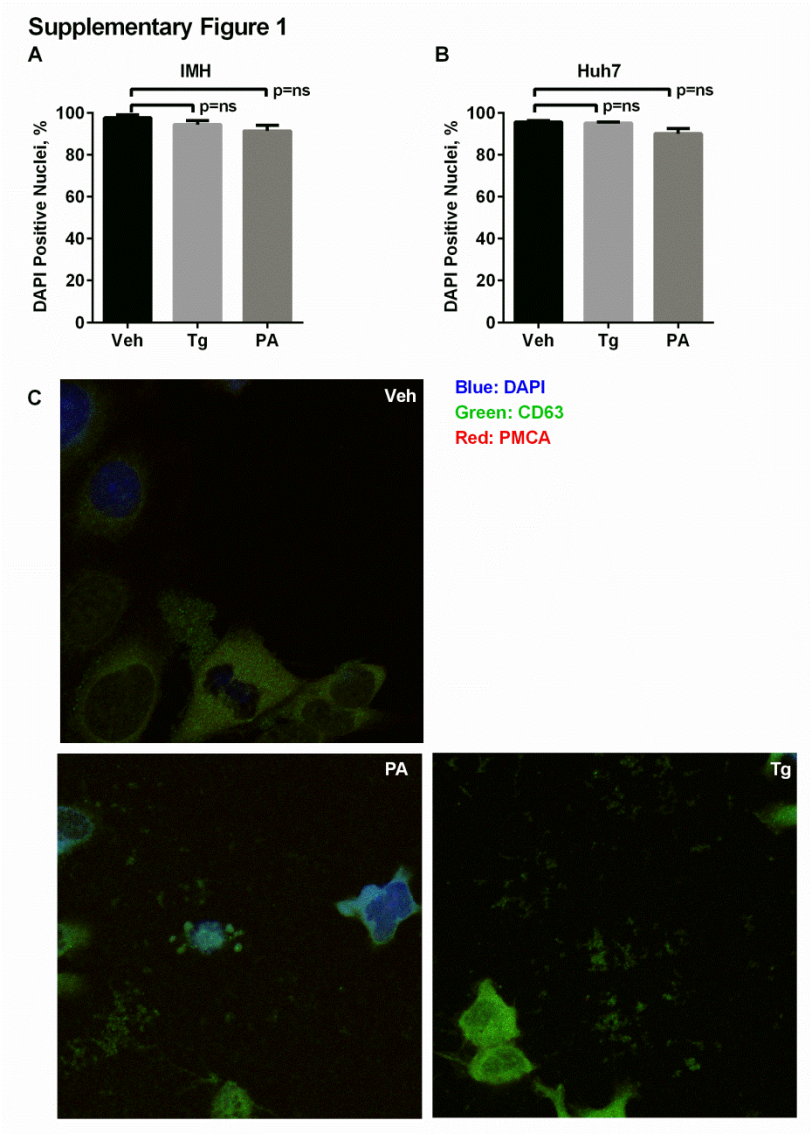
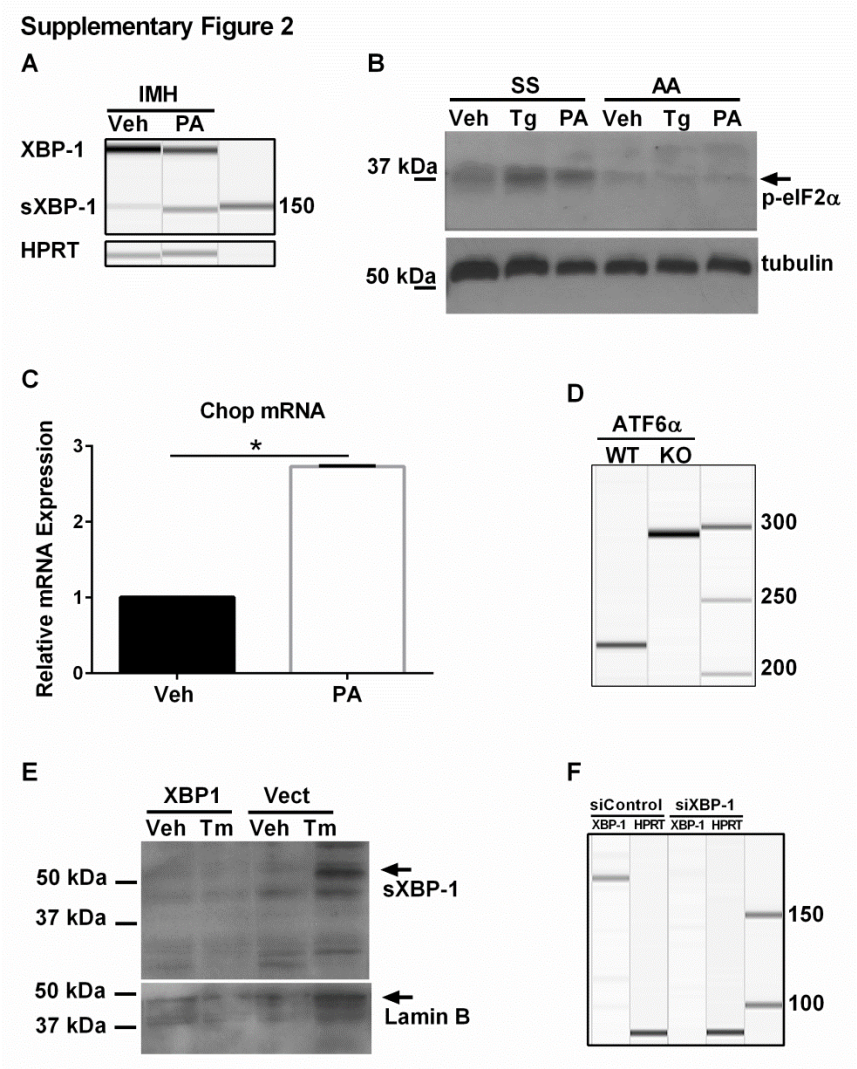
SUPPLEMENTARY INFORMATION

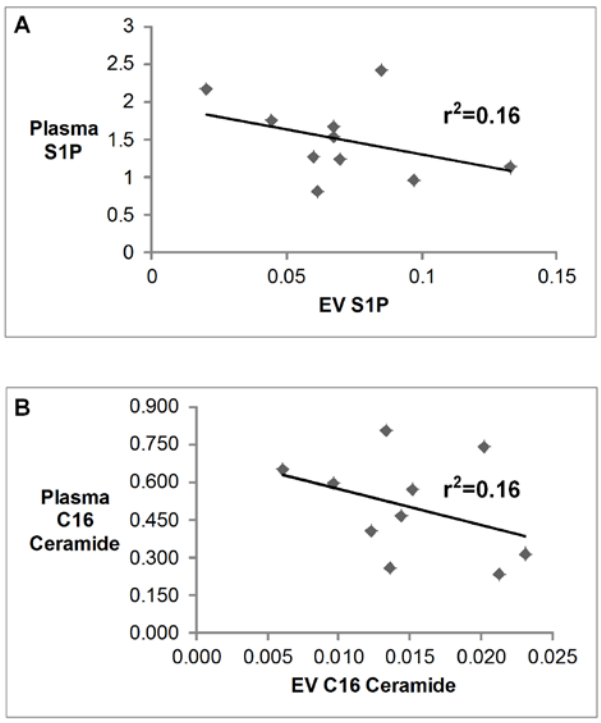


Supplementary Figure 1. Cell viability and extracellular CD63. A) Immortalized mouse hepatocytes (IMH) or B) human hepatoma cells Huh 7 were cultured with 2.5 nM thapsigargin (Tg) or 400 μM palmitate (PA) or vehicle (veh) for 16hr. Cell death was assessed by DAPI stained nuclear morphology. Percentage indicates live cell. C) Immunofluorescence for CD63 (green) was performed in IMH cells as treated in A, plated on poly-L-lysine coated coverslips to adhere secreted vesicles. Nuclei were stained with DAPI (blue), and plasma membrane with plasma membrane Ca^{2+} ATPase (PMCA) (red).



Supplementary Figure 2. Palmitate activates the unfolded protein response sensors in hepatocytes. A) Immortalized mouse hepatocytes (IMH) were treated with 400 μM palmitate (PA) or vehicle (veh) for 16hr. XBP-1 splicing was assessed by RT-PCR, HPRT was used as a control. PCR fragments were resolved by capillary electrophoreses. B) Wild-type (SS) or eIF2α phosphorylation resistant (AA) IMH were treated with 2.5 nM thapsigargin (Tg) or 400 μM palmitate (PA) for 5 hours. eIF2α phosphorylation was assessed with a phospho-specific antibody. Tubulin was used as loading control. C) CHOP mRNA was measured by q-PCR in IMH cells treated with 400 μM (PA) for 16 hours, and expressed relative to vehicle (veh) treated cells. * $p<0.05$. D) Genotype of ATF6α wild-type (WT) and knockout (KO) cells was confirmed by PCR on genomic DNA. E) Nuclei were extracted from Huh7 cells deleted in XBP-1 (XBP-1-/-) using Crispr/Cas9 or control cells (vector), treated with 4μg/ml tunicamycin (Tm) for 6 hours. XBP-1 deletion was confirmed by western blotting of nuclear extracts. F) IMH cells were transfected with siRNA targeting XBP-1 (siXBP-1) or a control siRNA (siControl). XBP-1 silencing was confirmed by PCR, HPRT is included as loading control. PCR fragments were resolved by capillary electrophoreses. Molecular weight marker is in the right most lane with size indicated.

Supplementary Figure 3



Supplementary Figure 3. Regression analysis for plasma versus extracellular vesicles. A) Regression analysis for S1P levels. B) Regression analysis for C16 Ceramide levels.