.5	0.8	0.8	1.1	1.1	1.8	1.6	1.1	0.1	0.5	1.6	0.8	1.4
Postn	1.7	0.6	1.5	1.4	0.5	1.2	0.7	0.9	0.7	1.0	1.4	1.1	0.9	1.3	1.1	1.3	0.6	1.2	0.6	0.5	0.4	0.1	0.4	0.4	0.3	0.1
Atf4	1.2	1.2	0.9	0.9	0.9	0.9	1.0	0.9	0.8	0.8	0.9	1.0	1.2	1.1	1.0	0.9	1.0	1.3	0.9	0.7	0.7	0.8	0.8	0.9	0.7	0.8
Ddit3	1.0	1.0	0.8	1.1	1.2	1.0	1.1	0.9	0.7	1.0	0.7	1.0	0.9	1.0	1.1	1.0	0.7	1.2	0.5	0.6	0.5	0.5	0.6	0.6	0.6	0.6
Eif2ak3	0.9	0.9	1.2	1.2	1.0	1.1	1.1	1.1	1.1	1.4	1.2	1.4	1.4	1.6	0.8	0.8	1.0	1.3	0.7	0.7	0.7	0.7	0.7	0.8	0.6	0.7
Hspa5	0.9	1.1	0.8	1.2	1.1	1.0	1.0	0.8	1.0	1.3	1.0	1.1	1.2	1.1	1.5	0.8	1.0	1.2	0.6	0.6	0.5	0.5	0.6	0.6	0.5	0.5
Atf6	0.8	1.2	0.9	1.1	0.7	1.0	1.2	1.0	1.0	1.2	1.4	1.1	0.9	0.9	1.1	0.9	1.1	0.9	1.0	1.3	0.9	1.2	1.0	1.0	0.9	1.2
Xbp1	1.3	0.9	1.0	1.0	1.0	1.0	1.1	1.4	1.2	1.6	1.0	1.4	1.1	1.4	0.8	1.0	1.0	1.1	1.0	1.0	0.9	1.0	1.0	1.1	0.8	1.0
Atg5	1.2	0.9	1.2	0.9	0.9	1.5	1.3	1.3	1.4	1.4	1.3	1.7	1.8	1.2	0.9	0.8	0.9	0.9	1.2	0.8	0.8	0.8	0.7	0.7	0.7	0.8
Atg7	1.1	1.0	1.1	1.0	0.9	1.3	1.1	1.7	1.1	1.4	1.1	1.6	1.7	1.2	1.2	1.0	1.1	0.9	0.9	1.0	0.8	0.9	0.8	1.1	0.9	1.1
Becn1	1.0	1.1	1.0	1.0	0.9	1.2	1.4	1.1	1.1	1.9	1.0	1.7	1.7	1.2	1.3	0.9	0.8	1.0	0.7	1.0	1.1	0.8	0.7	0.8	0.8	0.9
Gabarap	0.7	0.8	1.5	1.0	1.2	1.7	1.1	2.0	2.1	2.7	2.6	3.6	2.5	1.4	1.2	0.7	0.9	1.3	0.9	1.5	0.7	1.3	1.4	1.9	1.4	0.9
Gabarapl1	0.6	0.8	1.2	1.2	1.3	1.5	1.1	2.0	1.2	2.3	1.5	2.0	2.2	1.5	0.8	0.8	0.8	1.2	1.0	0.5	0.8	0.9	0.6	0.6	0.7	0.9
Lamp2	1.3	0.9	1.0	0.9	0.9	0.9	0.9	1.2	1.1	1.2	0.9	1.2	1.3	1.0	1.0	1.0	0.9	1.1	0.8	0.9	0.8	0.8	0.9	0.8	0.9	0.9
Map1lc3a	1.0	1.0	1.0	0.9	1.1	1.3	1.5	1.0	1.5	2.0	1.3	2.1	1.9	1.4	1.0	0.8	0.9	1.0	0.8	1.0	0.9	1.1	1.1	1.0	1.1	1.3
Map1lc3b	1.1	1.1	1.0	1.0	0.9	0.9	1.1	0.9	1.0	1.6	1.0	1.4	1.1	1.1	1.1	1.0	1.0	1.0	0.9	1.1	0.9	1.0	1.6	1.0	1.4	1.1
Pik3c3	1.0	0.9	1.0	1.2	0.9	1.0	1.1	1.4	1.2	1.6	1.0	1.7	1.6	1.0	0.9	0.9	1.2	0.9	0.8	1.0	1.0	0.9	0.9	0.9	1.0	1.0
Tfeb	1.6	0.5	1.5	1.0	0.9	1.8	2.1	2.4	2.2	3.0	2.1	3.2	3.2	1.4	0.7	0.8	0.9	1.3	1.6	1.8	1.8	1.8	1.5	2.1	1.9	2.2
Ulk1	1.0	1.2	1.1	0.9	0.8	1.0	0.8	1.3	1.1	1.4	1.1	1.7	1.7	1.3	1.0	1.6	0.7	0.8	0.7	0.8	0.6	1.0	1.1	1.1	1.3	1.3
Tnfrsf1b	1.2	1.1	0.9	1.0	0.9	0.7	0.8	1.2	0.7	0.8	1.2	0.7	0.9	1.0	0.9	0.9	1.4	1.0	0.3	0.8	0.7	0.5	0.6	0.7	0.8	1.0
Tnfrsf10b	1.2	1.1	0.9	1.1	0.8	0.7	1.1	1.4	1.0	0.9	0.7	0.9	0.9	1.0	1.0	1.2	1.0	0.8	0.8	0.9	1.0	0.3	0.4	0.4	0.5	1.0
Arf4	1.1	1.0	0.8	1.3	0.9	0.7	0.8	0.9	0.8	0.7	1.1	0.7	0.9	0.7	1.0	0.8	1.0	1.8	0.7	1.7	1.0	0.6	0.6	0.8	1.0	1.1

Supplementary Fig. 14. Characterization of Tam-treated CM-CreTRAP:*Lmna*$^{flox/flox}$ mice treated with metformin or azoramide. (**A**) Quantitation of % fibrosis based on Masson's trichrome staining of hearts from CM-CreTRAP:*Lmna*$^{flox/flox}$ mice at 4 weeks post Tam treatment alone or with either metformin or azoramide. Average % fibrosis was calculated from ~30 independent images from 3 mouse hearts per group. Error bars = standard deviation. NS = not significant. (**B**) mRNA fold change values obtained from qPCR analyses to generate the heatmap shown in fig. 7d. Numbers on top denote individual heart samples. Average ΔCt values from 4W Tam (n=5) were used as a reference to determine all ΔΔCt fold change values.

	Sex	CHF Etiology	*LMNA* Mutation	Tissue	Age (Years)
LMNA$^{+/+}$ 1	M	NF	None	LV	52
LMNA$^{+/+}$ 2	M	NF	None	LV	33
LMNA$^{+/+}$ 3	M	NF	None	LV	54
LMNA$^{+/+}$ 4	F	NF	None	LV	23
LMNA^{mut} 1	M	Ischemic LMNA	p Thr10Ile (T101)**	LV	47
LMNA^{mut} 2	M	Familial/Laminopathy	Inferred from family history/declined genetic testing	LV	49
LMNA^{mut} 3	M	LMNA NICM	p.Leu320Phefs*160	LV	45
LMNA^{mut} 4	F	LMNA NICM	p Thr10Ile (T101)	LV	33

Supplementary Table 1. Heart tissue samples from human subjects. LV = left ventricle, NF = non failing, NICM = non-ischemic cardiomyopathy. ** Father of patient *LMNA*^{mut} 4

Groups	Sex(n)	FS (%)	EF (%)	LVESD(mm)	LVEDD(mm)	LVESPW(mm)	LVEDPW(mm)
CreTRAP:*Lmna*$^{flox/flox}$ + corn oil (Veh)	M (7) F (5)	28.2±1.24	55.5±1.47	2.99±0.083	4.16±0.058	1.13±0.039	0.82±0.02
CreTRAP:*Lmna*$^{flox/flox}$ + 2 weeks post Tam	M (6) F (6)	24.7±1.13	48.3±1.81	3.22±0.085	4.27±0.076	1.12±0.063	0.84±0.046
CreTRAP:*Lmna*$^{flox/flox}$ + 2 weeks Tam+Met	M (3) F (5)	25.9±2.62	50.8±4.15	2.93±0.156	3.93±0.97	1.1±0.065	0.77±0.05
CreTRAP:*Lmna*$^{flox/flox}$ + 2 weeks Tam+Azor	M (6) F (2)	28.3±2.09	54.9±3.23	2.79±0.144	3.89±0.132	1.07±0.05	0.71±0.038
CreTRAP:*Lmna*$^{flox/flox}$ + 4 weeks post Tam	M (6) F (6)	9.02±1.43	19.6±2.99	4.29±0.153	4.7±0.114	0.893±0.05	0.85±0.053
CreTRAP:*Lmna*$^{flox/flox}$ + 4 weeks Tam+Met	M (3) F (5)	19.3±1.91	39.7±3.44	3.43±0.201	4.23±0.165	1.1±0.07	0.86±0.059
CreTRAP:*Lmna*$^{flox/flox}$ + 4 weeks Tam+Azor	M (6) F (2)	24.7±2.8	48.8±4.74	2.91±0.149	3.84±0.084	1.08±0.048	0.79±0.044

Supplementary Table 2. Echocardiography table for Fig. 7B. FS = fractional shortening, EF = ejection fraction, LVESD = left ventricular end systolic dimension, LVEDD = left ventricular end diastolic dimension, LVESPW = left ventricular end systolic posterior wall thickness, LVEDPW = left ventricular end diastolic posterior wall thickness.

Supplementary Table 3

Primers	Forward (5' - 3')	Reverse (5' - 3')
CreERT2	CGT ACT GAC GGT GGG AGA AT	CCC GGC AAA ACA GGT AGT TA
Nppa	TCG TCT TGG CCT TTT GGC T	TCC AGG TGG TCT AGC AGG TTC T
Nppb	AAG TCC TAG CCA GTC TCC AGA	GAG CTG TCT CTG GGC CAT TTC
Ccn2 **(CTGF)**	GTG CCA GAA CGC ACA CTG	CCC CGG TTA CAC TCC AAA
Postn	ATG TCA TTG ACC GTG TCC TG	AAG AGC GTG AAG TGA CCA TC
Col1a1	TTC TCC TGG CAA AGA CGG ACT CAA	AGG AAG CTG AAG TCA TAA CCG CCA
Col1a2	GGC CCC CTG GTA TGA CTG GCT	CGC CAC GGG GAC CAC GAA TC
Col3a1	GTT CTA GAG GATGGCTGTACTAAACACA	TTG CCT TGC GTG TTT GAT ATT C
Fn1 EDA	CAG AAA TGA CCA TTG AAG GT	ATG AGT CCT GAC ACA ATC AC
Eif2ak3 **(PERK)**	TCC CTG CTC GAA TCT TCC TA	CAT CCC AAG GCA GAA CAG AT
Atf4	ATG GGT TCT CCA GCG ACA	TCC ATT TTC TCC AAC ATC CAA
Ddit3 **(CHOP)**	CTG GAA GCC TGG TAT GAG GA	CCT CTG TCA GCC AAG CTA GG
Hspa5 **(BiP)**	CTT GGG GAC CAC CTA TTC CT	GGT TGG ACG TGA GTT GGT TC
Atf6	GCA GCA GTC GAT TAT CAG CA	GTT AGG TAG CTG TGC GGC TC
Xbp1 **total**	TAT CCT TTT GGG CAT TCT GG	ACA GAG AAA GGG AGG CTG GT
Xbp1 **spliced**	GAA CCA GGA GTT AAG AAC ACG	AGG CAA CAG TGT CAG AGT CC
Tnnt2	TAC AGA CTC TGA TCG AGG CTC ACT TC	TCA TTG CGA ATA CGC TGC TGC TC
Tnni3	TAA GAT CTC CGC CTC CAG AA	CGG CAT AAG TCC TGA AGC TC
Tnnc1	AGG CAG CCT TGA ACT CAT TC	TGT CCT GTG AGC TGT CTC CA
Myh6	ACG GTG ACC ATA AAG GAG GA	TGT CCT CGA TCT TGT CGA AC
Mef2d	TCA ACC ACT CCA ACA AGC TGT T	GTA CTC GGT GTA CTT GAG CAG CA
Gata4	GAG CCT GCC AAG CCA AGC	CTC CCG TCT ATC ACC TTT GTC C
Pdgfra	GGG AAG GAC TGG AAG CTT GGG GC	AGA TGA GGC CCG GCC CTG TGA GG
Ddr2	TTC CCT GCC CAG CGA GTC CA	ACC ACT GCA CCC TGA CTC CTC C
Tcf21	ATG CTG GAC TGT GAC TCC CT	GAG CGG GCT TTT CTT AGT GG
Cdh5	TCT TGC CAG CAA ACT CTC CT	TTG GAA TCA AAT GCA CAT CG
Pecam1	TCA CCA TCA ACA GCA TCC A	GGT GCT GAG ACC TGC TTT TC
Vcam1	CCG GCA TAT ACG AGT GTG AA	GAT GCG CAG TAG AGT GCA AG
Med25	GTG GTG GCG AGA GCT GTA GT	TCT CAA ACA GAA GCC GGA G
Atg5	ACA GCT GCA CAC ACT TGG AG	TTC CAG CAT TGG CTC TAT CC
Atg7	CCA GGA CAC CCT GTG AAC TT	GCT CTC CCT GGT GTC CAT TA
Becn1	CAG CTG GAC ACT CAG CTC AA	CTT GCG GTT CTT TTC CAC AT
Gabarap	TCC CGG TGA TAG TGG AAA AA	AAT TCG CTT CCG GAT CAA G
Gabarapl1	GAC CTC ACT GTT GGC CAG TT	TCT TCC TCG TGG TTG TCC TC
Lamp2	AGA CCA AAC TCC CAC CAC TG	TTG GAG TTG GAG TTG GAG TTG
Map1lc3a **(LC3B)**	GCC TGT CCT GGA TAA GAC CA	CCG TCT TCA TCC TTC TCC TG
Map1lc3b **(LC3A)**	CGT CCT GGA CAA GAC CAA GT	CAG GAA GCC GTC TTC ATC TC
Pik3c3	CTA ACG TGG AGG CAG ATG GT	CTG TCC AGC CAA TCC ACT TT
Tfeb	CTC AGT GGT CTT GGG CAA AT	TGT AGT CGA GGG GAG ACA GG
Ulk1	GCT CAC CTA AGC TGC CTG AC	ATT CTG AGA GCT GGG GGT TT
Arf4	CTG GCA AGA CGA CAA TTC TGT	CCA CAA AAA TGA GAC CCT GGG TA
Trappc13	CAA AGG ATG GCT CCA GGT TA	CAC GAG GTC CAT CAT CCT CT

Supplementary Table 3. PCR primer sequences used in the study (continued on the next page)

Supplementary Table 3 continued

Primers	Forward (5' - 3')	Reverse (5' - 3')
Tnfrsf1b	ACA CCC TAC AAA CCG GAA CC	AGC CTT CCT GTC ATA GTA TTC CT
Tnfrsf10b	CGG GCA GAT CAC TAC ACC C	TGT TAC TGG AAC AAA GAC AGC C
Gorasp1	AGT CTG GGG TGT GGT ATT GG	TTG TGA GGT CGT AGC TGG AG
Gorasp2	GGG TTT ACA GAG GTC CAG CT	TGC CGA GCT AAT GGA GAG TC
Sqstm1	AGA ATG TGG GGG AGA GTG TG	TTT CTG GGG TAG TGG GTG TC
Mbtps1	CTG GTG GTT TTG CTC TGT GG	GGC TGT GAA GTA TCC GTT GAA AG
Gapdh	TGC ACC ACC AAC TGC TTA G	GGA TGC AGG GAT GAT GTT C
Genotyping primers	CTA CGG TGT AAA AGA GGC AGG	CTT GCG AAC CTC ATC ACT CGT

Supplementary Table 3. PCR primer sequences used in the study.

Supplementary Table 4

Antibodies	Company	Catalogue #	Concentration IB = immunoblot IF = immunofluorescence
α-smooth muscle actin	Abcam	ab5694	IB(1:2000), IF(1:300)
α-tubulin	Santa Cruz Biotechnology	sc-5286	IB(1:2000)
ATF4	Cell Signaling Technology	11815	IB(1:1000)
β-actin	Cell Signaling Technology	3700	IB(1:4000)
Cre Recombinase	Cell Signaling Technology	12830	IB(1:200)
Desmin	Santa Cruz Biotechnology	sc-23879	IF(1:200)
GAPDH	Millipore Sigma	MAB374	IB(1:5000)
GFP	Abcam	ab6556	IB(1:500), IF(1:300)
GFP (TRAP)	Bi-Institutional Antibody and Bioresource Core Facility	HtzGFP_02 (clone 19C8) HtzGFP_04 (clone 19F7)	50ug each per sample
Lamin A/C	Santa Cruz Biotechnology	sc-376248	IB(1:2000), IF(1:300)
Lamin B1	Santa Cruz Biotechnology	sc-30264	IB(1:500)
LC3B	Cell Signaling Technology	2775	IB(1:1000)
MED6	Santa Cruz Biotechnology	sc-390474	IB(1:500)
MED25	Santa Cruz Biotechnology	Sc-393759	IB(1:500)
p62	Cell Signaling Technology	23214	IB(1:1000)
PDGFRα	RnD Systems	AF1062	IF(1:100)
PERK	Cell Signaling Technology	3192	IB(1:500)
phospho-eIF2α	Cell Signaling Technology	3398	IB(1:500)
eIF2α	Cell Signaling Technology	5324	IB(1:1000)
CHOP	Cell Signaling Technology	2895	IB(1:500)
sarcomeric actin	Invitrogen	MA1-21597	IF(1:20)
Troponin T	Invitrogen	MA5-12960	IB(1:2000), IF(1:200)
Vimentin	Cell Signaling Technology	5741	IF(1:300)
CREB3	Proteintech	11275-1-AP	IB(1:1000), IF(1:200)
RCAS1	Proteintech	66170-1-Ig	IF(1:200)
GOLPH3	Proteintech	19112-1-AP	IB(1:1000)
Donkey anti-goat 594	Invitrogen	A-11058	IF(1:400)
Goat anti-mouse 594	Invitrogen	A-21044	IF(1:400)
Goat anti-rabbit 488	Invitrogen	A-11034	IF(1:400)
Goat anti-rabbit 594	Invitrogen	R-37117	IF(1:8)
Licor green mouse	LI-COR Biosciences	926-32210	IB(1:5000)
Licor green rabbit	LI-COR Biosciences	926-32211	IB(1:5000)
Licor red mouse	LI-COR Biosciences	926-68070	IB(1:5000)
Licor red rabbit	LI-COR Biosciences	926-68071	IB(1:5000)

Supplementary Table 4. Antibodies and their dilutions used in the study.