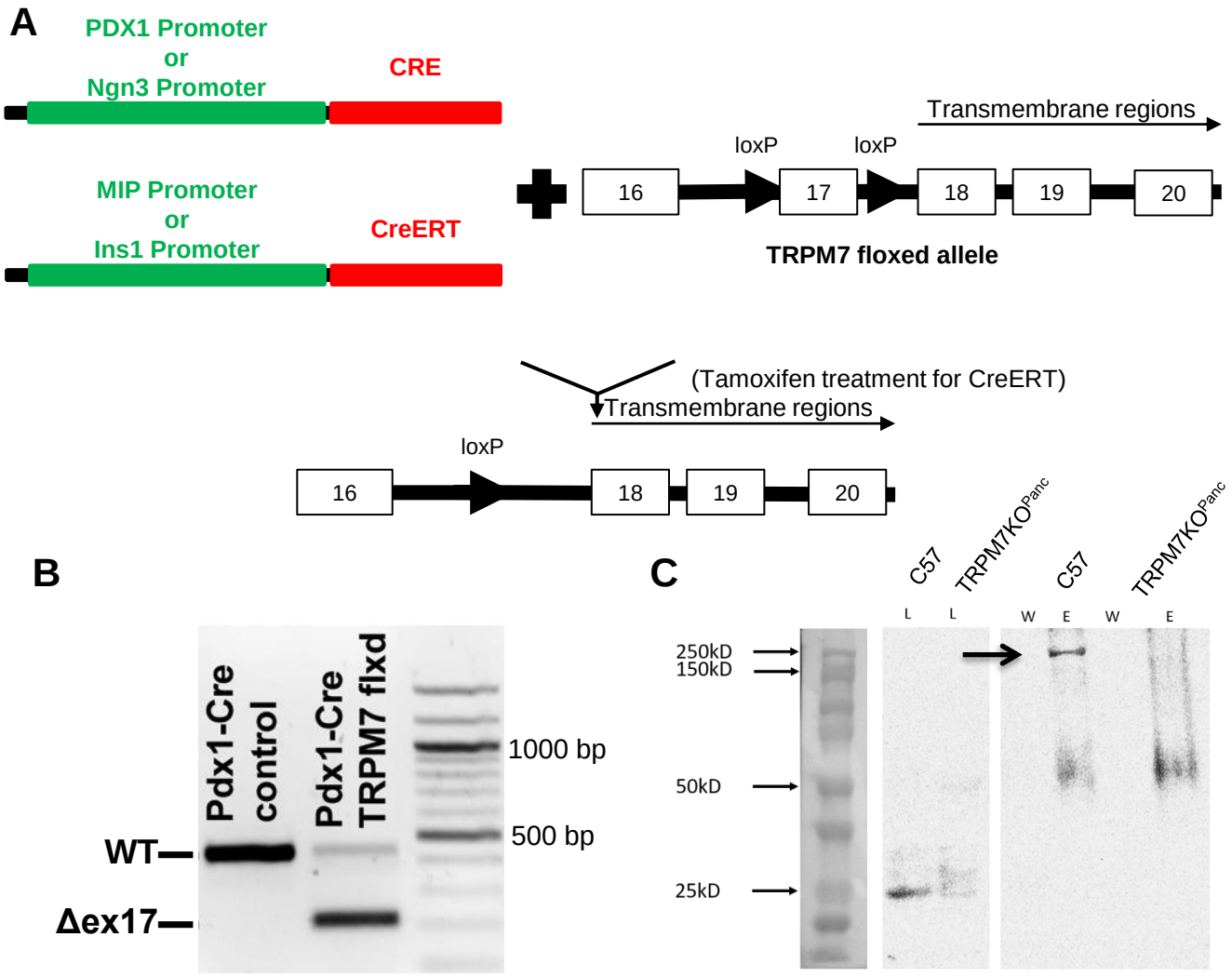

Fig. S1. Mouse model design and confirmation of successful PDX knockout.(A) Schematic of the transgenic design of mouse models with chronic (TRPM7KO^{Panc} or TRPM7KO^{Endo}) pancreatic specific and conditional β-cell specific tamoxifen-inducible (TRPM7KO^{MIPβ} or TRPM7KO^{Insβ}) TRPM7 ablation. (B) Islet genomic DNA from Pdx1-Cre or TRPM7KO^{Panc} mice analyzed by PCR for TRPM7 exon 17 deletion. (C) Immunoprecipitation showing knockdown of TRPM7 protein in whole cell lysate from C57/B6 (C57) or TRPM7KO^{Panc} mouse pancreas from 12-week animals. Black arrow indicates band associated with full length TRPM7 protein. L = load, W = wash, E = elution.

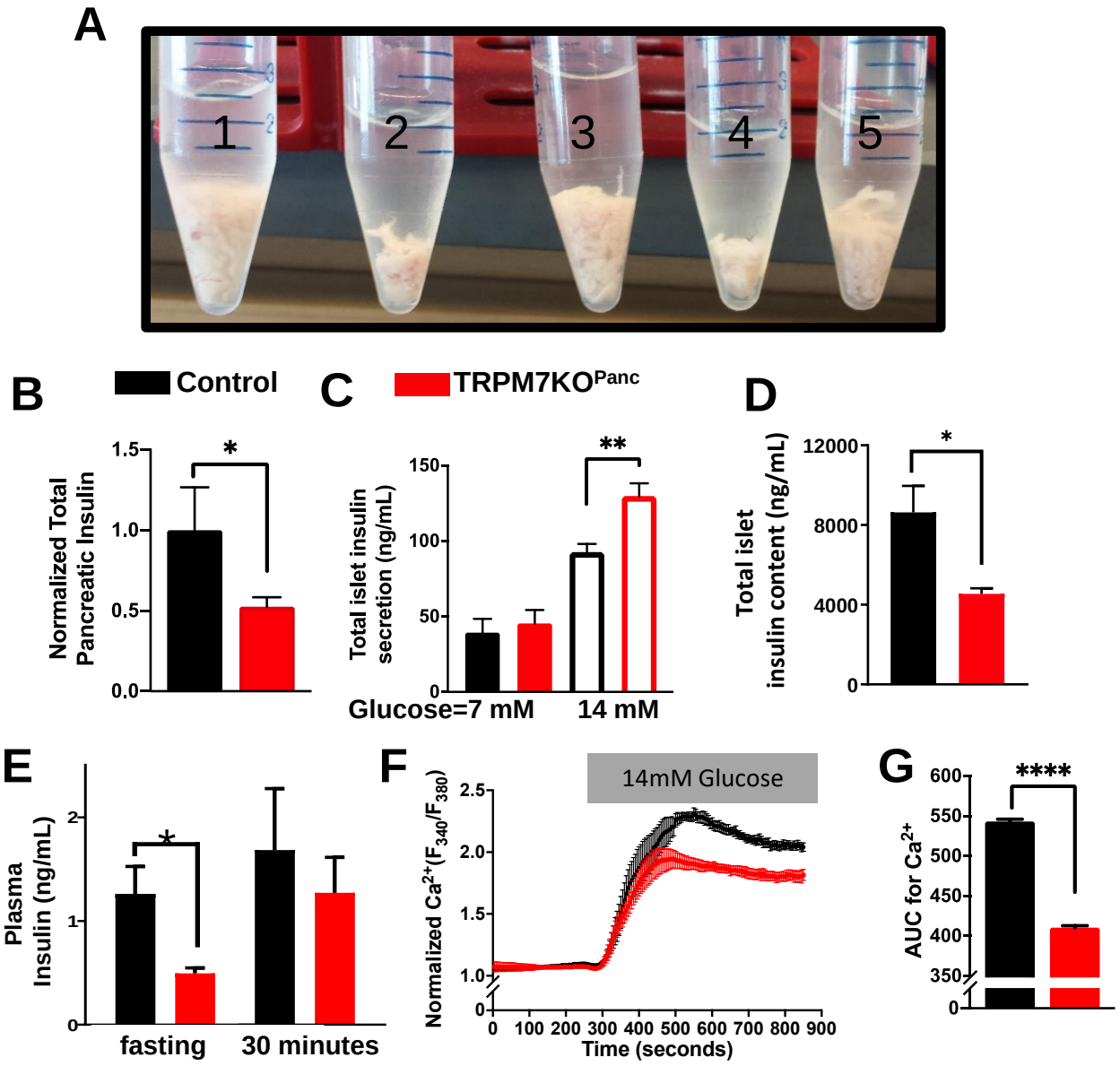

Fig. S2. Adult TRPM7KO^{Panc} pancreata showed diminished size and insulin content. (A) Pancreata harvested from TRPM7KO^{Panc} mice (2, 4) following distention appeared significantly smaller than those from control mice (1, 3, 5). (B) Total pancreatic insulin was significantly lower in TRPM7KO^{Panc} mice compared to controls (47.39 ± 15.75% reduction, n = 3 P<0.05). (C) GSIS was significantly increased in TRPM7KO^{Panc} mice compared to control (39.95 ± 10.69%, n = 5). *(D) Total islet insulin content was reduced in* TRPM7KO^{Panc} islets compared to controls (n= *3* mice each and 20 equivalent sized islets/mouse) (E) Fasting plasma insulin was reduced in TRPM7KO^{Panc} mice, but 30 minutes post GTT glucose bolus plasma insulin was equivalent between TRPM7KO^{Panc} mice and controls. Relative glucose-stimulated (14 mM) cytosolic Ca^{2+} responses (F) and total AUC (G) in control (black) and TRPM7KO^{Panc} (red) islets. Where applicable analysis are mean ± SEM. *P<0.05, **P<0.01, ****P<0.0001.

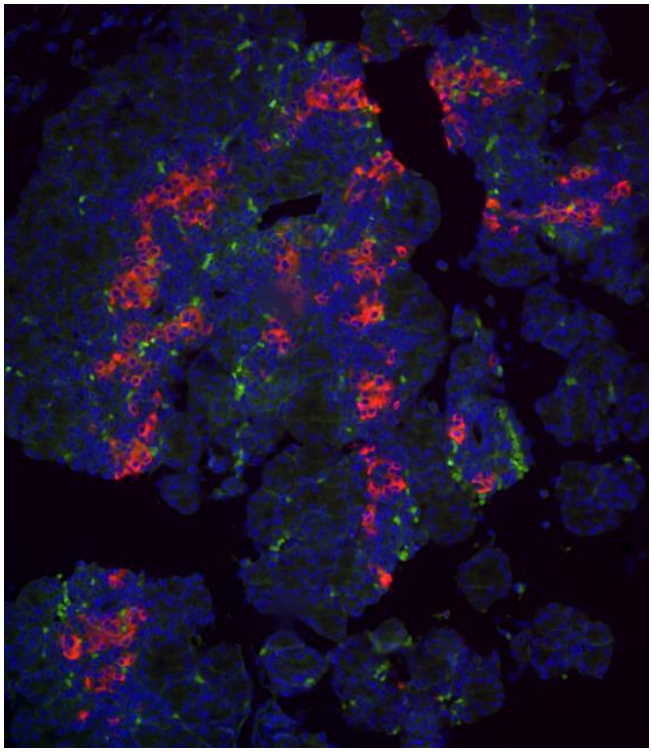

Fig. S3. Cre expression in E16.5 TRPM7KO^{Endo} mice. Representative immunofluorescent image of pancreatic section from TRPM7KO^{Endo} mouse (Cre -green, insulin - red) from a E16.5 pancreatic section.

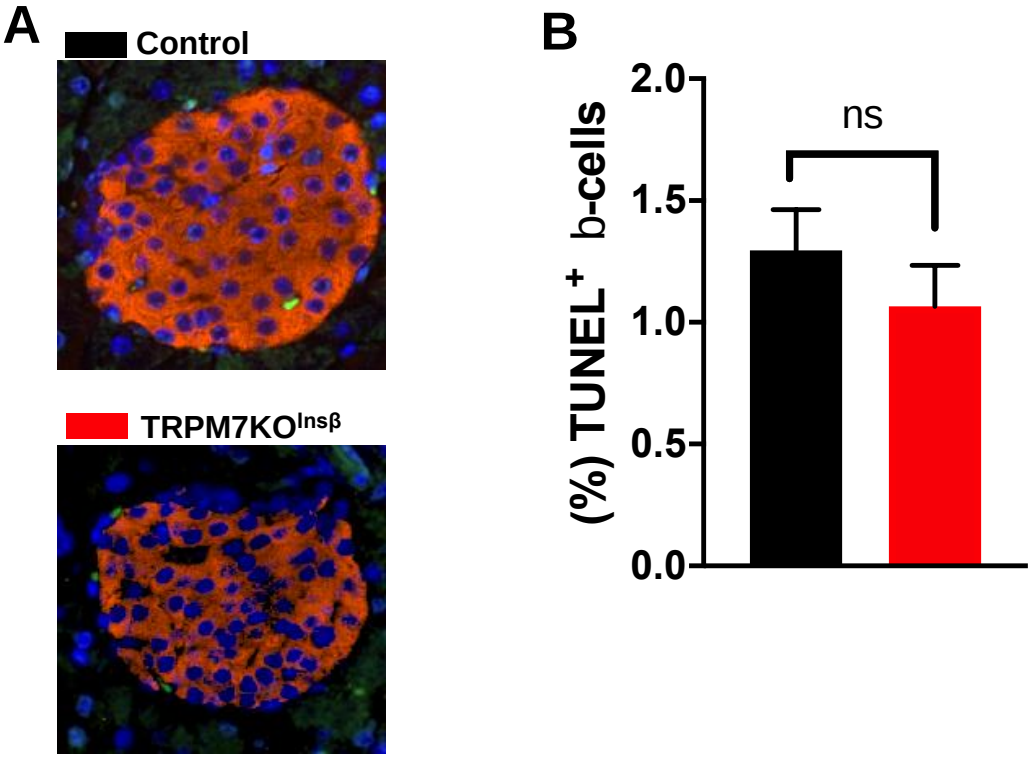

Fig. S4. β-cell specific ablation of TRPM7 (TRPM7KO$^{Ins\beta}$) did not affect apoptosis (HFD). Representative images of pancreas sections immunostained for insulin (red), TUNEL (green) and DAPI (blue) from control and TRPM7KO$^{Ins\beta}$ mice. (B) Percentage of TUNEL^{+} β-cells (*n=3, P=0.385*). Where applicable analysis are mean ± SEM.

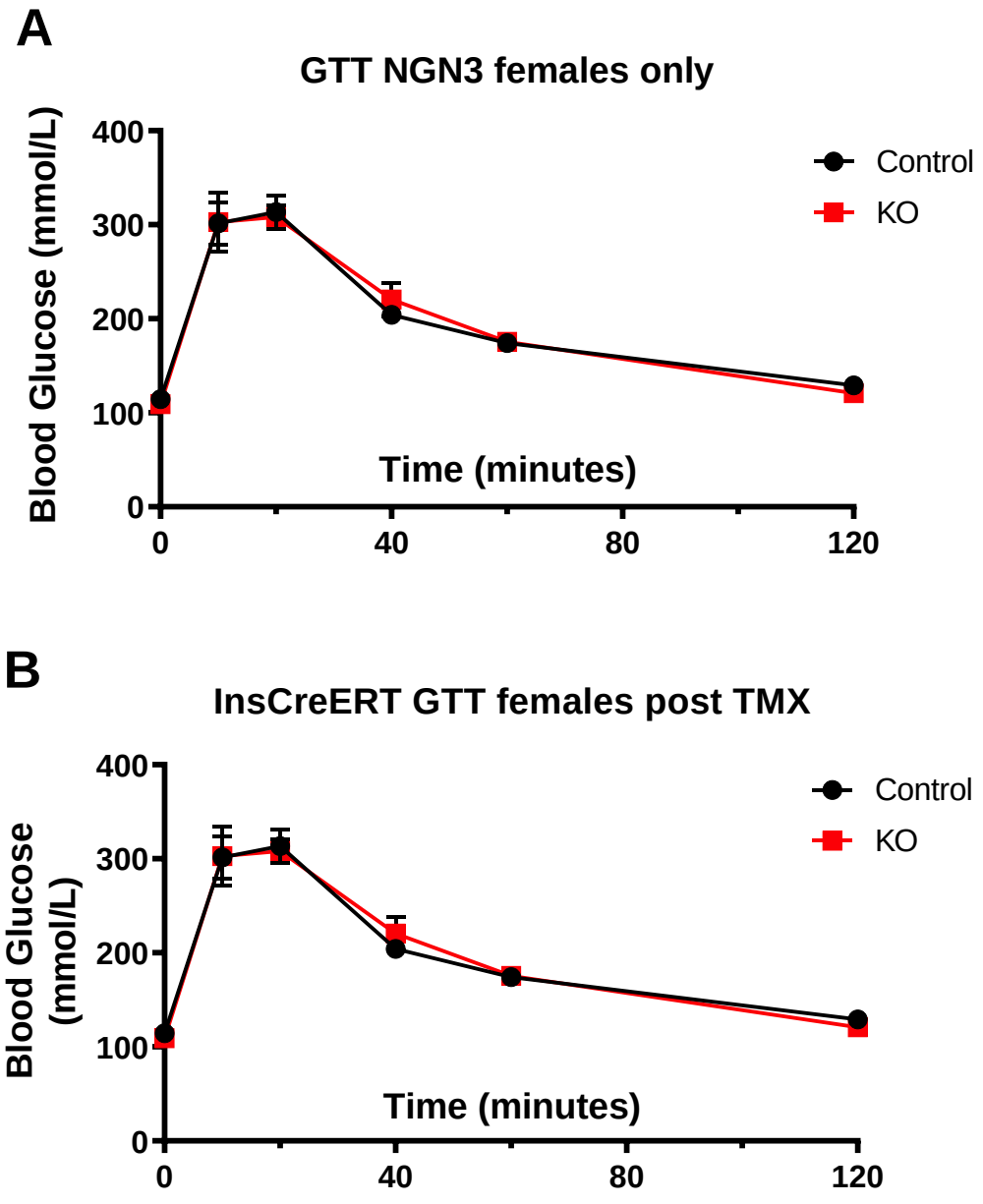

Fig. S5. Female TRPM7KO^{Endo} and TRPM7KO^{INSβ} show normal glucose tolerance. Glucose tolerance of 12-week-old female TRPM7KO^{Endo} (A) and TRPM7KO^{INSβ} (B) mice compared to controls. TRPM7KO^{INSβ} mice and their controls were treated with tamoxifen and allowed 2 weeks recovery post tamoxifen before GTT.

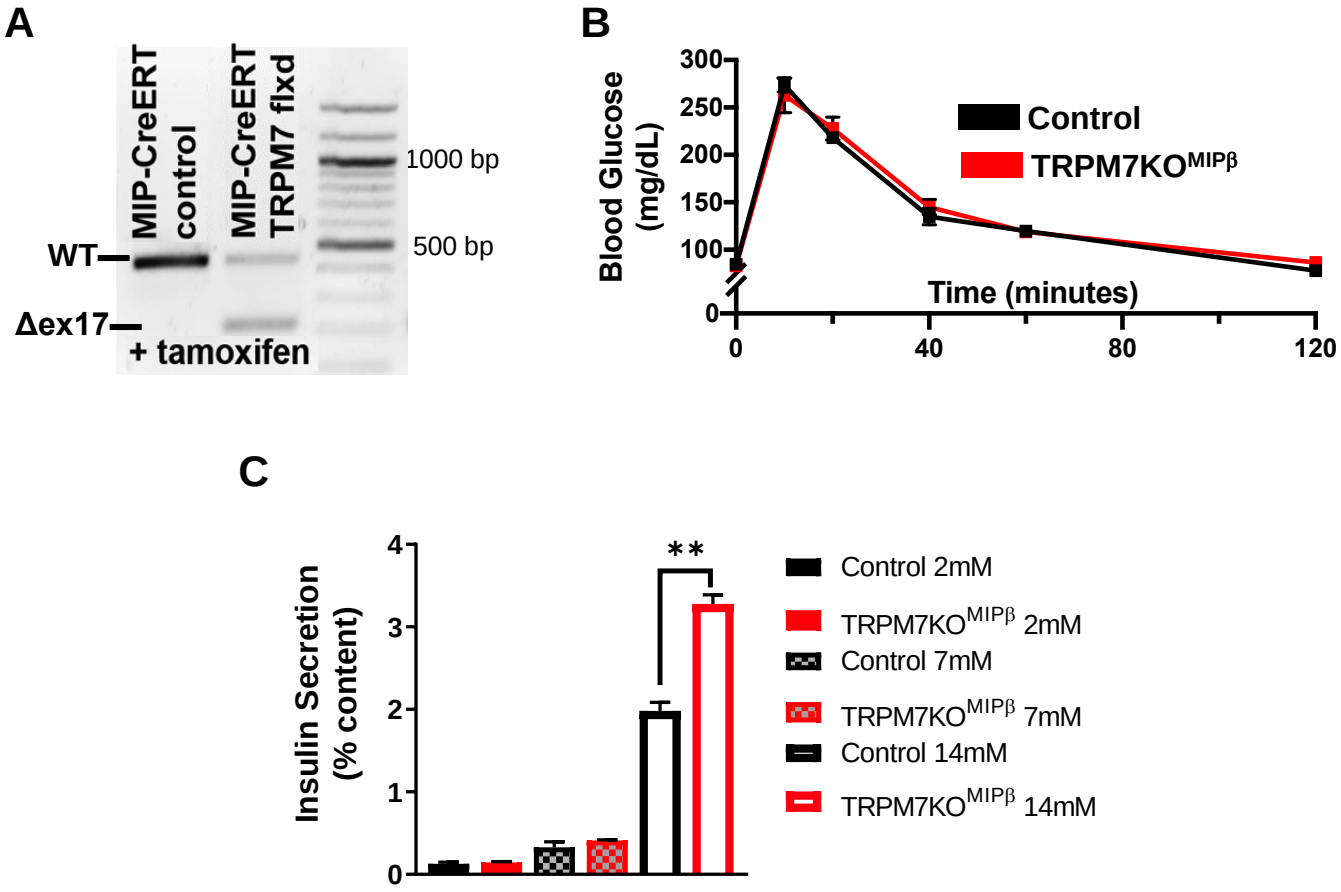

Fig. S6. β-cell knockdown of TRPM7 (TRPM7KO$^{MIP\beta}$) enhances GSIS but not GTT. (A) Islet genomic DNA from MIP-CreERT or TRPM7KO$^{MIP\beta}$ mice analyzed by PCR for TRPM7 exon 17 deletion post-tamoxifen treatment. (B) Glucose tolerance from 12-week-old MIP-CreERT and TRPM7KO$^{MIP\beta}$ males (n= 5 each). (C) Insulin secretion from TRPM7KO$^{MIP\beta}$ islets compared to controls normalized to content. Where applicable analysis are mean ± SEM. $^{**}P<0.01$.

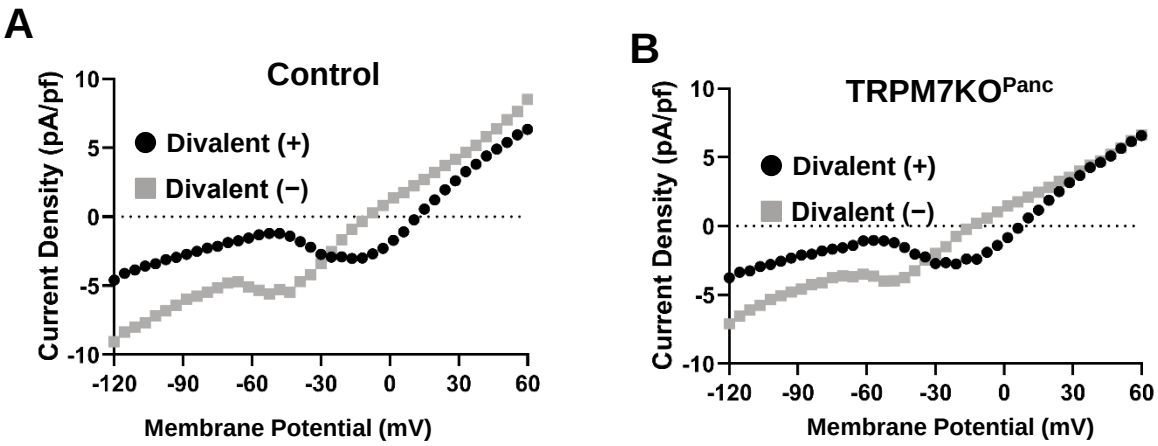

Fig. S7. TRPM7 alters β-cell whole cell currents. Representative TRPM7 currents recorded from control (A) and TRPM7KO^{Panc} (B) β-cells in the presence (black circles) or absence (grey squares) of divalent cations. Data analysis for these recordings can be found in Figure 4A.

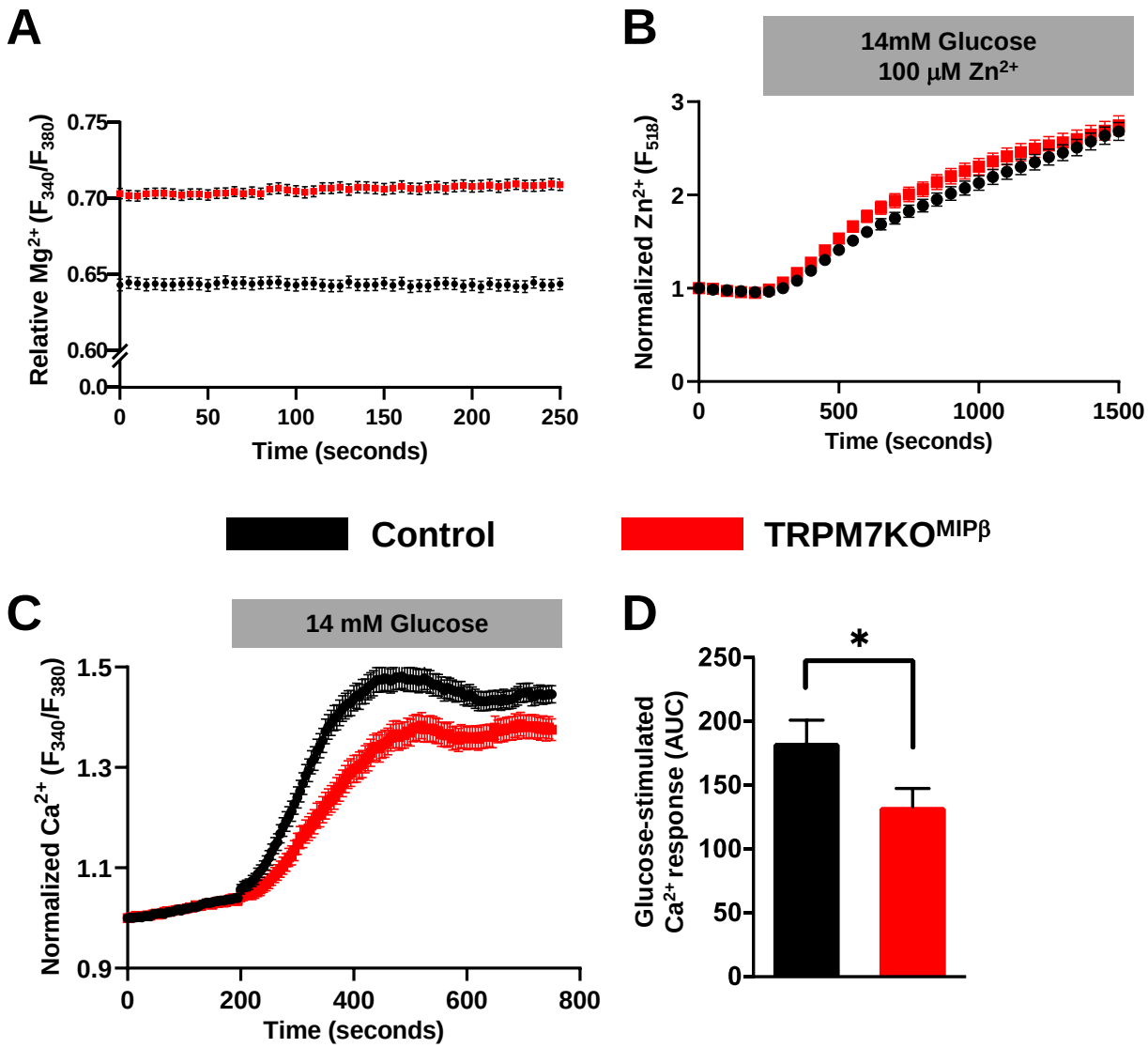

Fig. S8. β-cell specific ablation of TRPM7 (TRPM7KO^{MIPβ}) decreases Ca^{2+} influx and Mg^{2+} efflux. (A) Relative intracellular Mg^{2+} levels in β-cells from control (black) and TRPM7KO^{MIPβ} (red) in the absence of extracellular Mg^{2+}. (B) Relative β-cell intracellular Zn^{2+} levels from TRPM7KO^{MIPβ} and control mice after in response to 100 μM Zn^{2+} and 14 mM glucose (grey bar). (C) Glucose-stimulated (14 mM) islet Ca^{2+} responses and corresponding total AUC (D, 24.21 ± 10.91% reduction, $P<0.05$) from control and TRPM7KO^{MIPβ} mice. Where applicable, data are mean ± SEM and significance is calculated with a two-tailed Student's *t*-test. *$P<0.05$.

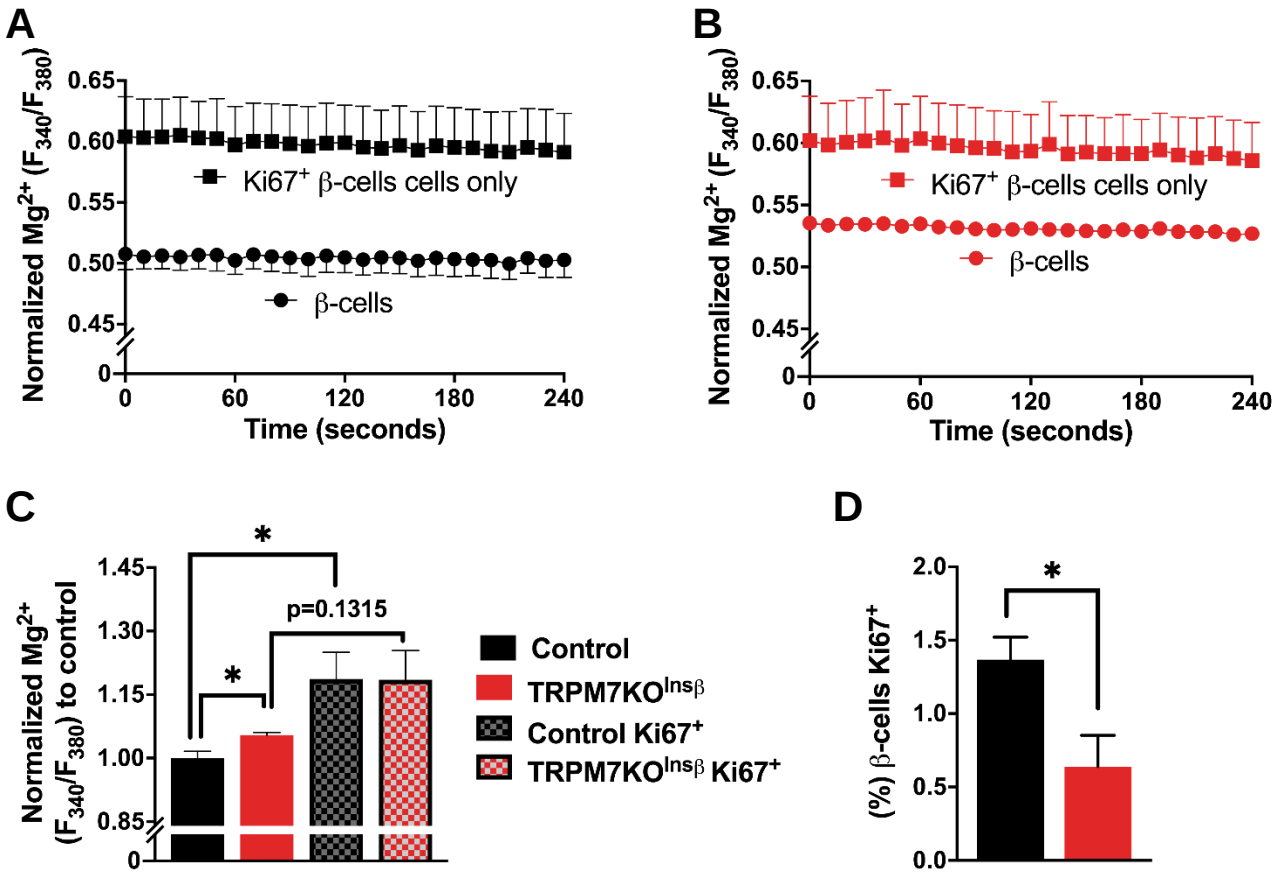

Fig. S9. TRPM7 lowers Mg^{2+} levels within nonproliferating single β-cells as well as β-cells with islet cell clusters. β-cell Mg^{2+} levels recorded from non-proliferating(●) and proliferating(■) cells; the β-cell were from control (A) and TRPM7KO$^{Ins\beta}$ (B) mice 2 weeks post exposure to HFD. Note: this data combines Mg^{2+} levels from both single β-cells and from those within islet cell clusters. (C) Fold change in Mg^{2+} levels for the indicated β-cell cohorts normalized to non-proliferating controls (β-cells from islets of animals fed a HFD for 2-weeks). (D) Percent of Ki67-positive β-cells from cohorts shown in A and B. Data are mean±SEM, *P<0.05.