

Supplemental Figure 1.

Rotarod test was performed to assess locomotive coordination of C57/Bl6 WT and β elF4G1KO mice, over the course of 4 days (n=7, 5) (**A**). Body weight of 2-months-old male (**B**) and female (**C**) Rip-Cre WT, eIF4G1f/+, β elF4G1HET, eIF4G1f/f and β elF4G1KO (n=7, 8, 11, 7, 11 males; n=5, 5, 6, 5, 7 females). *In vivo* glucose tolerance (2 g/kg glucose, i.p.) was performed on 5-months-old Male C57/Bl6 WT, eIF4G1f/f and β elF4G1KO (n=7, 5, 5). Area under curve (AUC) of the blood glucose curve is also presented (**D**). eIF4G1 protein level from acute eIF4G1 knockdown INS1 cells (**E**) (n=4). WT are mix of Rip-Cre (+) and (-) mice with no floxed genes. Statistical analyses were conducted using unpaired, two-way student t-test for AUC data with significance *p<0.05.

Supplemental Figure 2.

Average β -cell size (Insulin⁺ area / Insulin⁺DAPI⁺ nuclei #) (**A**) was determined from immunofluorescence staining of pancreatic sections of islets with Insulin (green), DAPI (blue) from Figure 4F. Spliced over unspliced XBP (**B**) and CHOP (**C**) transcripts from isolated islets of WT and β elF4G1KO mice (n=3-4). Representative western blot (**D**) and quantification (relative to vinculin; normalized to WT avg.) from islets of WT and β elF4G1KO showing: phospho-S6 S240 (relative to total S6) (**E**) and total S6 (**F**) (n=4-6). WT are mix of Rip-Cre (+) and (-) mice with no floxed genes. Statistical analyses were conducted using unpaired, two-way student t-test with significance *p<0.05.

Supplemental Figure 3.

β -cell replication (via Ki67) (**A**, **B**), apoptosis (via TUNEL) (**C**, **D**) (Ki67⁺ or TUNEL⁺ β -cells % to total β -cells counted), and β -cell size (via E-Cadherin membrane marker) (**E**, **F**) were measured using pancreas sections from mice fed HFD for 10-wks (n=4). Yellow (**A**) and White (**C**) arrows

indicate the Ki67 or TUNEL positive β -cells respectively. Scale bars: 100 μ M. WT are mix of Rip-Cre (+) and (-) mice with no floxed genes. Statistical analyses were conducted using unpaired, two-way student t-test with significance $*p < 0.05$.

Supplemental Figure 4.

In vivo GSIS of 6-months-old Female eIF4G1f/f and β eIF4G1KO (n=3-4) (**A**). Quantification of glucose-stimulated, non-mitochondrial, maximum respiration, proton leak, and spare capacity (**B**) of Seahorse experiment from Figure 7E. Representative graph of Seahorse OCR and calculated parameters (**C**). Quantification of CIII and CIV protein levels from western blot from Figure 7G (**D**) Oxygen consumption rate of eIF4G1 knockdown INS-1 cells (OCR; pmol/min/normalized to ng DNA content) (**E**) and quantification of basal respiration, ATP production, non-mitochondrial, maximum respiration, proton leak, and reserve capacity (**F**) (n=5). Immunoblot of INS-1 siCtrl vs siEIF4G1 cells for electron transport chain subunits (Complex I, II, III and V) and quantification (**G**) (n=4-8). Complex IV (expected size at ~37kDa) was not detected in the tested samples. Additional traces showing 340/380 Fura-2 for calcium measurements from groups of 100 WT and β eIF4G1KO islets (**H**). WT are mix of Rip-Cre (+) and (-) mice with no floxed genes. Statistical analyses were conducted using 2-way ANOVA for (**A**) ($*p = \text{WT vs. } \beta\text{eIF4G1KO}$; $\#p = \text{T0 vs. T1}$) with significance $*p < 0.05$.

Supplemental Figure 5.

Representative western blot and quantification (relative to vinculin or β -actin; normalized to WT avg.) from islets of WT and β eIF4G1KO showing: SERCA2 (n=4-7) (**A, B**) and Kir6.2 (n=4) (**C, D**). WT are mix of Rip-Cre (+) and (-) mice with no floxed genes. Statistical analyses were conducted using unpaired, two-way student t-test with significance $*p < 0.05$.

Supplemental Figure 6.

NeuroD1 transcript (**A**) (relative to β -Actin, log₂ fold-change to WT) and representative immunoblot and quantitation of PDX1 protein levels (**B**) (relative to β -Actin, normalized to WT) in isolated islets of WT, eIF4G1 f/f and β eIF4G1KO (n=4). Transcript levels and quantification of immunoblot (from Figure 8C) of eIF4G2 (**C, D**), eIF4G3 (**E, F**) and eIF4A (**G, H**) from isolated islets of WT, eIF4G1 f/f and β eIF4G1KO islets. Insulin content was assessed for cells transfected with GFP-tagged eIF4E (vs. GFP control) in INS-1 cells (normalized to DNA) (**I**). Diagram of single islet cell insulin content assay, where only transfected GFP and GFP-eIF4E cells were harvested, under fluorescent microscopy at 60x magnification. Subsequently, cells were lysed in 20 μ L of RIPA lysis buffer, and insulin contents were measured by ELISA (**J**). WT are mix of Rip-Cre (+) and (-) mice with no floxed genes.