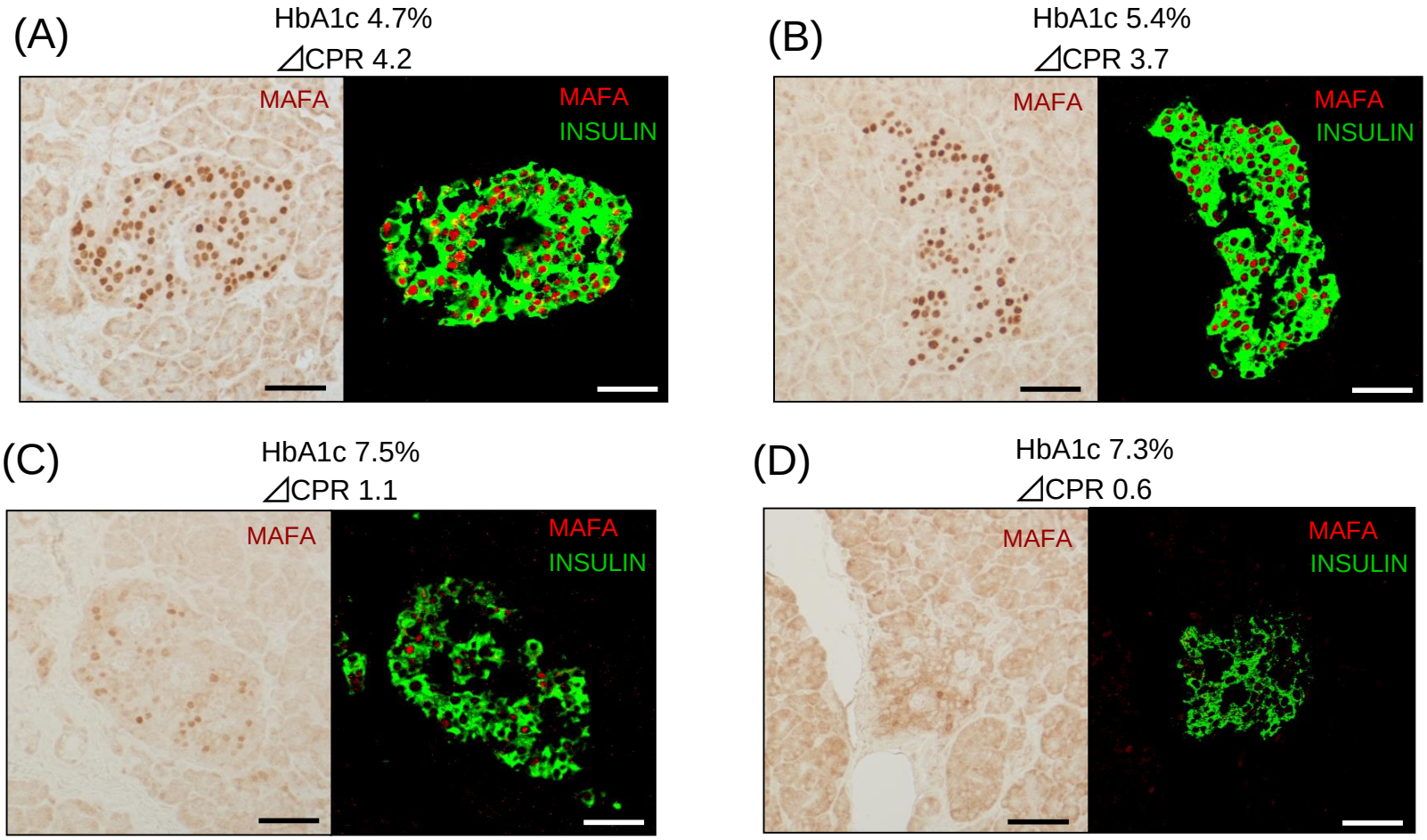
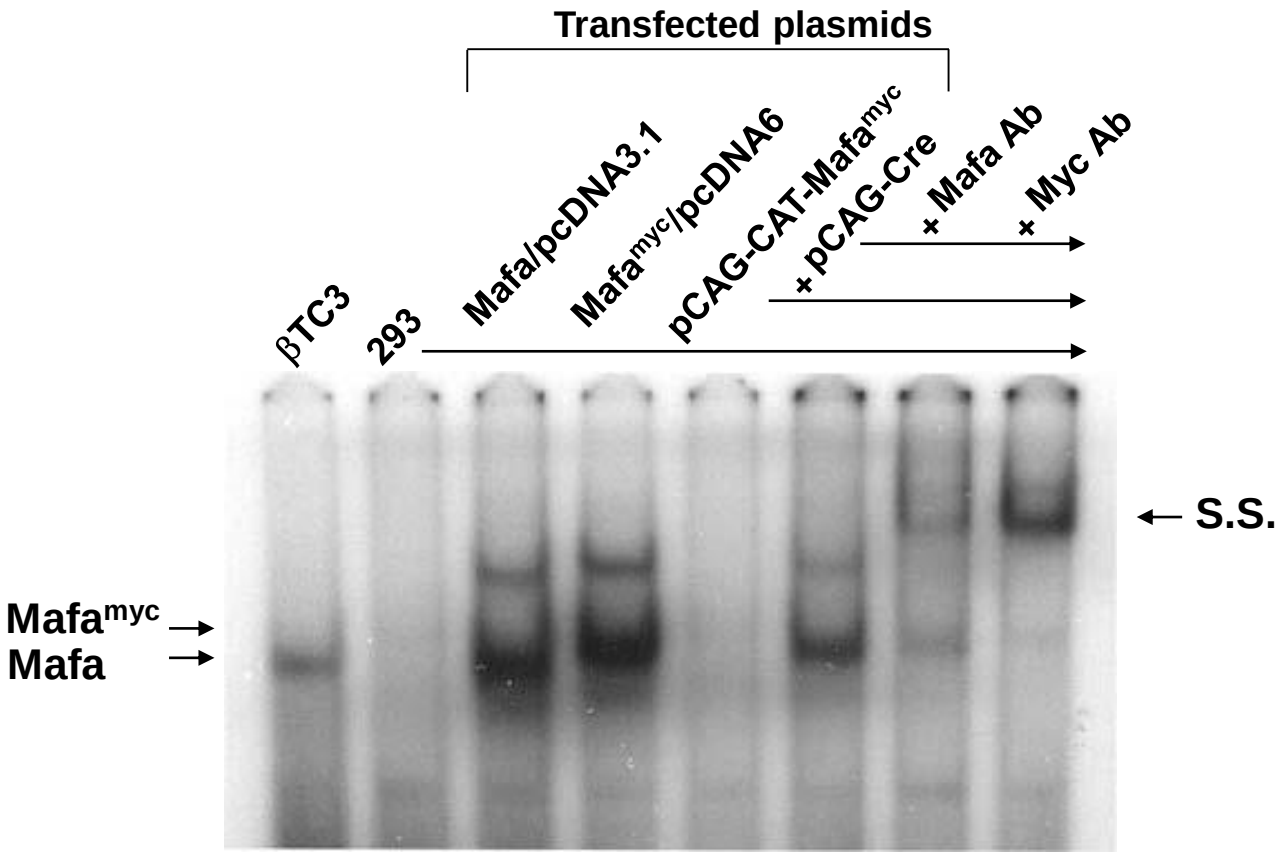
Supplemental Figure 1

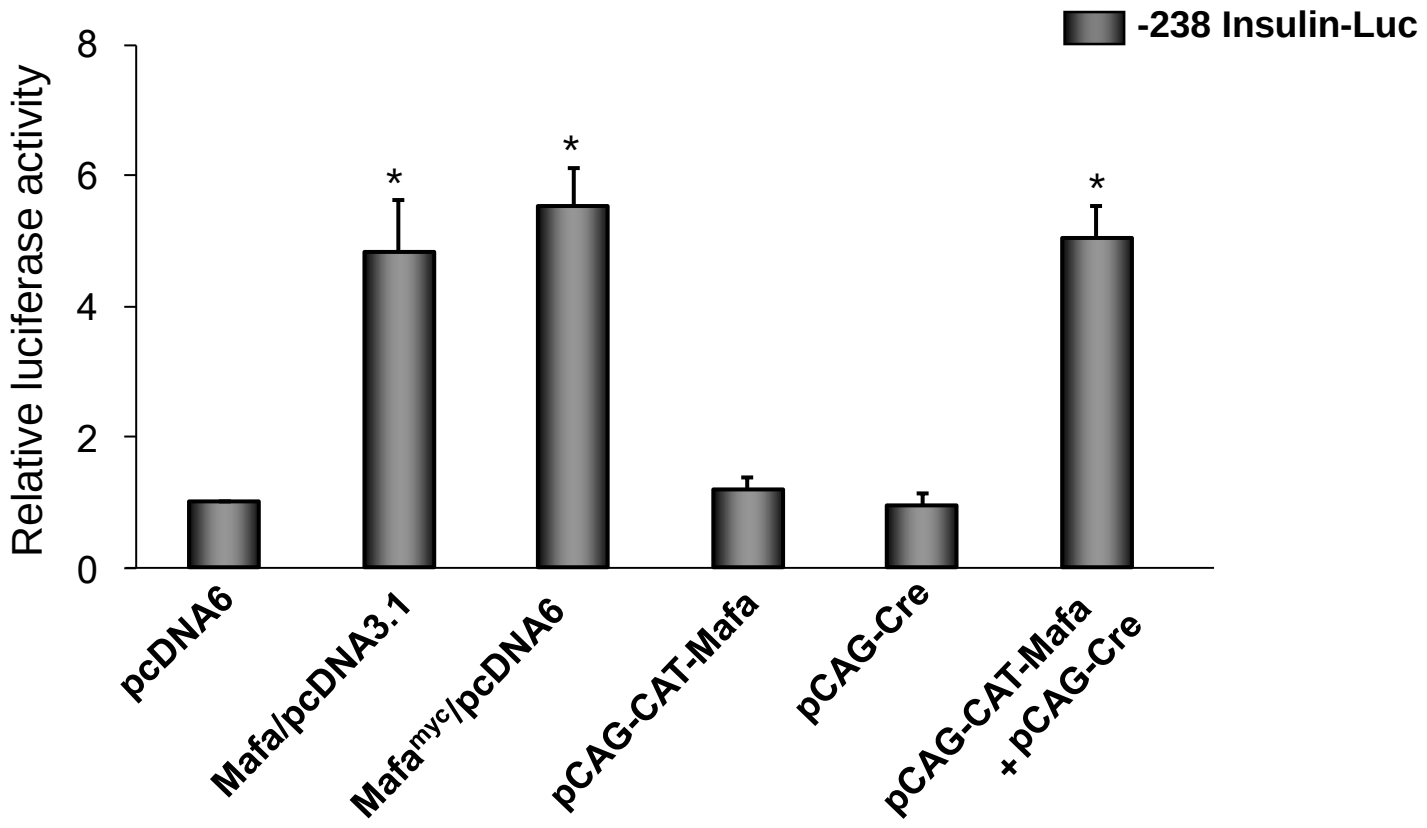


Supplemental Figure 1. There is a marked decrease of MAFA in human T2DM islets.
The non-tumor areas of the pancreas from (A, B) non-diabetic and (C, D) T2DM patients was embedded in paraffin. DAB staining for insulin and MAFA immunofluorescence were performed. The T2DM patients had the following clinical and treatment properties, (C) diabetic for 10 years and treated with sulfonylurea or (D) diabetic for 40 years with insulin. Glycemic control properties are represented by HbA1c levels and insulin secretory capacity by ΔCPR, with the latter defined as the increase in plasma insulin C-peptide level within 6 min after a 1 mg glucagon-injection. HbA1c levels greater than 6.5% were defined as T2DM. More clinical data is provided in Supplemental Table 1. Scale bars: 50 μm.

Supplemental Figure 2A

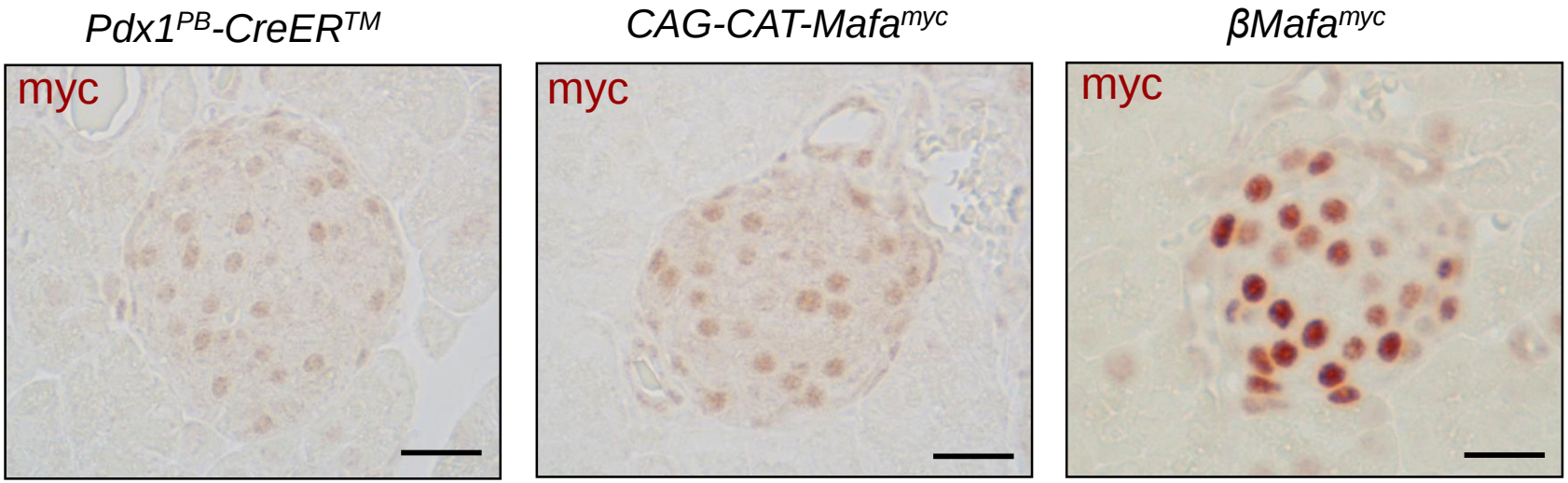


Supplemental Figure 2B

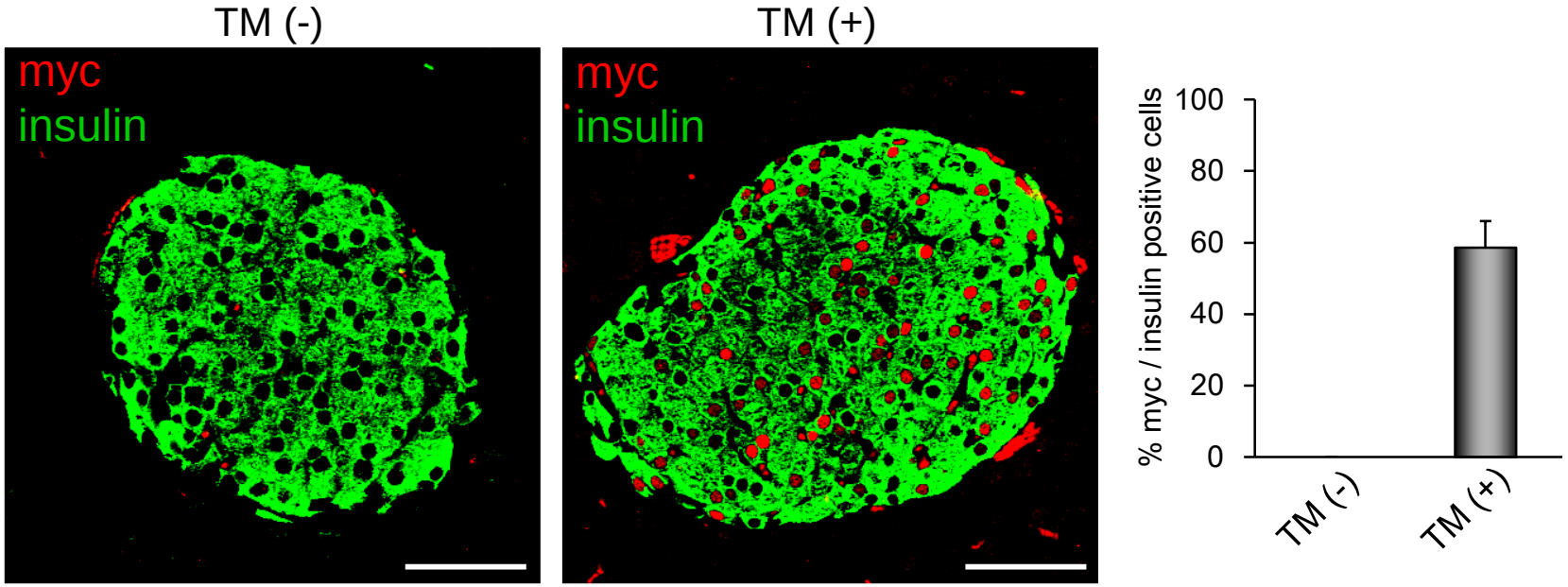


Supplemental Figure 2. The epitope tag does not affect Mafa^{myc} activity.
(A) *pCDNA3.1*, *pCAG-CAT*-Mafa, or pCAG-*CAT-Mafa^{myc}* was transfected into 293 cells with or without the Cre expression plasmid, *pCAG-Cre*. The gel-mobility shift binding activity of Mafa was measured in nuclear extracts with the rat *insulin II C1/RIPE3b1* element probe. The Mafa^{myc} bands were super-shifted (S.S.) with antibodies raised to Mafa or the myc-tag.
(B) Mafa^{myc} activates *insulin* promoter activity similarly Mafa. The -238 *Insulin* driven-Luc expression plasmid and *Mafa/pcDNA3.1*, *Mafa^{myc}/pcDNA6*, *pCAG-CAT-Mafa^{myc}*, *pCAG-Cre*, or *pCAG-CAT-Mafa^{myc}* + *pCAG-Cre* were co-transfected into 293 cells. Luciferase assays were performed 48 hours after transfection. Mafa^{myc} produced after Cre recombinase activation increased *insulin* promoter activity to the same extent as Mafa. * $p < 0.01$ versus control pcDNA6. n=6. Error bars represent S.D.

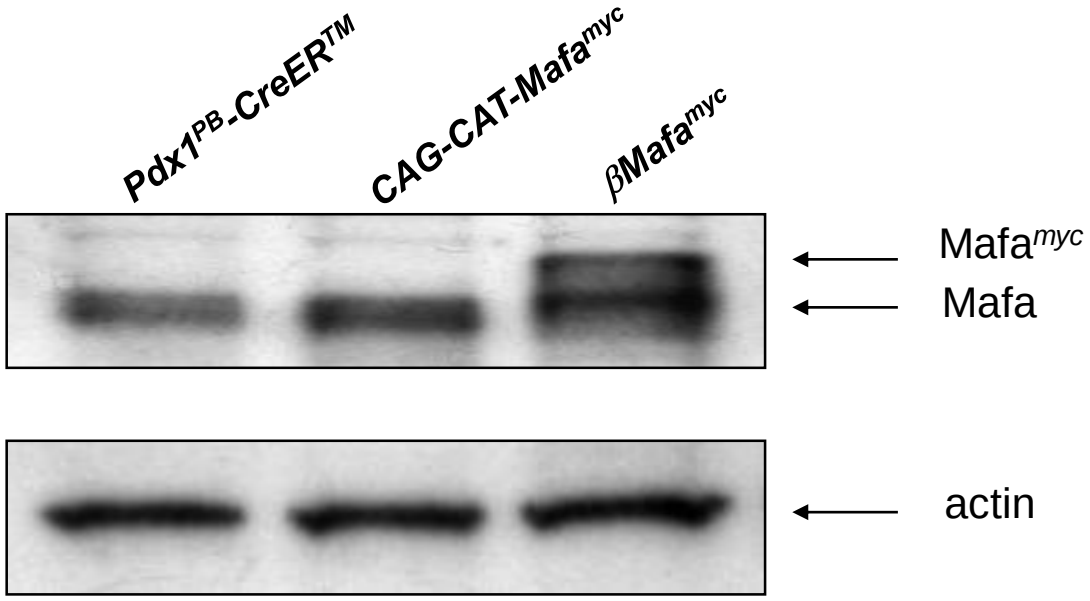
Supplemental Figure 3A



Supplemental Figure 3B

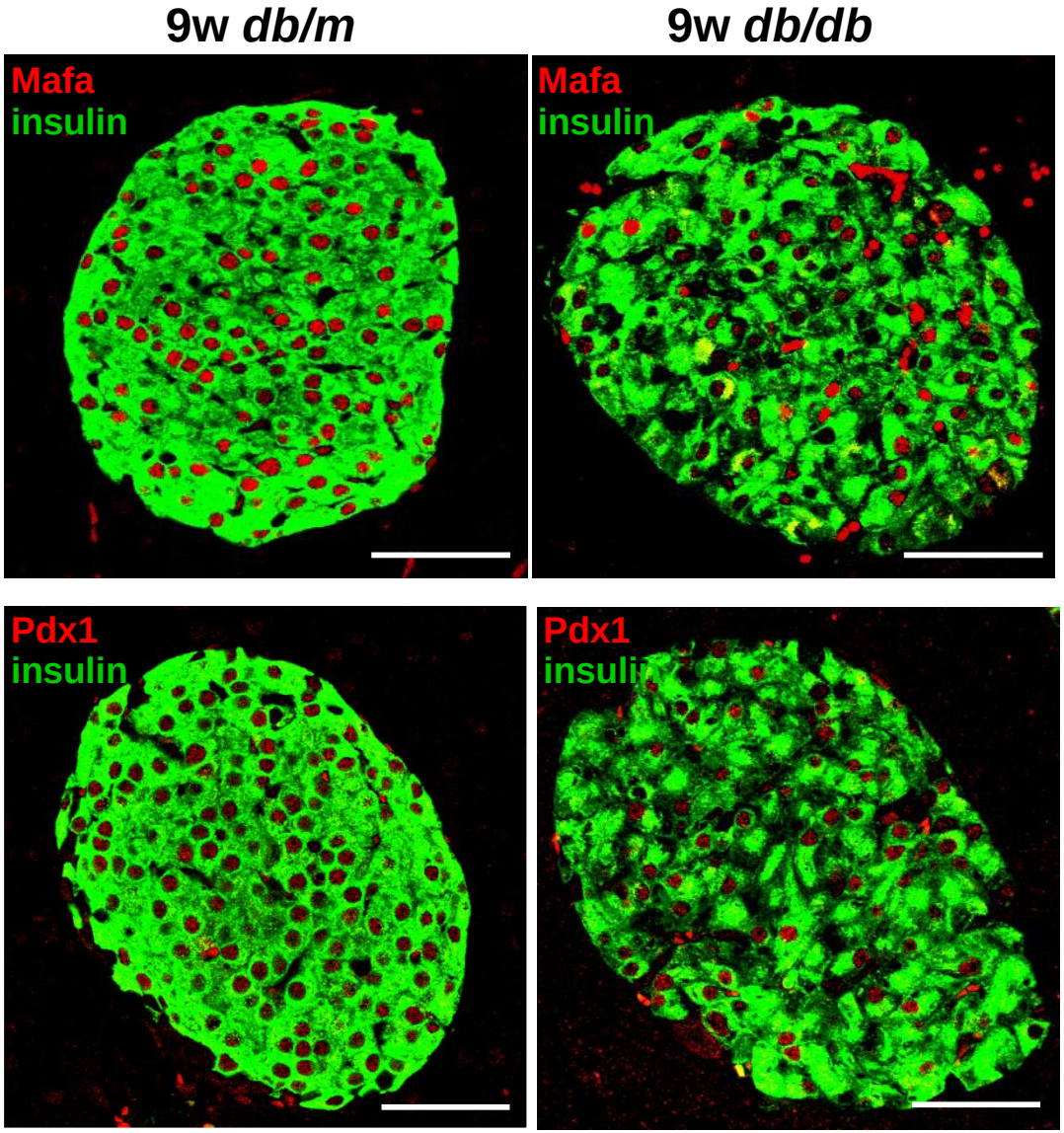


Supplemental Figure 3C



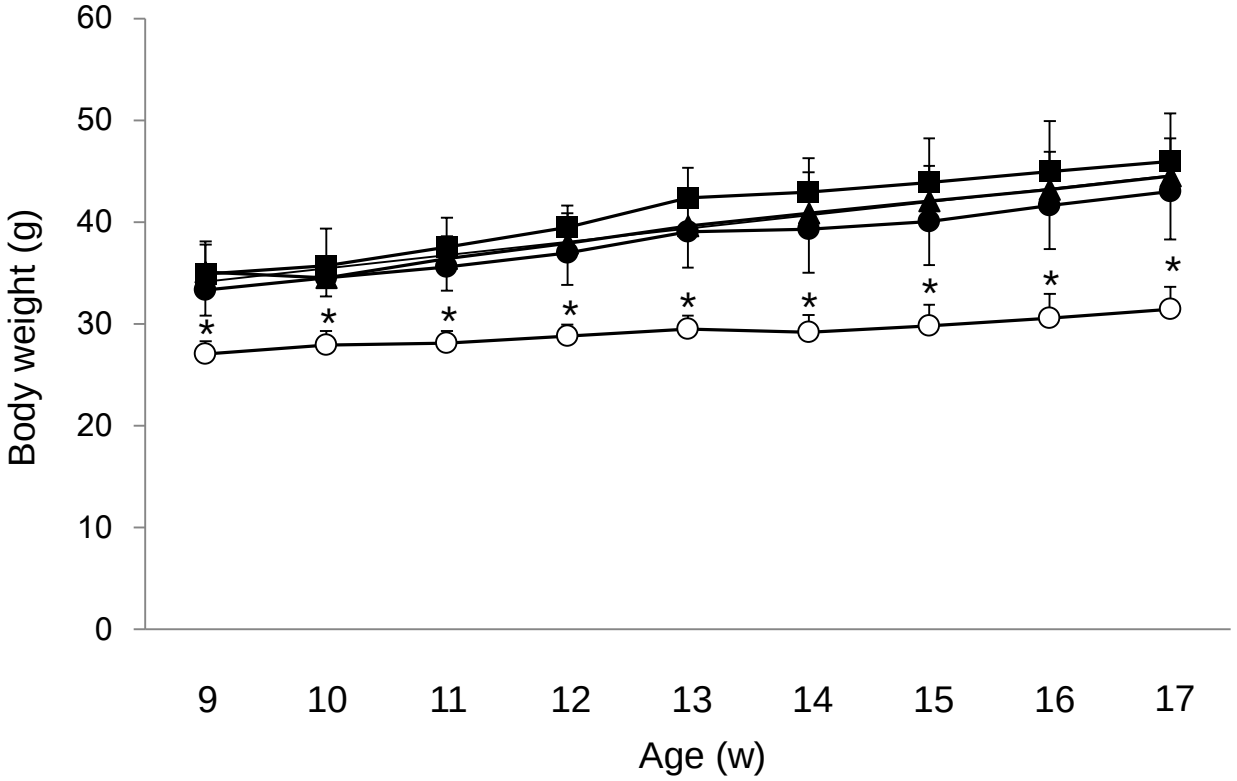
Supplemental Figure 3. Expression properties of *βMafa*^{myc} mice.
(A) Pancreatic islets from *βMafa*^{myc} mice and control single transgenic mice were immunostained with an anti-myc antibody two weeks after TM injection. Scale bars: 25μm. (B) The percent of insulin^{+} cells staining for myc in *βMafa*^{myc} islets is shown. Scale bars: 50 μm. Error bar represents S.D. (C) Immunoblot analysis of total nuclear Mafa produced in *Pdx1*^{PB}-*CreER*^{TM}, *CAG-CAT-Mafa*^{myc} and *βMafa*^{myc} islets following 2 weeks of TM treatment. The relative level of *Mafa*^{myc} to *Mafa* was determined by densitometry.

Supplemental Figure 4



Supplemental Figure 4. Mafa, Pdx1, and insulin levels in *db/db* mice before Mafa^{myc} induction.
Immunohistochemical analysis revealed that Mafa and insulin levels were reduced in 9 week-old *db/db* islets, just before Mafa^{myc} initiation. In contrast, there was no apparent change in Pdx1, as previously found (12). Scale bars: 50 μm.

Supplemental Figure 5

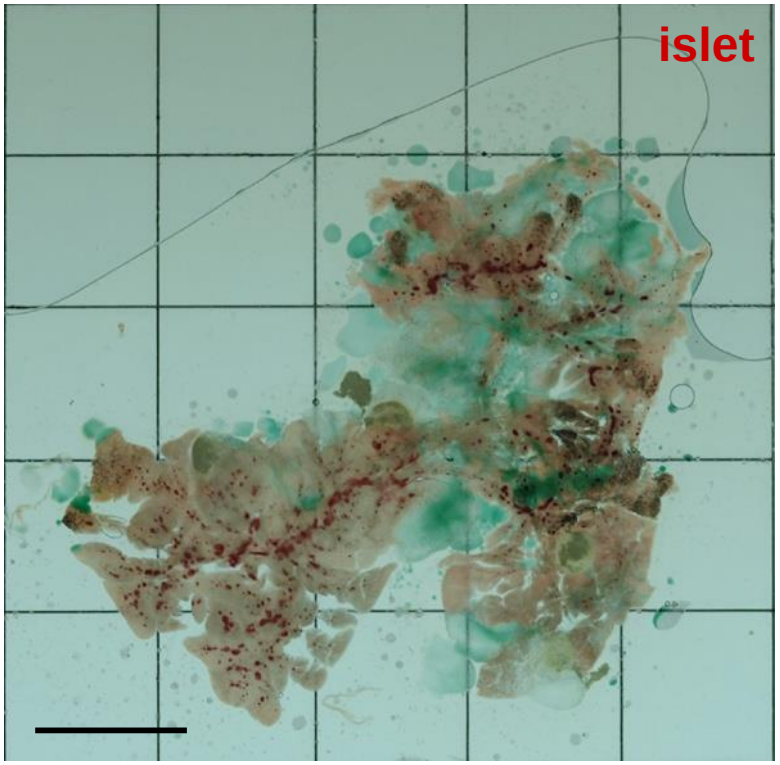


Supplemental Figure 5. There was no difference in body weight between *βMafa^{myc};db/db* and control diabetic *db/db* mice.

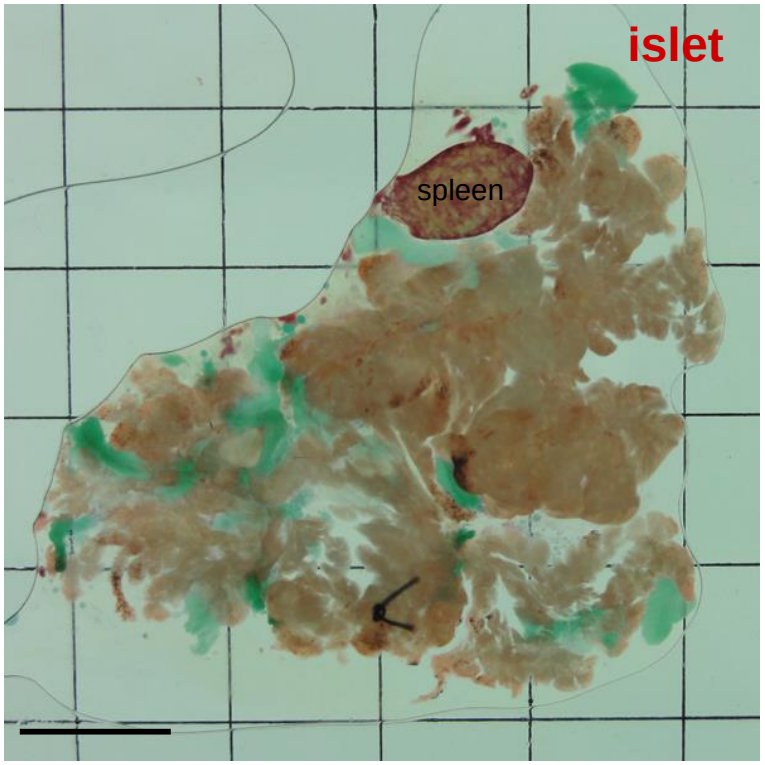
The body weight of *βMafa^{myc};db/db* (●), control diabetic *Pdx1^{PB}-CreER^{TM};db/db* (■), control diabetic *CAG-CAT-Mafa^{myc};db/db* (▲), and non-diabetic control *db/m* mice (○) was measured at 4 pm each week. There was no statistical difference between the various *db/db* lines. * $p < 0.01$ vs. *db/db* mice. Error bars represent S.D.

Supplemental Figure 6A

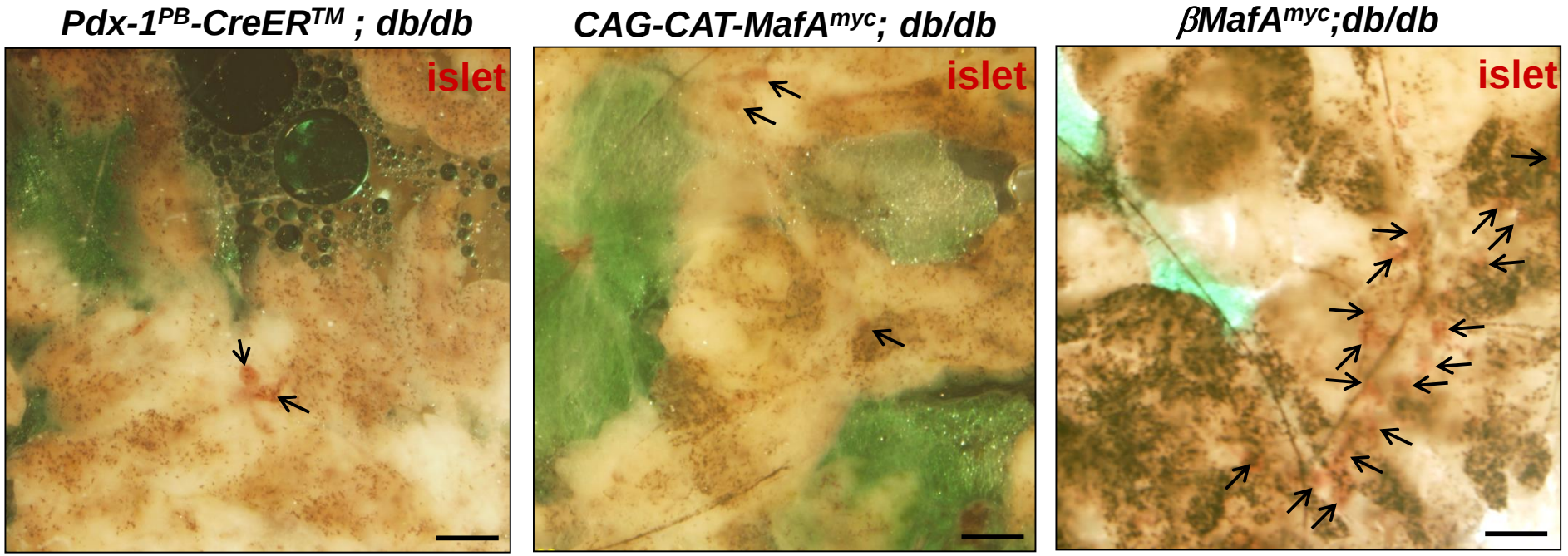
db/m
pancreas

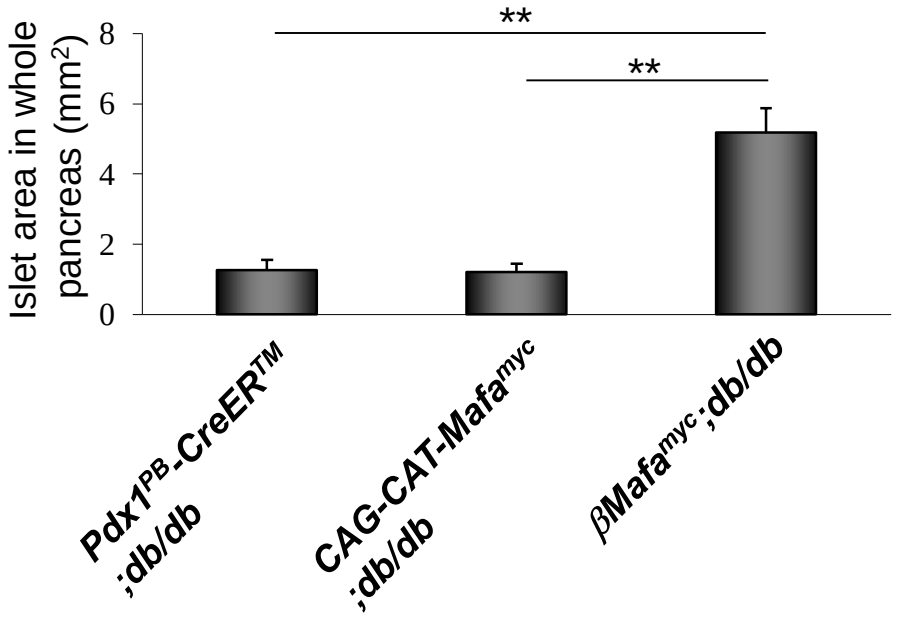


db/db
pancreas



Supplemental Figure 6B

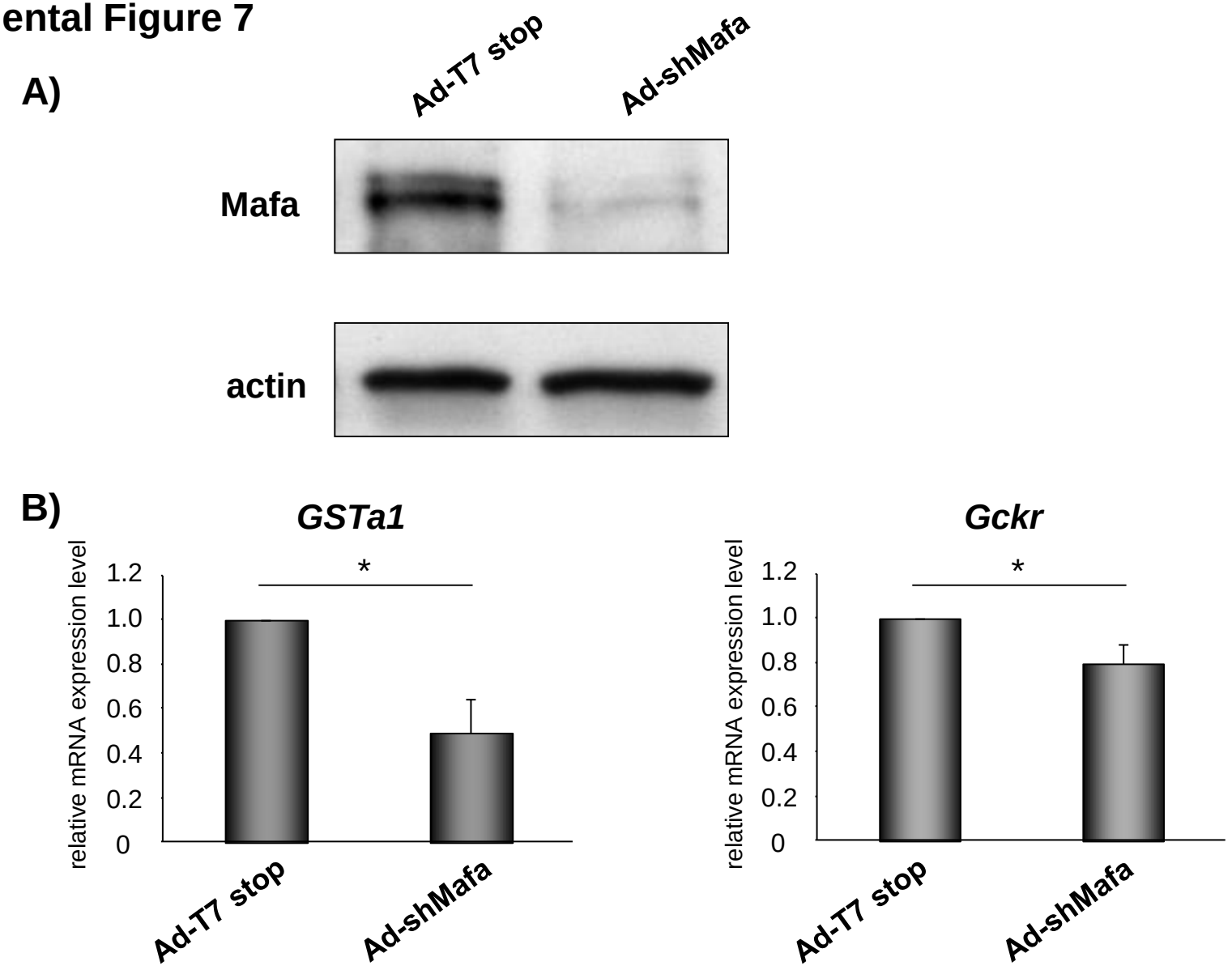




Supplemental Figure 6. Islet area increases in *βMafa^{myc};db/db* mice relative to diabetic non-Mafa^{myc} producing *db/db* mice.

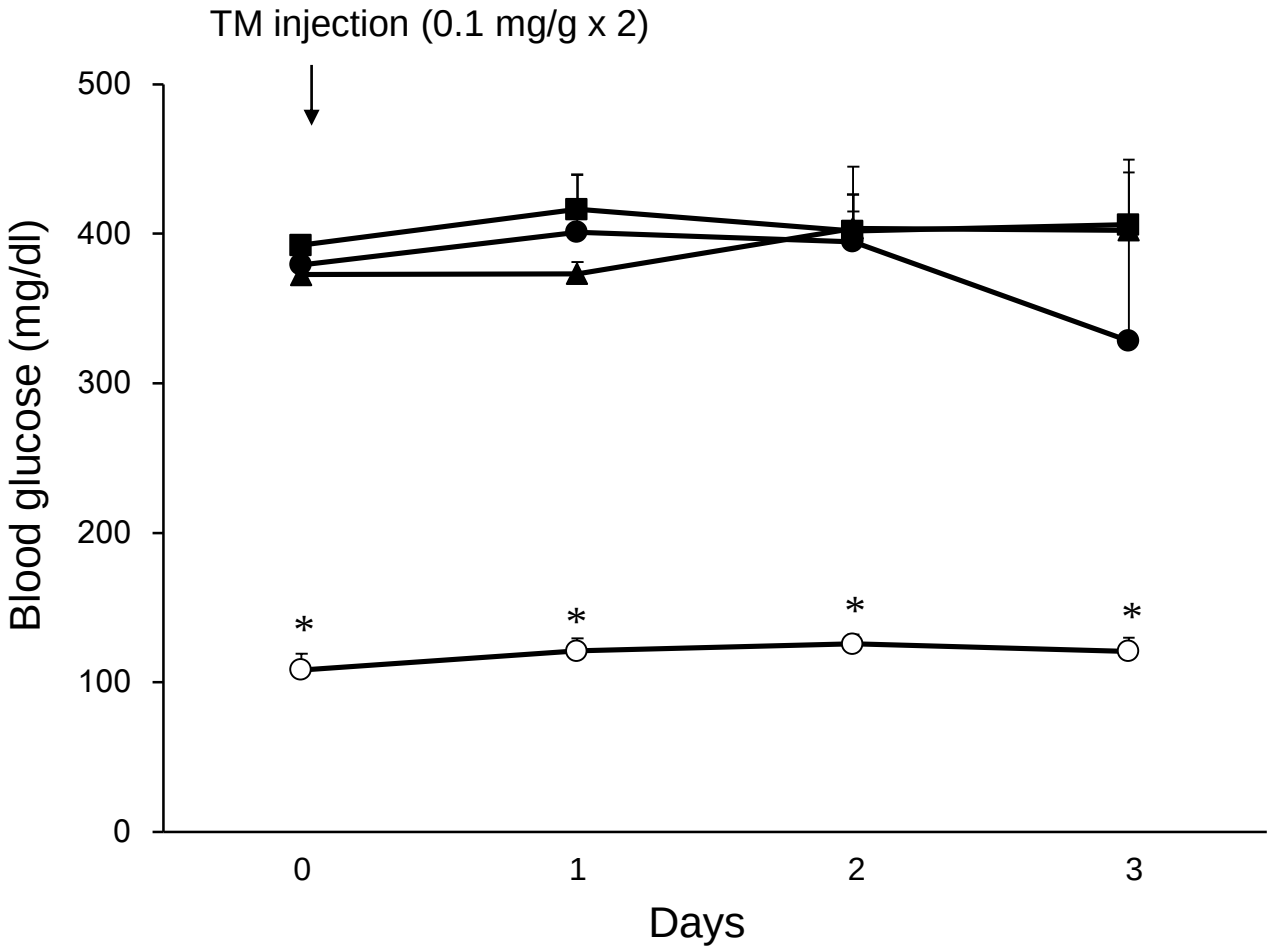
(A) Pancreatic islets stained by dithizone (red) in 17 week-old normal *db/m* and diabetic *db/db* mice. Scale bars: 1 cm. Very few islets are detected in the *db/db* pancreas. (B) Dithizone stained islets (red) in the *βMafa^{myc};db/db*, *Pdx1^{PB}-CreER^{TM};db/db*, and *CAG-CAT-Mafa^{myc};db/db* pancreas of 17 week-old mice (8 weeks after TM injections). Arrows mark islets; fat tissue is stained in green. Scale bars: 1 mm. Notably, the levels of the zinc transporter Slc30a8 in these islet groups was not significantly different, so dithizone staining could be used to measure islet mass. There was a significant increase in islet mass in *βMafa^{myc};db/db* mice compared to diabetic non-Mafa^{myc} expressing *db/db* mice. Error bars represent S.D.

Supplemental Figure 7



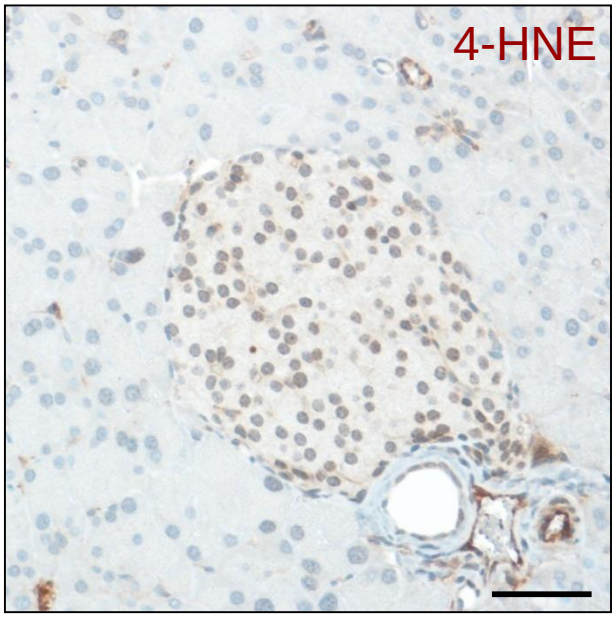
Supplemental Figure 7. Mafa regulates Gsta1 and Gckr mRNA levels in MIN6 cells.
(A) Immunoblot analysis was performed for Mafa and actin in nuclear extracts prepared 60 hours after Ad-shMafa and control Ad-T7stop infection. (B) RNA was isolated and real-time RT-PCR analysis performed on shRNA treated cells. *P < 0.05. n=6. Error bars represent S.D.

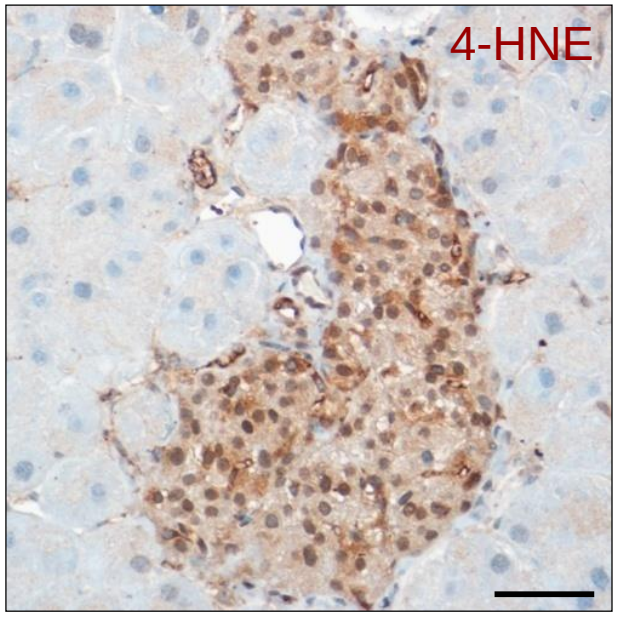
Supplemental Figure 8

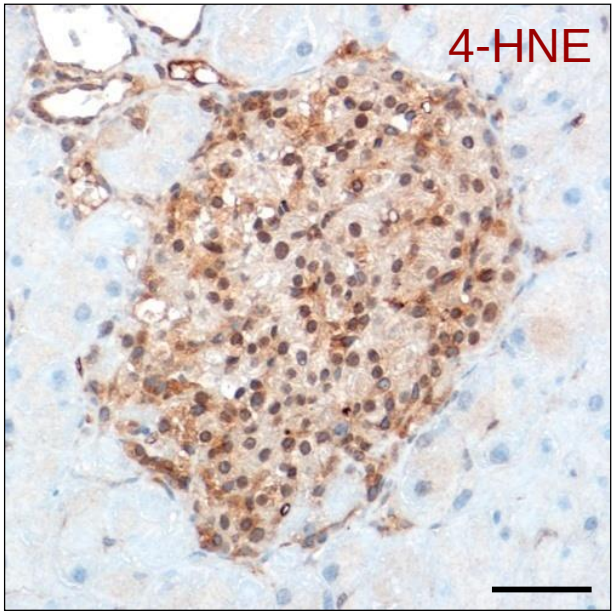


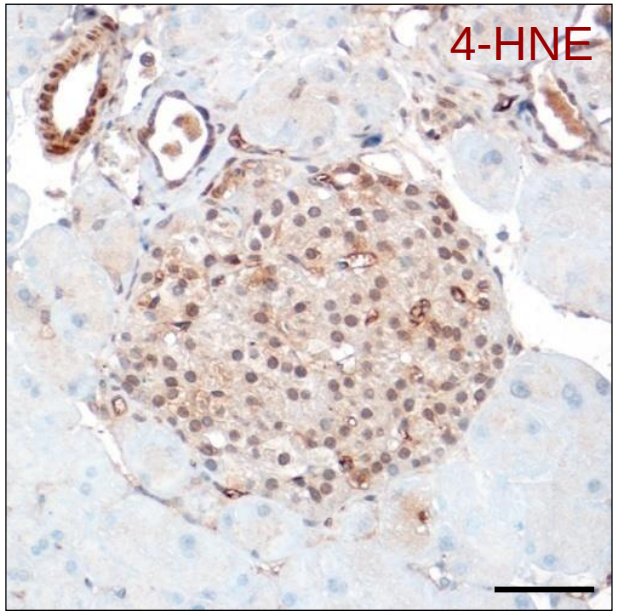
Supplemental Figure 8. TM injection alone does not alter blood glucose levels in *db/db* mice.
Fed blood glucose levels were measured at 4 pm before and after TM injection in *db/m* (○), *Pdx1^{PB}-CreER^{TM};db/db* (■), *CAG-CAT-Mafa^{myc};db/db* (▲) and *βMafa^{myc};db/db* (●) mice. * $p < 0.01$ vs. *db/db* mice. n=3-4. Error bars represent S.D.

Supplemental Figure 9



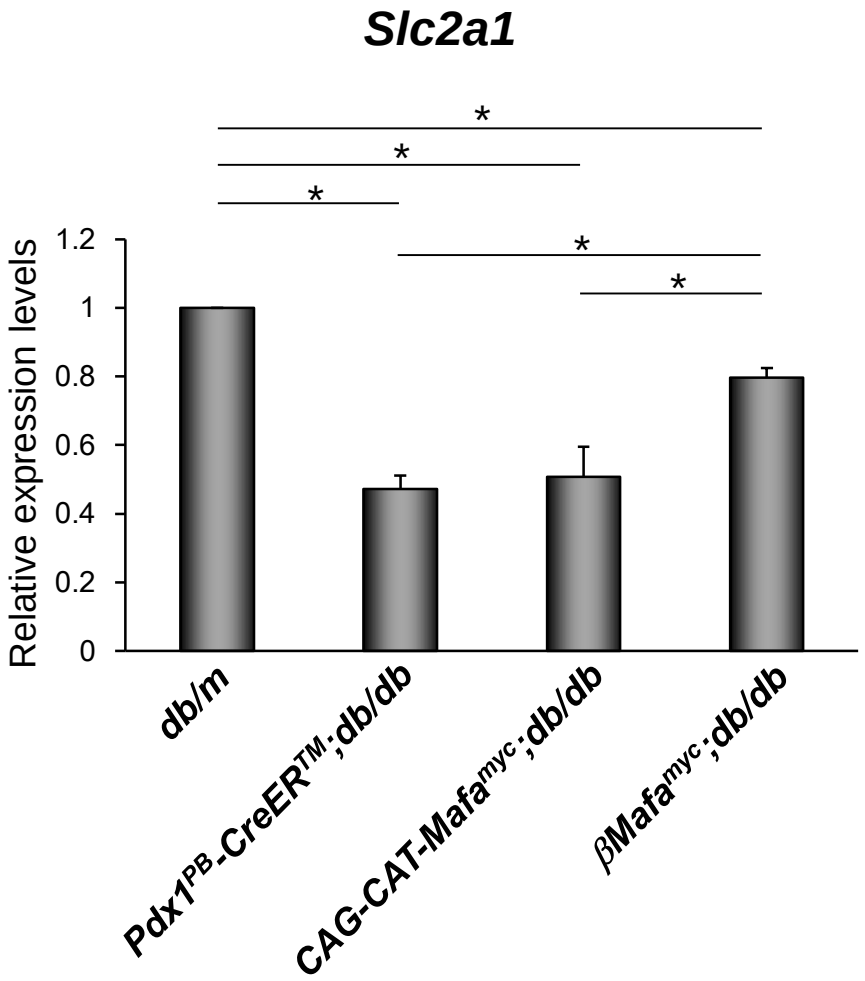






Supplemental Figure 9. Reactive oxygen species levels is reduced in *bMafa^{myc};db/db* islets.
Immunostaining of pancreatic sections from 18 week-old mice with 4-HNE to detect lipid peroxidation.

Supplemental Figure 10



Supplemental Figure 10. *Slc2a1* levels increased in *βMafa^{myc};db/db* islets
Slc2a1 mRNA expression was examined in islets purified from 14 week-old mice by RT-PCR. * $p < 0.01$. n=4. Error bars represent S.D.