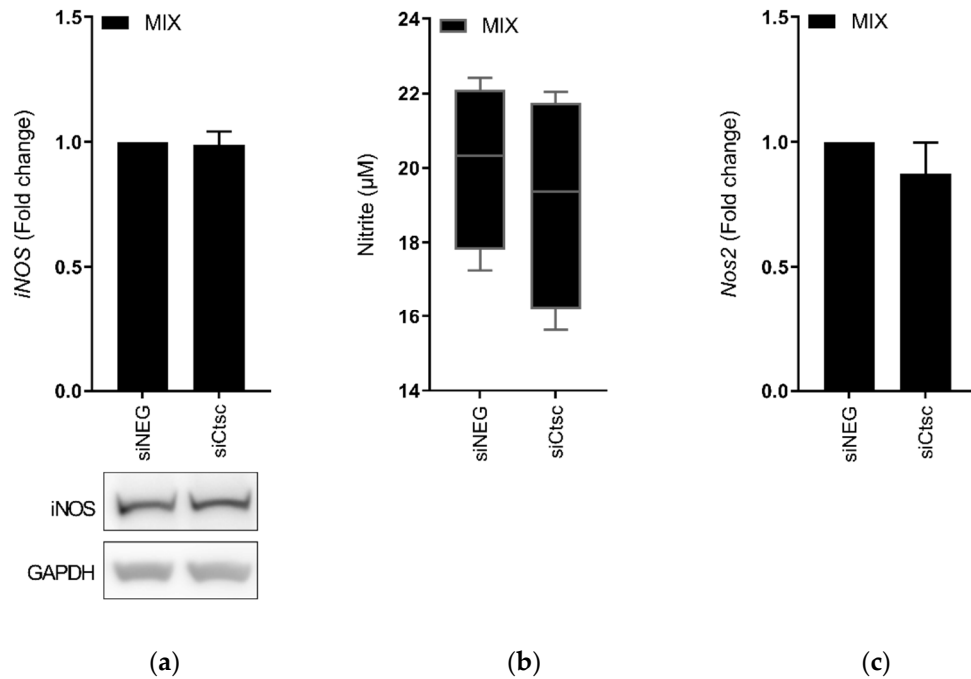
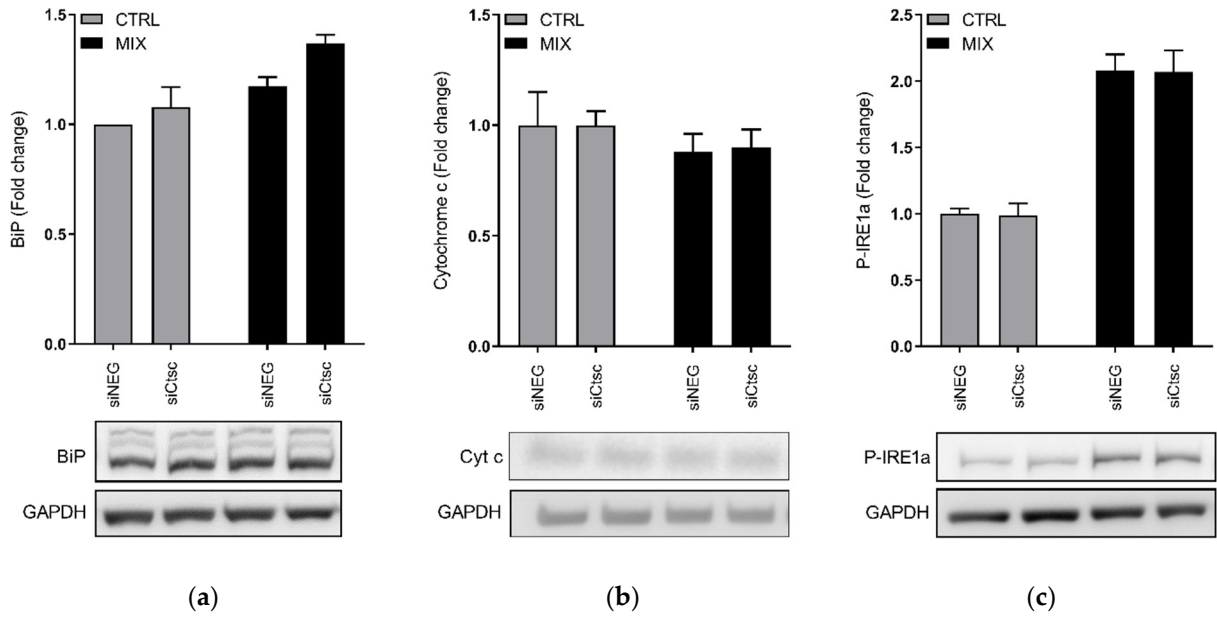


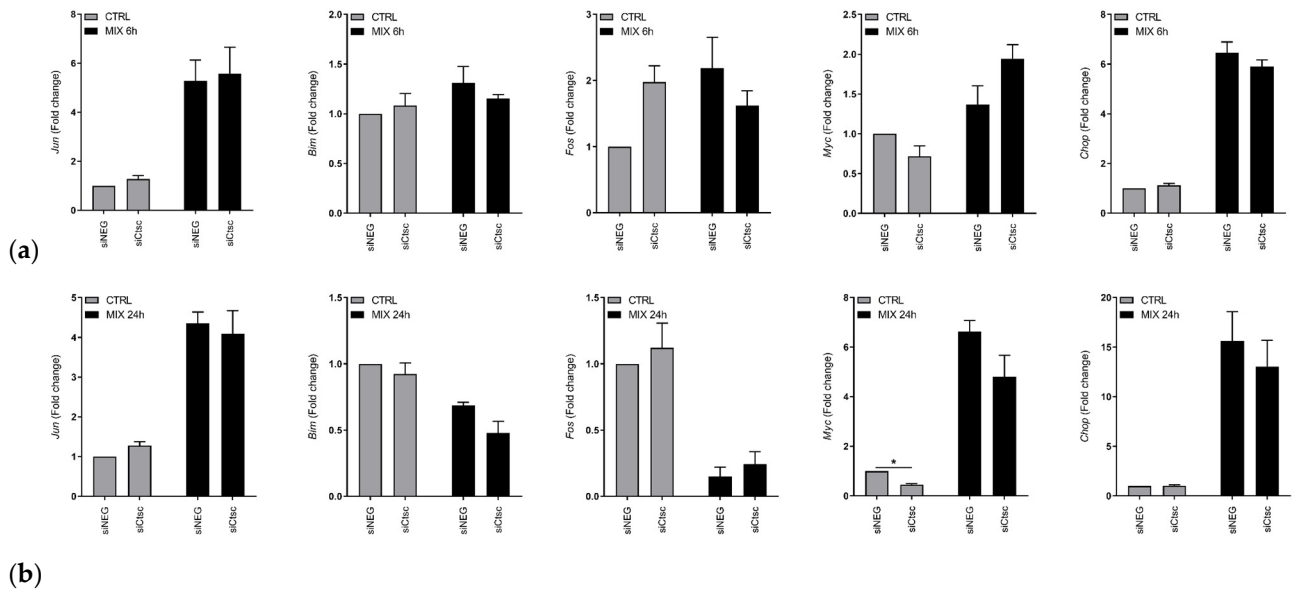
Supplementary



Supplementary Figure S1. Effect of *Ctsc* KD on iNOS, NO production and *Nos2* mRNA expression. INS-1E cells were transfected with a siRNA pool against *Ctsc* (siCtsc) or a non-targeting negative control siRNA pool (siNEG) and then exposed to pro-inflammatory cytokines IL-1 β and IFN- γ (MIX). (a) iNOS protein was examined by immunoblotting after 6 h of cytokine exposure. *GAPDH* was used as loading control. Data are presented as fold change with mean and SEM (n=4). (b) NO production was assessed using the Griess Reagent System by measuring the accumulated nitrite in the cell culture medium after 24 h of cytokine exposure. Data are presented as (μ M) with min., first quantile (25 %), median, third quantile (75 %) and max., (n=4). (c) The mRNA expression of iNOS (*Nos2*) was investigated by real-time qPCR after 24 h of cytokine exposure. Data were normalized to *Hprt* and presented as fold change with mean and SEM, (n=4).



Supplementary Figure S2. Effect of *Ctsc* KD on BiP, cytochrome c and p-IRE1a. INS-1E cells were transfected with a siRNA pool against *Ctsc* (siCtsc) or a non-targeting negative control siRNA pool (siNEG) and then exposed to pro-inflammatory cytokines (IL-1 β and IFN- γ). (a) BiP, (b) cytochrome c, and (c) p-IRE1a were evaluated at the protein level by immunoblotting at baseline and after 6 h of cytokine exposure. *GAPDH* was used as loading control. Data are presented as fold change with mean and SEM (n=4).



Supplementary Figure S3. Effect of *Ctsc* KD on downstream MAPK signaling gene expression. INS-1E cells were transfected with a siRNA pool against *Ctsc* (siCtsc) or a non-targeting negative control siRNA pool (siNEG) and then exposed to pro-inflammatory cytokines (IL-1 β and IFN- γ). The mRNA expression of *Jun*, *Bim*/*Bcl2l11*, *Fos*, *Myc*, and *Ddit3*/*Chop*, were analyzed by real-time qPCR after (a) 6 and (b) 24 h of cytokine exposure. Data were normalized to *Hprt1* and presented as fold change with mean and SEM, (n=4 (a) and n=5 (b)). Bonferroni-adjusted p<0.05.