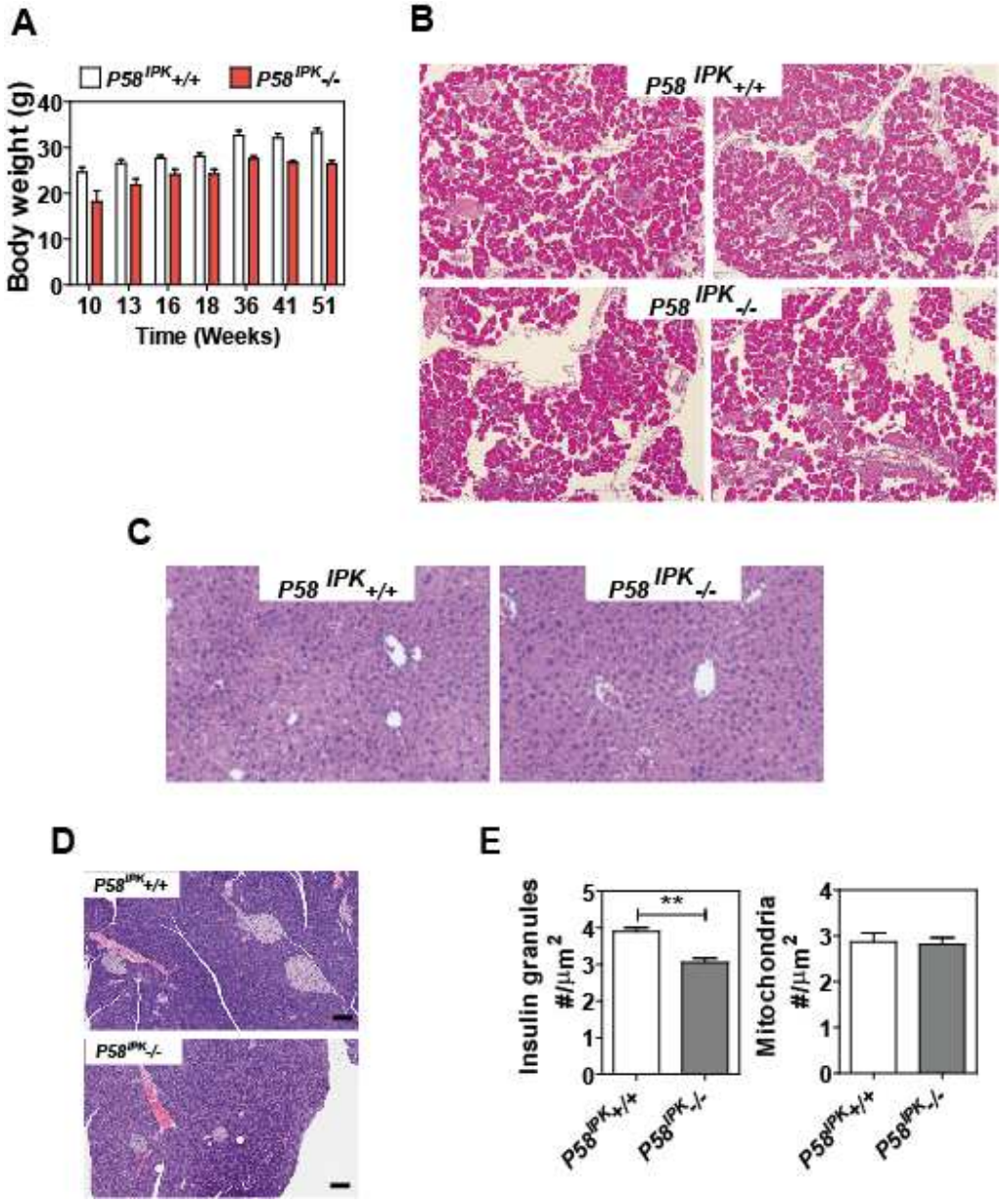
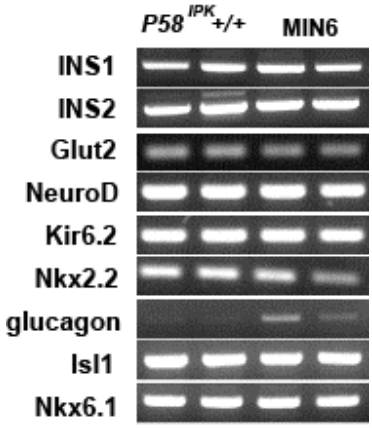
SUPPLEMENTARY DATA

Supplementary Figure 1. Deletion of *P58^{IPK}* in mice causes β cell failure.
(A) Body weight measurements were performed on mice of the indicated genotypes for up to 51 weeks. (B) Hematoxylin and eosin (H&E) staining was performed on pancreatic sections from *P58^{IPK}*-/- mice and their littermates at postnatal day 1. (C) Representative image of H&E staining on liver sections from 10-12 week-old *P58^{IPK}*-/- mice and their littermates. (D) Representative image of H&E staining on pancreatic sections from 10-12 week-old *P58^{IPK}*-/- mice and their littermates. (E) Insulin granules (left panel) and mitochondria (right panel) were counted in TEM micrographs shown in Fig. 1I.

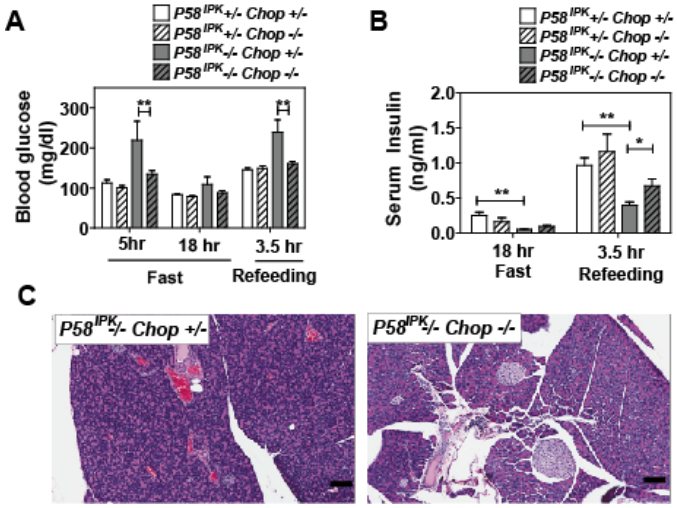


SUPPLEMENTARY DATA

Supplementary Figure 2. Murine β cell lines are similar to MIN6 and INS1 cells.
Expression of β cell-specific genes was analyzed by RT-PCR. Total RNAs were isolated from MIN6 cells and the newly generated beta cell line from *P58*^{IPK}+/+ mice. Amplified products were visualized by electrophoresis on an agarose gel.

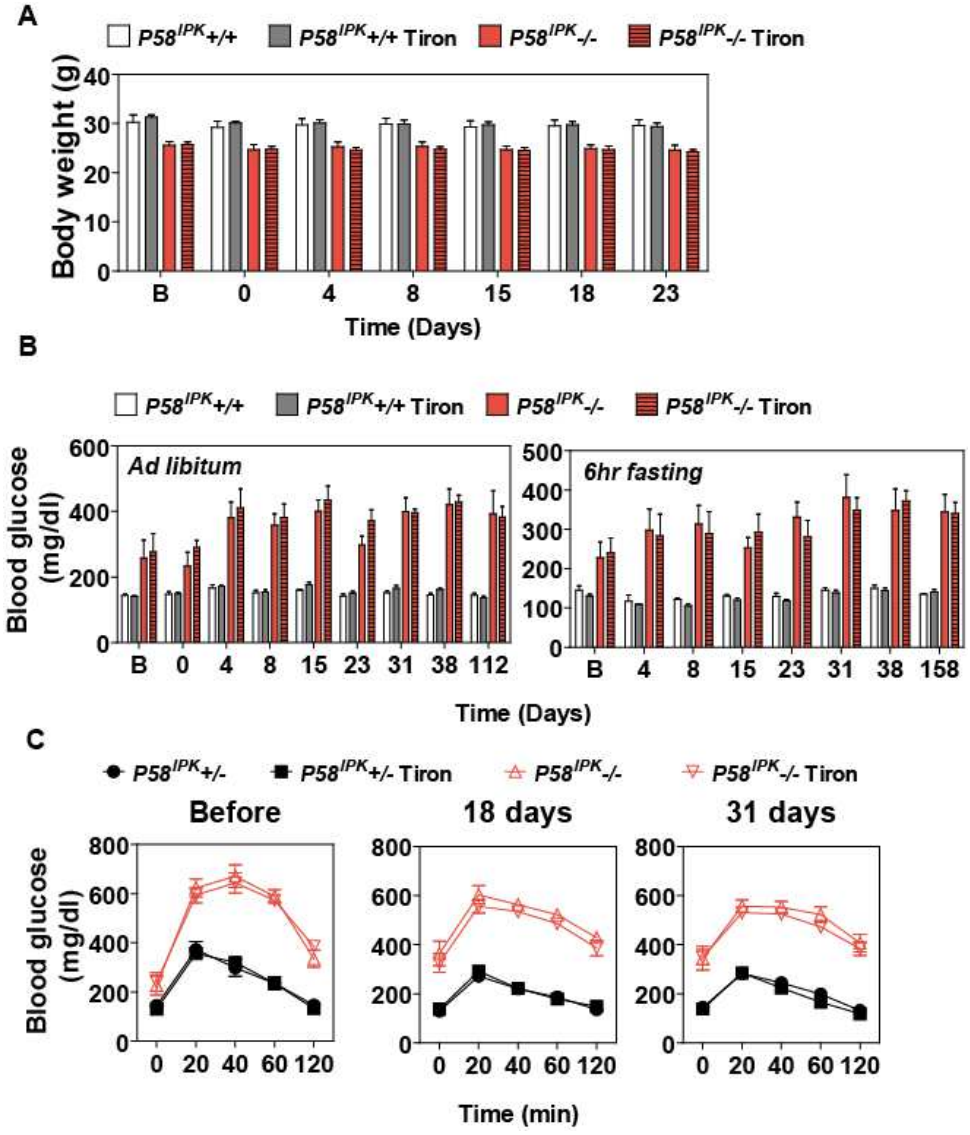


Supplementary Figure 3. *Chop* deletion preserve β cell function in *P58*^{IPK}-/- mice.
(A) Blood glucose and (B) Serum insulin were measured after a 5 hour fast or an 18 hour fast with subsequent re-feeding for 3.5 hours in mice of the indicated genotypes. n=6-8 mice at 14-21 weeks of age per group. (C) Pancreatic sections from 16 week-old mice of the indicated genotypes were stained with Hematoxylin and Eosin (H&E). Representative images are shown. Scale bar represents 100 μm.



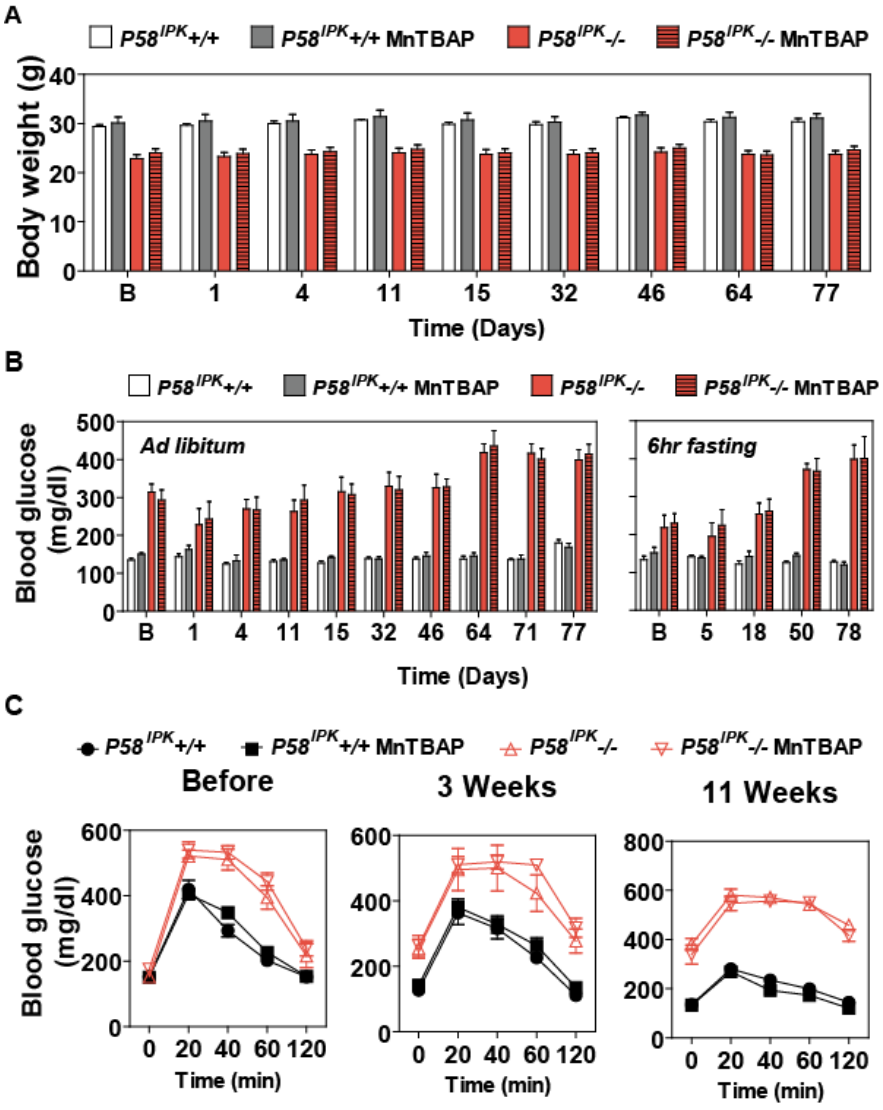
SUPPLEMENTARY DATA

Supplementary Figure 4. Tiron treatment does not restore glucose homeostasis in *P58^{IPK}*-/- mice. Mice of the indicated genotypes (28-30 weeks old) were treated with Tiron (500mg/kg BW, twice a day, IP) or saline for up to 38 days. (A) Body weight and (B) Blood glucose levels were measured in the morning between 9-10 AM *ad libitum* or after a 5-6 hr fast. N=5-6 mice per group. (C) Glucose tolerance tests (GTTs) were performed oin mice of the indicated genotypes at 2 weeks before or at 18 days and 31 days after Tiron treatment. Glucose (2 g/kg before Tiron treatment and 1 g/kg body weight after Tiron treatment) was administered intraperitoneally to mice faster for 5-6 hr. N=5-6 mice per group.



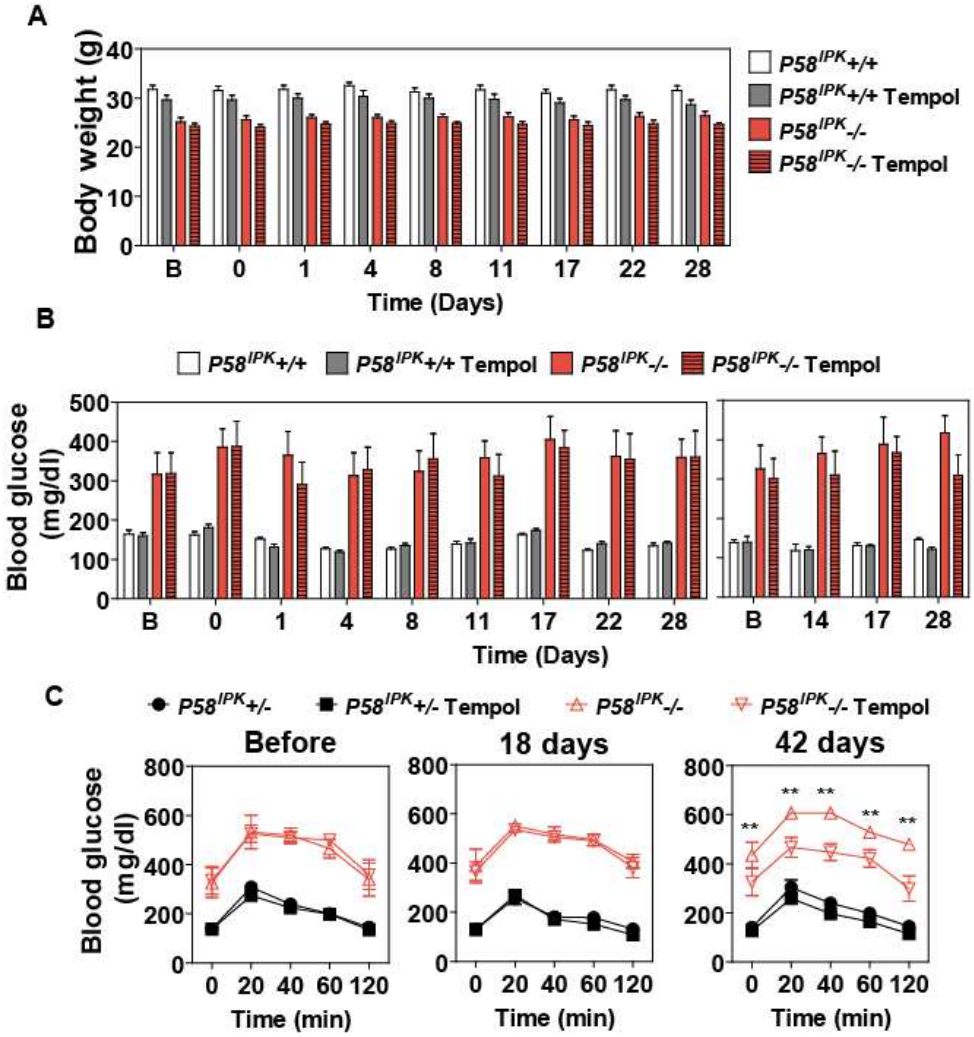
SUPPLEMENTARY DATA

Supplementary Figure 5. MnTBAP treatment does not restore glucose homeostasis in *P58I*^{PK}*-/-* mice. Mice of the indicated genotypes (32-37 weeks old) were treated with MnTBAP (10 mg/kg BW, daily, IP) or saline for up to 78 days. Body weight (A) and (B) blood glucose (B) were measured in the morning between 9-10 AM for *ad libitum* and between 3-5 PM after a 5-6 hr fast. N=4-6 mice per group. (C) Glucose tolerance tests (GTTs) were performed on mice of the indicated genotypes at 2 weeks before or at 3 and 11 weeks after MnTBAP treatment. Glucose (2 g/kg before and after 3 weeks of MnTBAP treatment or 1 g/kg body weight after 11 weeks of MnTBAP treatment) was administered intraperitoneally to mice fasted for 5-6. N=4-6 mice per group.



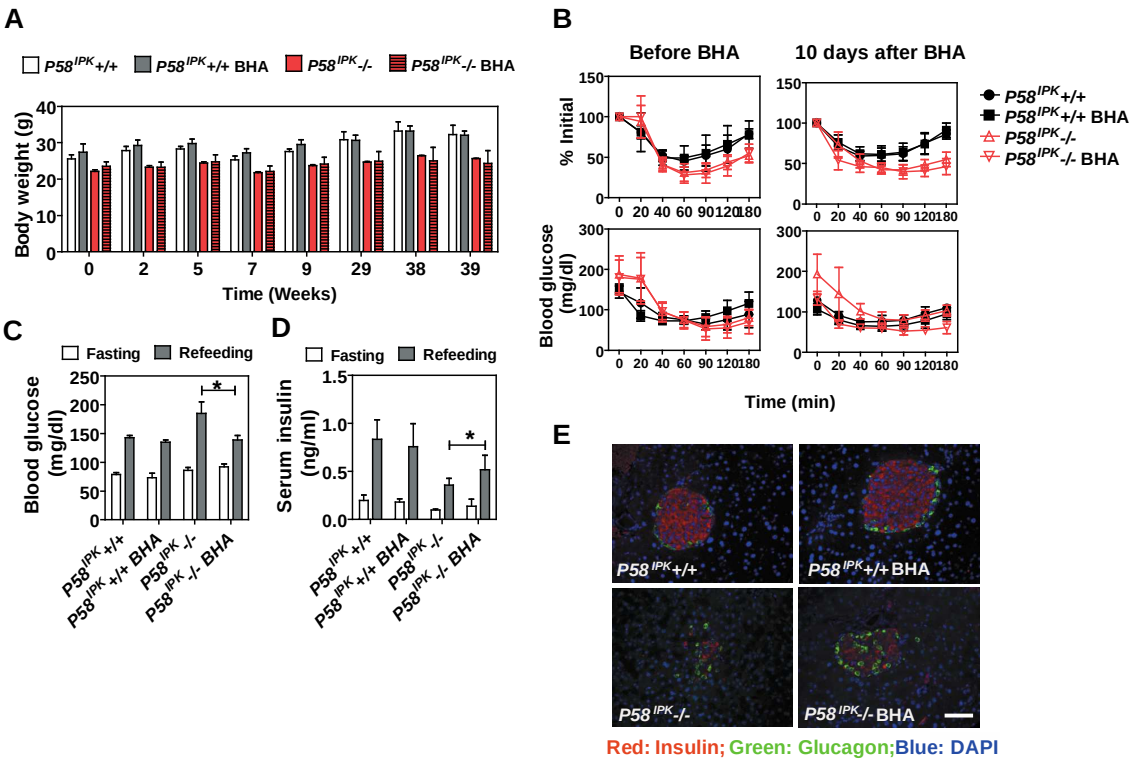
SUPPLEMENTARY DATA

Supplementary Figure 6. Tempol treatment improves glucose homeostasis in *P58^{IPK}*-/- mice. Mice of the indicated genotypes (31-33 weeks old) were treated with Tempol (500 mg/kg BW, daily, IP) or saline for up to 28 days. (A) Body weight and (B) Blood glucose levels were measured between 9-10 AM *ad libitum* and between 3-5 PM after a 5-6 hr fast. N=4-5 mice per group. (C) Glucose tolerance tests (GTTs) were performed in mice of the indicated genotypes at 2 weeks before or after 18 and 42 days of Tempol treatment. Glucose (1 g/kg body weight) was administered intraperitoneally to mice fasted for 5-6 hr. N=5-6 mice per group. * , *P<0.05; **, P<0.01*. Significance was shown between *P58^{IPK}*-/- and *P58^{IPK}*-/- with PBA treatment.



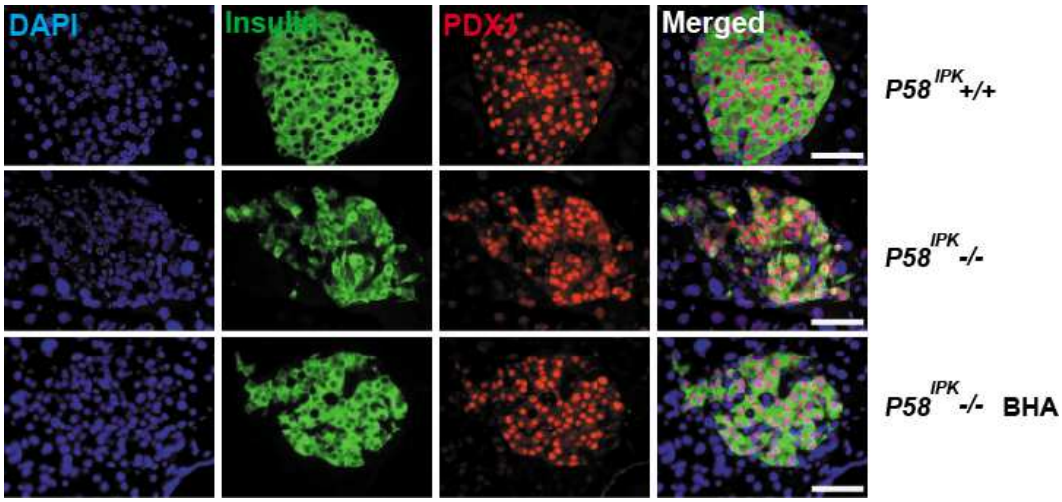
SUPPLEMENTARY DATA

Supplementary Figure 7. Antioxidant treatment prevents β cell failure in *P58^{IPK}*-/- mice.
(A) Body weight measurements were performed on mice of the indicated genotypes (18-20 weeks old) fed with control chow or BHA-supplemented chow for up to 39 weeks. (B) ITTs were performed in mice at 20-22 weeks of age before and at 10 days after feeding control chow or BHA-supplemented chow. Insulin (0.7 IU insulin/kg body weight) was administered intraperitoneally to 5-6 hr fasted animals. N=5-9 mice per group. (C, D) Blood glucose and serum insulin were measured after an 18 hour fast and subsequent re-feeding for 3.5 hr in mice of the indicated genotypes fed control or BHA-supplemented chow for 8 weeks. n=5-9 mice per group. (E) Insulin and glucagon immunohistochemistry were performed on pancreatic sections from *P58^{IPK}*/+/+ and *P58^{IPK}*-/- mice fed with control or BHA-supplemented chow for 40 weeks. Representative images are shown. Scale bars represent 100 μm.



SUPPLEMENTARY DATA

Supplementary Figure 8. PDX-1 localization is not altered in islets of *P58^{IPK}*-/- mice.
Immunohistochemistry for PDX-1 and Insulin was performed on pancreatic sections from *P58^{IPK}*+/+ or *P58^{IPK}*-/- mice fed with control or BHA-supplemented diet for 6 weeks. Representative images are shown. Scale bar represents 100μm.



SUPPLEMENTARY DATA

Supplementary Table 1. Sequences of primers used for RT-PCR or real-time qPCR

	forward	reverse	Usage
β-actin	GAT CTG GCA CCA CAC CTT CT	GGG GTG TTG AAG GTC TCA AA	qPCR
MafA	TTC TCG CTC TCC AGA ATG TG	GAG GAG GTC ATC CGA CTG AA	qPCR
Pdx1	TGG ATG AAA TCC ACC AAA GC	ACG GGT CCT CTT GTT TTC CT	qPCR
Ins1	CCA GCT ATA ATC AGA GAC CAT CA	GTT TGA CAA AAG CCT GGG TG	qPCR
Ins2	GGA GCG TGG CTT CTT CTA CA	GGT CTG AAG GTC ACC TGC TC	qPCR
Iapp	CCT CAT CCT CTC TGT GGC AC	CAC GTT GGT TGG TGG GAG	qPCR
Glut2	GGA TTA AGC GGA CAA TTC CA	CCG AAC TGG AAG GAA CTC AG	qPCR
Atf4	ATG GCC GGC TAT GGA TGA T	CGA AGT CAA ACT CTT TCA GAT CCA TT	qPCR
Atf6α	CCA ACA GAA AGC CCG CAT T	TGG ACA GCC ATC AGC TGA GA	qPCR
Chop	CTG CCT TTC ACC TTG GAG AC	CGT TTC CTG GGG ATG AGA TA	qPCR
Ero1α	CAC AGG TAC AGT CGT CCA GGT	CTT GCT CGT TGG ACT CCT G	qPCR
Gadd34	TTT TGG CAA CCA GAA CCG	GGA GAT AGA AGT TGT GGG CG	qPCR
Xbp1-s	GAG TCC GCA GCA GGT G	GTG TCA GAG TCC ATG GGA	qPCR
Xbp1-t	AAG AAC ACG CTT GGG AAT GG	ACT CCC CTT GGC CTC CAC	qPCR
Cat	CCC GCG GTC ATG ATA TTA AGT	GAT GAA GCA GTG GAA GGA GC	qPCR
Hmox1	GAG CCT GAA TCG AGC AGA AC	CCT TCA AGG CCT CAG ACA AA	qPCR
Gpx1	GTT TCC CGT GCA ATC AGT TC	CAA TGT AAA ATT GGG CTC GAA	qPCR
Gpx2	GAA AGA CAA GCT GCC CTA CC	TCC ATA TGA TGA GCT TGG GA	qPCR
Sod1	GAA CCA TCC ACT TCG AGC A	TAC TGA TGG ACG TGG AAC CC	qPCR
Sod2	ACT GAA GTT CAA TGG TGG GG	GCT TGA TAG CCT CCA GCA AC	qPCR
Ucp2	TCC TGC TAC CTC CCA GAA GA	TGA GAC CTC AAA GCA GCC TC	qPCR
P53	AAA ACC ACT TGA TGG AGA GTA TTT CA	GCT CCC GGA ACA TCT CGA A	qPCR
P21	CGA GAA CGG TGG AAC TTT GAC	TCC CAG ACG AAG TTG CCC T	qPCR
Tnfrsf10b	ATA AAA AGA GGC TGT GAA CGG G	GGT CCA AGA GAG ACG A	qPCR
Noxa	CGC CAG TGA ACC CAA CG	TTA TGT CCG GTG CAC TCC AC	qPCR
Tnfr1	CAT CCC CAA GCA AGA GTC ATG	GCT ACA GAC GTT CAC GAT GC	qPCR
P58IPK	TCC TGG TGG ACC TGC AGT ACG	CTG CGA GTA ATT TCT TCC CC	qPCR
NeuroD1	ACG CAG AAG GCA AGG TGT C	CGC TCT CGC TGT ATG ATT TG	RT-PCR
Kir6.2	CCC ACC CAT TCT CTG TCT GT	CTC AGC CTT CCA GCA GAG TC	RT-PCR
Nkx2.2	CCG AGG GCC TCC AAT ACT	TTG TCA TTG TCC GGT GAC TC	RT-PCR
Glucagon	TGT CTA CAC CTG TTC GCA GC	TGC CTT GCA CCA GCA TTA T	RT-PCR
Isl1	GGT TAG GGA TGG GAA AAC CT	CAC GAA GTC GTT CTT GCT GA	RT-PCR
Nkx6.1	GGA TGA CGG AGA GTC AGG TC	CGA GTC CTG CTT CTT CTT GG	RT-PCR