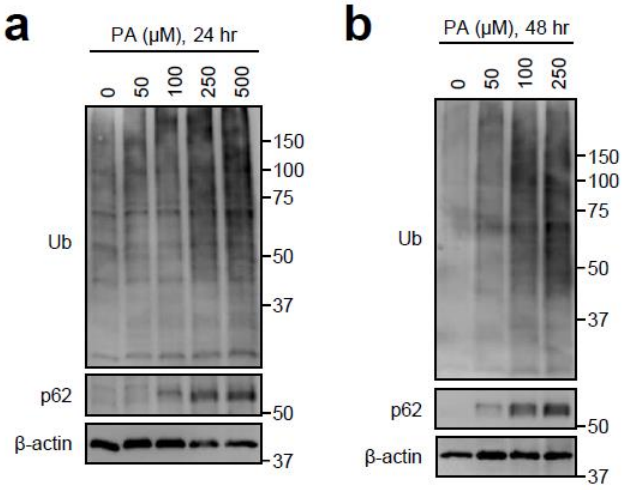
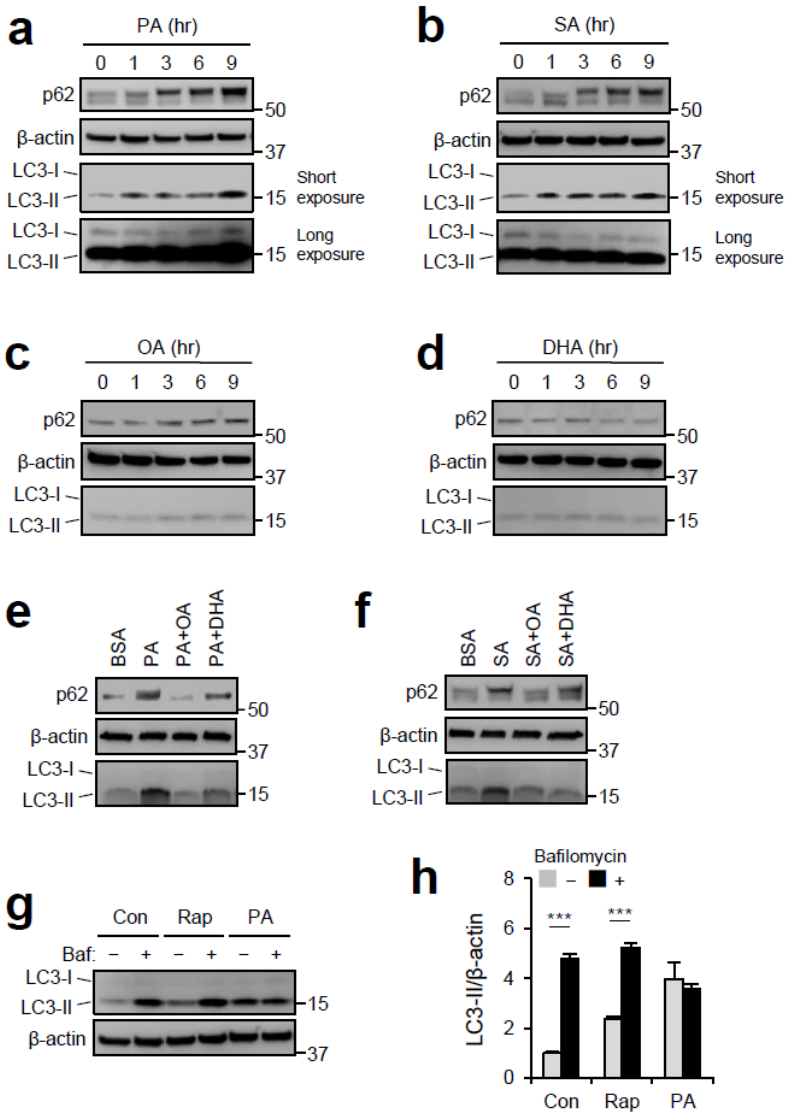
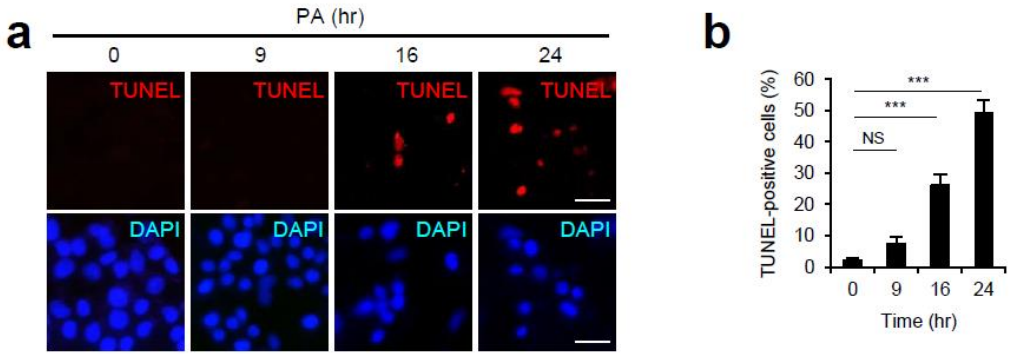


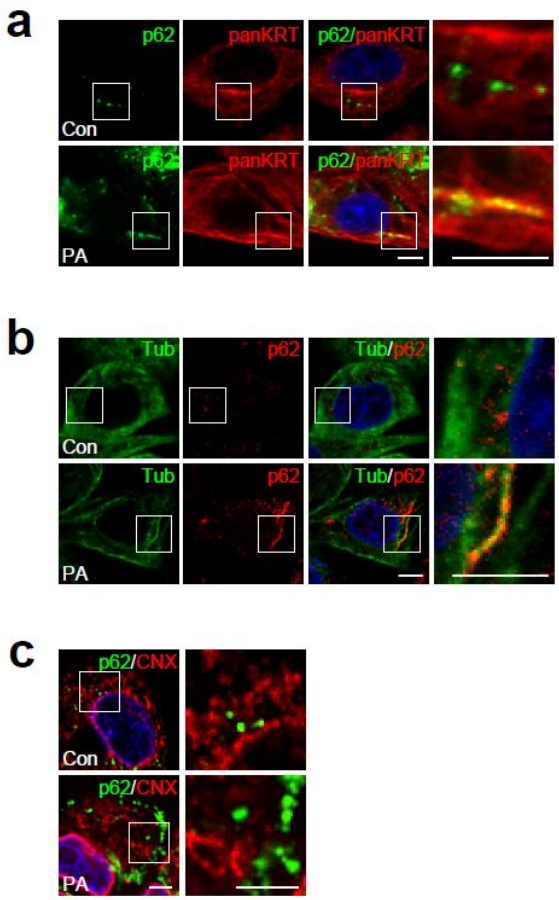
Supplementary Figure 1 | Palmitic acid-induced accumulation of ubiquitin and p62 is dose- and time-dependent. (**a**,**b**) HepG2 cells were treated with indicated concentrations of palmitic acid (PA) for 24 hr (**a**) and 48 hr (**b**) and analyzed by immunoblotting. Molecular weight markers are indicated in kDa.



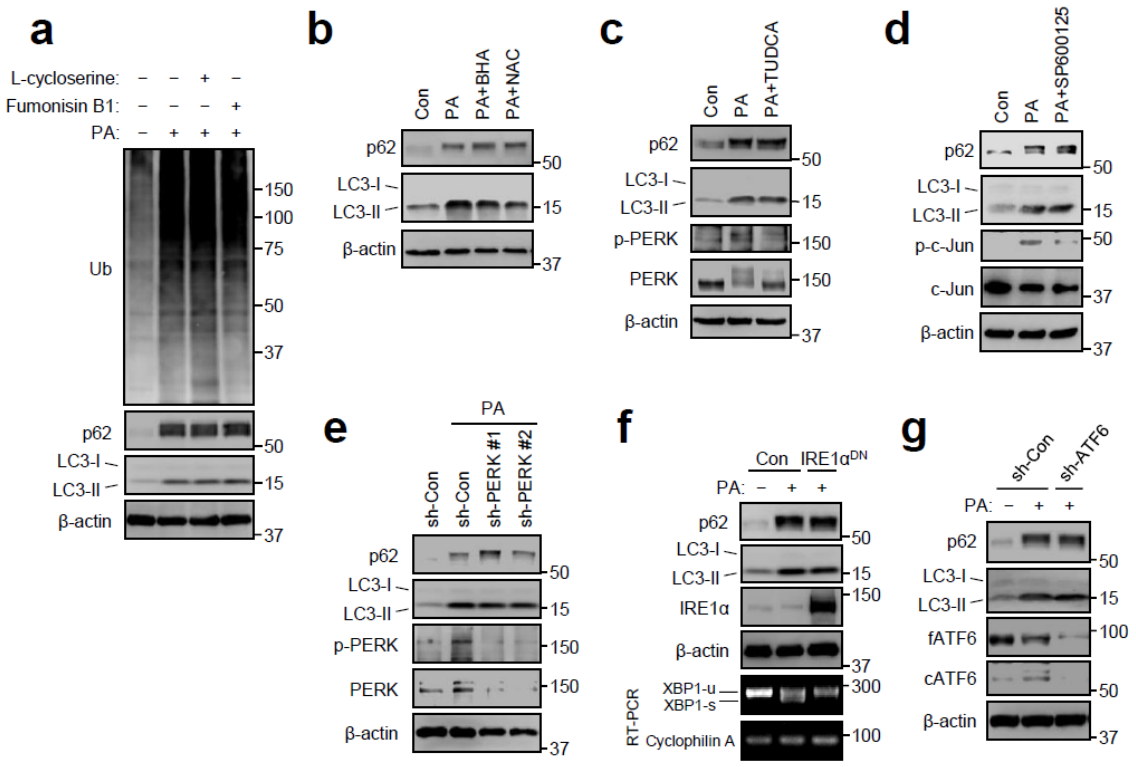
Supplementary Figure 2 | Saturated fatty acids, but not unsaturated fatty acids, induce accumulation of p62 and LC3. (**a**-**f**) HepG2 cells were treated with BSA, PA, stearic acid (SA), oleic acid (OA) and/or docosahexaenoic acid (DHA) (500 μM) for indicated hr (**a**-**d**) or 9 hr (**e**,**f**) and analyzed by immunoblotting. (**g**,**h**) Cells were treated with BSA (Con), rapamycin (Rap, 100 nM) or PA (500 μM) for 9 hr. Bafilomycin (Baf, 100 nM) was treated for last 3 hr as indicated. Cell lysates were analyzed by immunoblotting (**g**) and quantified through densitometry (**h**, $n = 3$). All data are shown as mean ± s.e.m. ***$P < 0.001$ (Student's t test). Molecular weight markers are indicated in kDa.



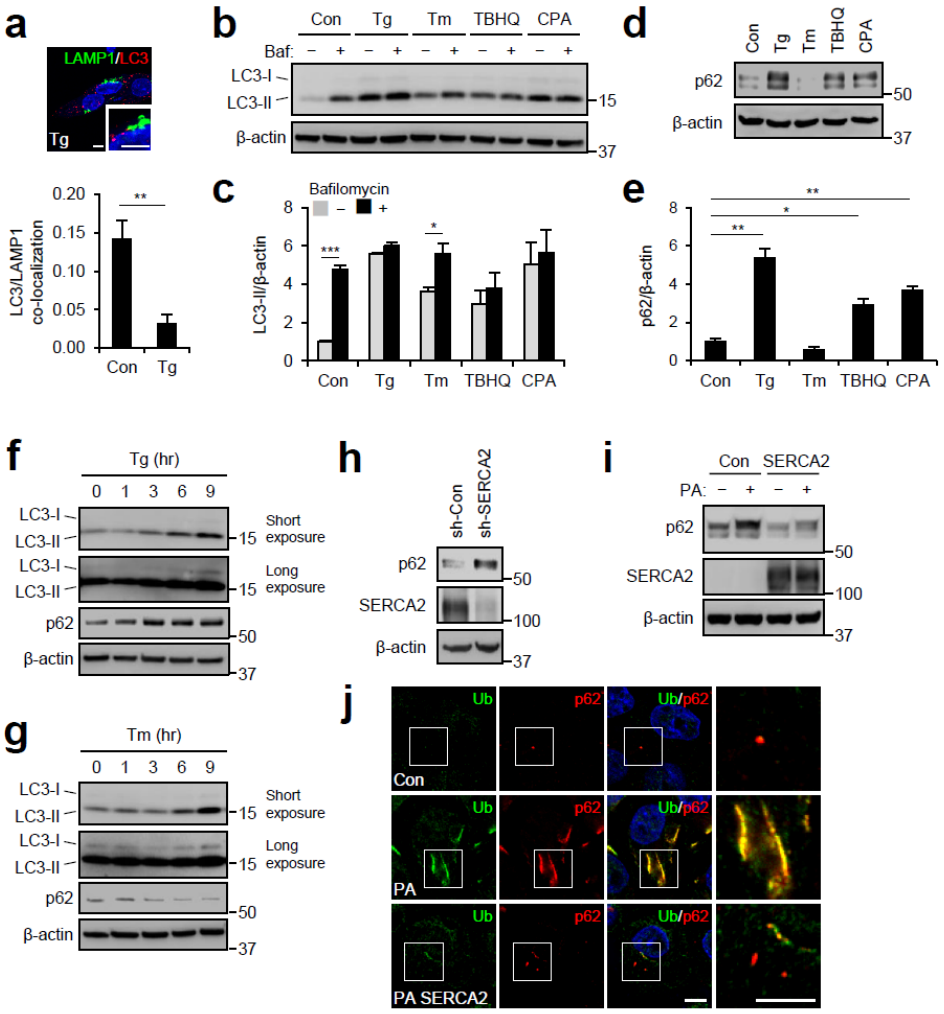
Supplementary Figure 3 | The effect of palmitic acid on HepG2 cell apoptosis. (**a**,**b**) HepG2 cells were treated with 500 μM palmitic acid (PA) for indicated hr and analyzed by TUNEL (red) and DAPI (blue) staining (**a**). TUNEL-positive cells were quantified (**b**, $n = 3$). Scale bar, 20 μm. All data are shown as mean ± s.e.m. ***$P < 0.001$ (Student's t test).



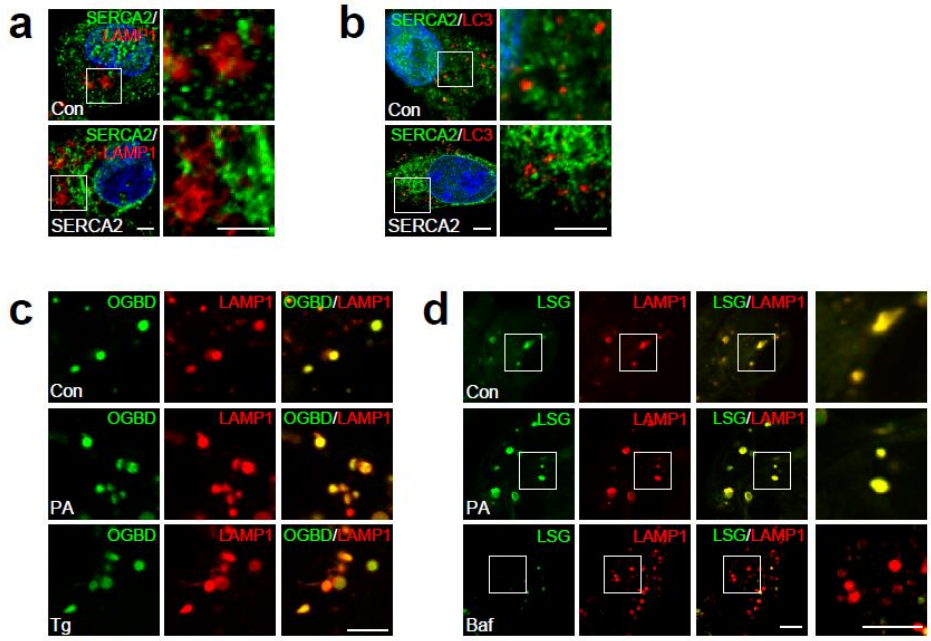
Supplementary Figure 4 | Palmitic acid-induced protein inclusion associates with keratin and tubulin fibers but not with ER. (**a-c**) HepG2 cells were treated with BSA (Con) or 500 μM palmitic acid (PA) for 9 hr and stained with p62, pan-keratin (panKRT), tubulin (Tub) and calnexin (CNX, an ER and outer nuclear envelop membrane marker) antibodies and DAPI (blue). Boxed areas are magnified in right-most panels. Scale bars, 5 μm.



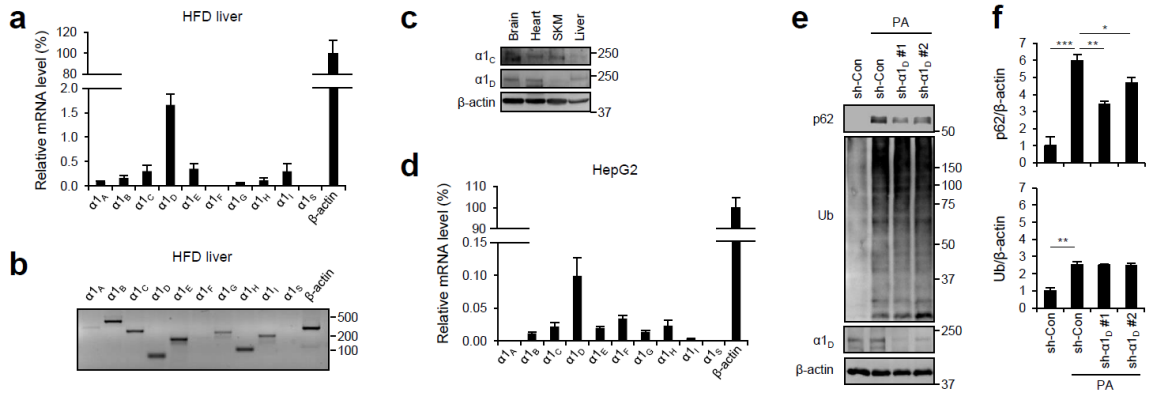
Supplementary Figure 5 | Ceramides, oxidative stress, ER stress and JNK signaling do not mediate palmitic acid-induced p62 accumulation. (**a-d**) Effects of ceramide synthesis inhibitors, L-cycloserine (100 μM) and fumonisin B1 (10 μM) (**a**), antioxidants, butylated hydroxyanisole (BHA, 100 μM) and N-acetylcysteine (NAC, 10 mM) (**b**), a chemical chaperone TUDCA (500 μg/ml) (**c**) or a JNK inhibitor SP600125 (50 μM) (**d**) on PA-induced accumulation of ubiquitinated proteins (**a**), p62 and LC3-II (**a-d**) were analyzed through immunoblotting. L-cycloserine, fumonisin B1, BHA, NAC, TUDCA and SP600125 were all treated 1 hr before 9 hr of PA treatment. (**e-g**) Effects of ER stress signaling inhibition on PA-induced accumulation of p62 and LC3-II were analyzed through immunoblotting. At 48 hr after infection with lentiviruses expressing GFP (Con) and dominant-negative IRE1α ($IRE1\alpha^{DN}$) (**f**) or shRNAs targeting luciferase (sh-Con), PERK (**e**) or ATF6 (**g**), cells were treated with BSA (-) or PA for 9 hr. XBP1-u, unspliced XBP1; XBP1-s, spliced XBP1; fATF6, full-length ATF6; cATF6, cleaved ATF6. Molecular weight markers are indicated in kDa.



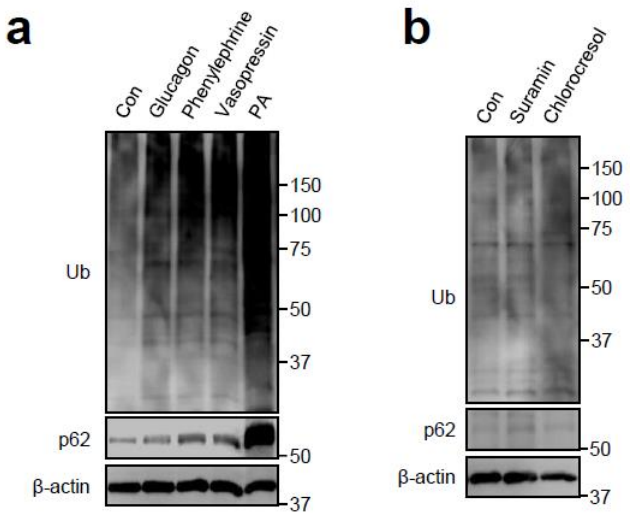
Supplementary Figure 6 | Palmitic acid impairs autophagy through inhibition of SERCA. (**a**) HepG2 cells were treated with thapsigargin (Tg) for 9 hr and subjected to immunostaining with LAMP1 and LC3 antibodies (upper panel). Co-localization between LAMP1 and LC3 was quantified and compared to untreated (Con) cells (lower panel) (*n* = 4). **(b-e**) Cells were treated with DMSO (Con), Tg (1 μM), tunicamycin (Tm, 5 μg/ml), tert-butylhydroquinone (TBHQ, 50 μM) or cyclopiazonic acid (CPA, 50 μM) for 9 hr. Bafilomycin (Baf, 100 nM) was treated for last 3 hr as indicated. Cell lysates were analyzed by immunoblotting (**b**,**d**) and quantified through densitometry (**c**,**e**) (*n* = 3). **(f**,**g**) Cells were treated with Tg (1 μM) or Tm (5 μg/ml) for indicated hr and analyzed by immunoblotting. (**h**) Cells were transduced with adenoviruses expressing shRNA targeting luciferase (sh-Con) or SERCA2b (sh-SERCA2b). At 48 hr after transduction, cells were analyzed by immunoblotting. (**i**,**j**) Cells were transduced with control or SERCA2b-overexpresing adenoviruses. At 48 hr after transduction, cells were treated with BSA (-) or PA (500 μM) for 9 hr and subjected to immunoblotting (**i**) or immunostaining (**j**). DNA was visualized by DAPI (blue). Boxed areas in fluorescence images are magnified in right-most panels. Scale bars, 5 μm. All data are shown as mean ± s.e.m. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 (Student's t test). Molecular weight markers are indicated in kDa.



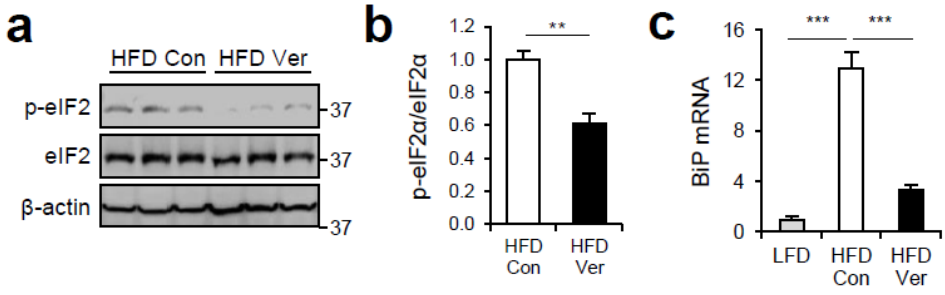
Supplementary Figure 7 | Palmitic acid does not affect lysosomal calcium and proton homeostasis. (**a**,**b**) HepG2 cells were either untreated (Con) or transduced with adenoviruses overexpressing SERCA2b. Endogenous and overexpressed SERCA2 proteins were visualized by immunostaining. Lysosomes were visualized by anti-LAMP1 immunostaining (**a**). Autophagosomes were visualized by anti-LC3 immunostaining (**b**). DNA was visualized by DAPI (blue). (**c**,**d**) Cells were transduced with lentiviruses expressing LAMP1-mRFP that labels lysosomes. (**c**) Two days after transduction, cells were treated with BSA (Con), PA (500 μM) or Tg (1 μM) for 9 hr and loaded with Oregon Green 488 BAPTA-1-dextran (OGBD), a calcium indicator that accumulates in lysosomes. OGBD's fluorescence intensity is proportional to calcium concentration in lysosome lumen[1]. (**d**) Two days after transduction, cells were treated with BSA, PA or bafilomycin (Baf, 100 nM) for 9 hr and loaded with LysoSensor Green (LSG), a pH indicator that labels lysosomes. LysoSensor's fluorescence intensity is proportional to proton concentration in lysosome lumen[2]. Bafilomycin is an inhibitor of lysosomal proton pump, therefore was used as a positive control. Boxed areas in fluorescence images are magnified in right-most panels. Scale bars, 5 μm.



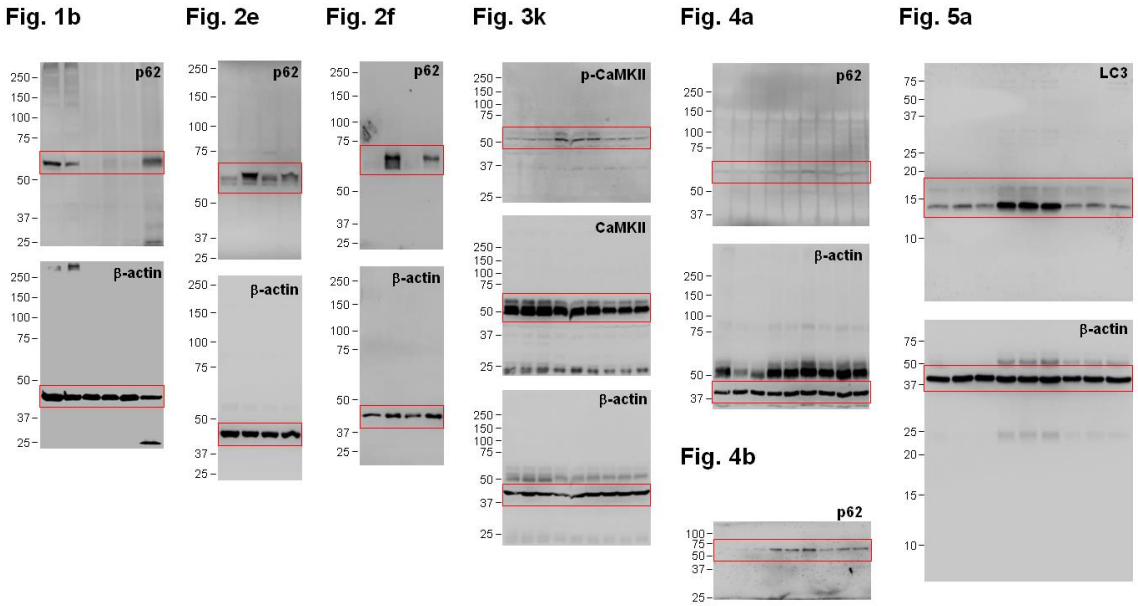
Supplementary Figure 8 | $\alpha 1_D/Ca_v1.3$ is expressed in hepatocytes and plays a role in palmitic acid-induced p62 inclusion. (**a**,**b**) mRNA expressions of calcium channel isoforms were analyzed by qRT-PCR from livers of obese mice on HFD (**a**). Endpoint PCR products were analyzed by agarose gel running (**b**). (**c**) Expression of $\alpha 1_C/Ca_v1.2$ and $\alpha 1_D$ proteins were examined from brain, heart, skeletal muscle (SKM) and liver lysates by immunoblotting. (**d**) mRNA expression of calcium channel isoforms were analyzed by qRT-PCR from HepG2 cells. (**e**,**f**) At 48 hr before PA treatment, HepG2 cells were infected with lentiviruses expressing shRNAs targeting luciferase (sh-Con) or $\alpha 1_D$ and their insoluble fractions were subjected to immunoblotting with anti-p62, anti-ubiquitin and anti-actin antibodies (**e**). $\alpha 1_D$ expression was examined from soluble fractions. Levels of p62 and ubiquitinated proteins were quantified (**f**) (n = 3). All data are shown as mean ± s.e.m. *P < 0.05, **P < 0.01, ***P < 0.001 (Student's t test). Molecular weight markers are indicated in kDa.



Supplementary Figure 9 | Activation of IP3 receptor, but not ryanodine receptor, resulted in modest accumulation of ubiquitinated proteins and p62. (**a**,**b**) HepG2 cells were treated with glucagon (100 nM), phenylephrine (100 μM), vasopressin (1 μM), suramin (400 μM), chlorocresol (100 μM) or PA (500 μM) for 12 hr and analyzed by immunoblotting. Molecular weight markers are indicated in kDa.



Supplementary Figure 10 | Effects of verapamil on ER stress of mouse hepatocytes. 4 month-old C57BL/6 male mice kept on HFD for two months were subjected to daily administration of PBS (Con, $n = 4$) or verapamil (Ver, 25 mg/Kg body weight, i.p., $n = 3$) for 10 days. LFD-kept mice ($n = 5$) of same age were used as a negative control. (**a-c**) Levels of eIF2α phosphorylation from livers were analyzed by immunoblotting (**a**) and quantified (**b**). Levels of BiP mRNA expression from livers were analyzed by qRT-PCR (**c**). All data are shown as mean ± s.e.m. $^{**}P < 0.01$, $^{***}P < 0.001$ (Student's t test). Molecular weight markers are indicated in kDa.



Supplementary Figure 11 | Uncropped images of blots presented in the main paper. Red boxes indicate the cropped regions. Molecular weight markers are indicated in kDa.

Supplementary Table 1 | Effect of calcium channel blockers on metabolic homeostasis of humans and animals.

a. Positive effects of calcium channel blockers on metabolism.

Compound	Organism	Metabolic effects	Refs.
Amlodipine	Obese humans	Improved glucose tolerance	3
	Hypertensive humans	Increased insulin sensitivity	4
	Obese humans	Reduced insulin resistance	5, 6
Azelnidipine	Hypertensive humans	Improved glucose tolerance	7
Benidipine	Hypertensive humans	Improved insulin resistance	8
Cilnidipine	Obese humans	Reduced insulin resistance	5
Isradipine	SHR rats	Improved insulin sensitivity	9
Lercanidipine	CRDH rats	Reduced blood glucose level	10
Manidipine	T2DM humans	Increased insulin sensitivity	11
	Obese humans	Reduced insulin resistance	5
Nifedipine	CHD patients with LGT	Reduced blood glucose level	12
	NASH mice on MCD	Reduced liver damage	13
		Reduced fibrosis	
	Agouti-induced obese mice	Reduced obesity	14
		Improved insulin sensitivity	
	SHHF obese rats	Improved insulin response	15
	STZ-injected rats	Reduced hyperglycemia	16
		Reduced hyperlipidemia	
Nisoldipine	STZ-injected SHR rats	Reduced blood glucose level	17
Nitrendipine	Obese humans	Reduced insulin resistance	18, 19
		Reduced hyperinsulinemia	
		Improved glucose tolerance	
	SHR rats	Improved glucose tolerance	20
Verapamil	T2DM humans	Improved glucose tolerance	21, 22, 23,
		Reduced blood glucose level	24
		Reduced blood glucose turnover	25
	Obese humans	Reduced hyperinsulinemia	26
	Obese *ob/ob* mice	Improved glucose tolerance	27
		Improved insulin sensitivity	

SHR, Spontaneously Hypertensive; CRDH, Cohen Rosenthal Diabetic Hypertensive; T2DM, Type 2 Diabetes Mellitus (also known as NIDDM); CHD, Coronary Heart Disease; LGT, Low Glucose Tolerance; NASH, Non-Alcoholic Steatohepatitis; MCD, Methionine-Choline-deficient Diet; SHHF, Spontaneously Hypertensive Heart Failure; STZ, streptozotocin;

b. Neutral or negative effects of calcium channel blockers on metabolism.

Compound	Organism	Metabolic effects	Refs.
CCB in general	Hypertensive humans	No effects on incidental diabetes	[28]
Amlodipine	Hypertensive humans	No effects on blood lipid level	[29]
Diltiazem	Hypertensive humans	No effects on insulin sensitivity	[30]
Felodipine	Hypertensive humans	No effects on blood glucose level No effects on blood lipid level	[31]
	T2DM humans	No effects on blood glucose level	[32]
Nicardipine	T2DM humans	No effects on glucose tolerance	[33]
	Hypertensive humans	No effects on blood lipid profile	[34]
Nifedipine	Obese *cp/cp* rats	No effects on blood glucose level Slight increase in insulin level	[35]
	Dogs	No effects on blood glucose level Slight decrease in insulin level	[36]
Nitrendipine	Hypertensive humans	No effects on blood glucose level No effects on blood lipid level	[37]
Verapamil	Healthy humans	No effect on glucose tolerance No effect on basal glucose level Slight decrease in insulin sensitivity Induction of hyperglycemia	[38] [39]
	Healthy dogs	Systemic insulin resistance*	[40]
	Nondiabetic rats	Induction of glucose intolerance	[41]

CCB, Calcium Channel Blocker; T2DM, Type II Diabetes Mellitus; *, treated with toxic concentration of verapamil

Supplementary Table 2 | Primers used in this study

Gene	Forward	Reverse	Refs.
Adiponectin	TGTTCCTCTTAATCCTGCCCA	CCAACCTGCACAAGTTCCCTT	[42]
TNFα	AGGGTCTGGGCCATAGAACT	CCACCACGCTCTTCTGTCTAC	[43]
Interleukin-6	ACCAGAGGAAATTTTCAATAGGC	GATGCACTTGCAGAAAACA	[43]
mouse BiP	GGTGCAGCAGGACATCAAGTT	CCCACCTCCAATATCAACTTGA	[44]
mouse $\alpha1_A$	CACCGAGTTTGGGAATAACTTCA	ATTGTGCTCCGTGATTTGGAA	[42]
mouse $\alpha1_B$	AAGTGGCATCAAGGAGTCGC	GCTAGGCGTGGCATAGAGG	[42]
mouse $\alpha1_C$	ATGAAAACACGAGGATGTACGTT	ACTGACGGTAGAGATGGTTGC	[42]
mouse $\alpha1_D$	AGAGGACCATGCGAACGAG	CCTTCACCAGAAATAGGGAGTCT	[42]
mouse $\alpha1_E$	GATGGAGACTCGGACCAGAG	TGACCGTGAAACAGTTCTGCC	[42]
mouse $\alpha1_F$	ATGTCGGAATCTGAAGTCGGG	ACCGCCACAGTCTTGTGTTT	[42]
mouse $\alpha1_G$	TGTCTCCGCACGGTCTGTAA	AGATACCCAAAGCGACCATCTT	[42]
mouse $\alpha1_H$	GAACGTGGTTCTTTACAACGGC	GCACATAGTTCCCAAAGGTCA	[42]
mouse $\alpha1_I$	GGGCGTGGCCTGTTTAGTC	TGAGGGTCTCGGAGTGCTC	[42]
mouse $\alpha1_S$	CAGCGGGGGACTGTATTGC	TGTGGCACACCTGAAGAGC	[42]
mouse β-actin	CAAAAGCCACCCCCACTCCTAAGA	GCCCTGGCTGCCTCAACACCTC	[45]
human $\alpha1_A$	CGCTTCGGAGACGAGATGC	TGCGCCATTGACTGCTTGT	[42]
human $\alpha1_B$	GACAACGTCGTCCGCAAATAC	CCCGATGAAATAGGGCTCCG	[42]
human $\alpha1_C$	GAAGCGGCAGCAATATGGGA	TTGGTGGCGTTGGAATCATCT	[42]
human $\alpha1_D$	TCAGCCGAATAGCTCCAAGC	TCGGATGGGGTTATTGAGTGA	[42]
human $\alpha1_E$	CCATGTCCCGAAGACTGGAGA	CCATTGCGGAGGTAAGAGC	[42]
human $\alpha1_F$	CCATGTCCCGAAGACTGGAGA	CCATTGCGGAGGTAAGAGC	[42]
human $\alpha1_G$	TGTCTCCGCACGGTCTGTAA	AAGCCGGTTCCAAGTGTCTC	[42]
human $\alpha1_H$	ATGCTGGTAATCATGCTCAACTG	AAAAGGCGAAAATGAAGGCGT	[42]
human $\alpha1_I$	GGAGCTGATCCTCATGTCCC	CACGGGTTGCACACCATCT	[42]
human $\alpha1_S$	TTGCCTACGGCTTCTTATTCCA	GTTCCAGAATCACGGTGAAGAC	[42]
human XBP1	TTACGAGAGAAAACTCATGGC	GGGTCCAAGTTGTCCAGAATGC	[46]
human cyclophilin A	GCAAAGTGAAAGAAGGCATGAA	CCATTCCTGGACCCAAAGC	[47]

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