SUPPLEMENTARY DATA

Primary antibodies used:

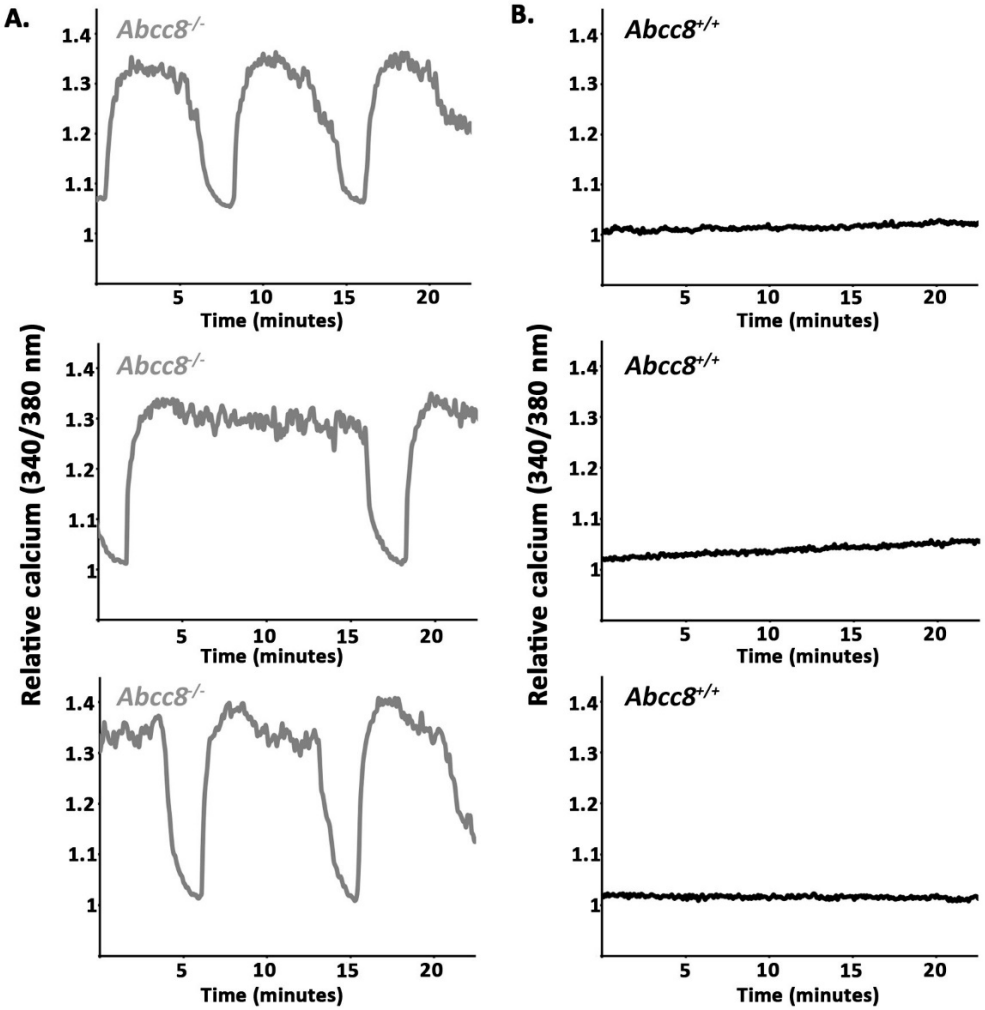
Antibody	Species	Company	Dilution
Aldh1a3	Rabbit	Novus Biologicals	1:500
GFP	Chicken	Invitrogen	1:2000
Glucagon	Rabbit	Linco	1:1000
Insulin	Guinea pig	Invitrogen	1:1000
Insulin	Rabbit	Cell Signaling	1:100
Pancreatic polypeptide	Guinea pig	Linco	1:1000
Somatostatin	Rabbit	ICN Biomedicals	1:1000
S100a6	Sheep	R&D Systems	1:100

qRT-PCR primer sequences:

Gene	Forward Primer	Reverse Primer
Aldh1a3	5'-GGGTCACACTGGAGCTAGGA	5'-CTGGCCTCTTCTTGGCGAA
Ascl1	5'-GACTTTGGAAGCAGGATGGCA	5'-CACCCCTGTTTGCTGAGAAC
Hprt	5'-TACGAGGAGTCCTGTTGATGTTGC	5'-GGGACGCAGCAACTGACATTTCTA
S100a4	5'-AGCACTTCCTCTCTCTTGGTC	5'-TCATCTGTCCTTTTCCCCAGG
S100a6	5'-CACATTCCATCCCCTCGACC	5'-GTGGAAGATGGCCACGAGAA

SUPPLEMENTARY DATA

Supplementary Figure 1. *Abcc8*$^{-/-}$ β-cells exhibit oscillations in intracellular Ca^{2+} at sub-stimulatory glucose. **(A-B)** Intracellular Ca^{2+} was monitored in *Abcc8*$^{-/-}$ (A) and *Abcc8*$^{+/+}$ (B) intact islets with Fura-2 AM at 2mM glucose for 20 minutes. Traces from three representative islets are shown for each genotype. *Abcc8*$^{-/-}$ islets exhibit oscillations of variable frequency and elevated $[Ca^{2+}]_i$, while *Abcc8*$^{+/+}$ islets show no oscillatory behavior and low $[Ca^{2+}]_i$. \

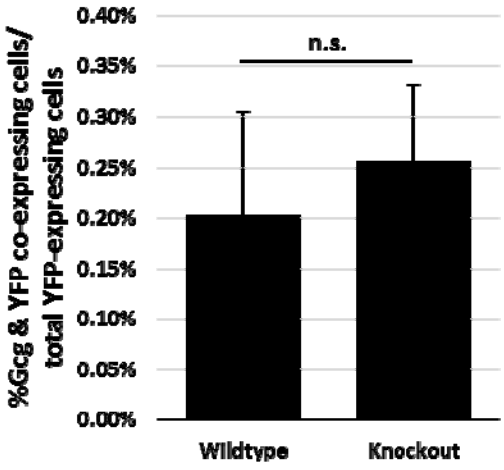


SUPPLEMENTARY DATA

Supplementary Figure 2. *Abcc8*$^{-/-}$ β-cells don't transdifferentiate to α- or δ-cells. (A, B) We performed β-cell lineage tracing using *Abcc8*$^{-/-}$*; RIP-Cre; R26*$^{LSL.YFP}$ animals and assessed β-cell dedifferentiation at 12 weeks of age. Quantification of YFP/Glucagon double^{+} cells (A) or YFP/Somatostatin double^{+} cells (B) shows no difference in the prevalence of these cells in wild type and knockout mice, suggesting that *Abcc8*$^{-/-}$ β-cells do not transdifferentiate to α- or δ-cells. N=3-4 animals, 10-15 islets counted per animal. **(C)** Summary of the total number of YFP and PP double-positive, but insulin-negative, cells observed in *Abcc8*$^{+/+}$*; RIP-Cre; R26*$^{LSL.YFP}$ and *Abcc8*$^{-/-}$*; RIP-Cre; R26*$^{LSL.YFP}$ animals at 12 weeks of age. **(D)** Quantification of PP/Insulin double^{+} cells in frozen pancreatic sections shows a trend towards a decrease in polyhormonal cells in 8-9-week-old *Abcc8*$^{-/-}$ mice after 3 weeks of verapamil administration (p=0.26). However, the difference is not statistically significant. **(E)** Quantification of the number of YFP-positive, hormone-negative cells observed in *Abcc8*$^{+/+}$*; RIP-Cre; R26*$^{LSL.YFP}$ and *Abcc8*$^{-/-}$*; RIP-Cre; R26*$^{LSL.YFP}$ animals at 12 weeks of age. N=3 animals per group. *p<0.05, ***p<0.001, n.s. = Not Significant.

SUPPLEMENTARY DATA

A



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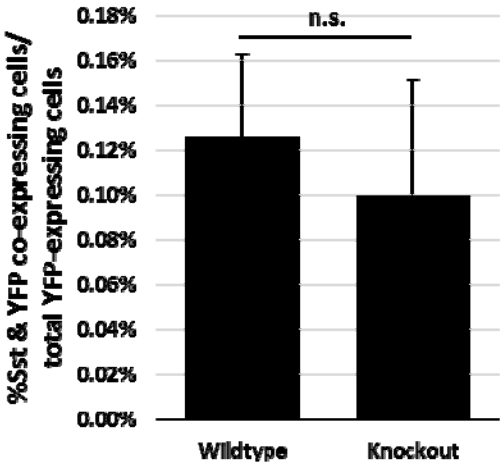
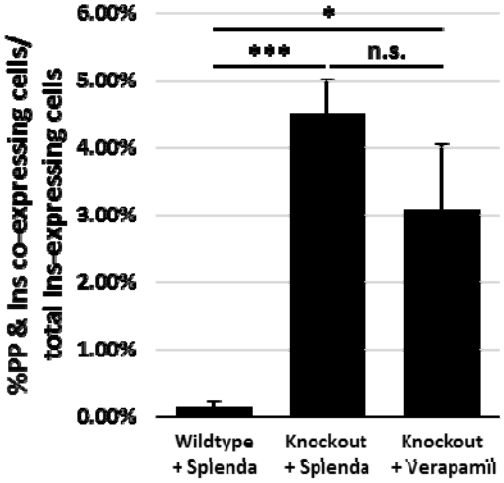


C

Genotype	Total YFP$^+$ cells	Total YFP/PP$^+$ cells	Total YFP/PP$^+$, Ins$^-$ cells
Wildtype	2585	8	0
Knockout	1645	40	4

D



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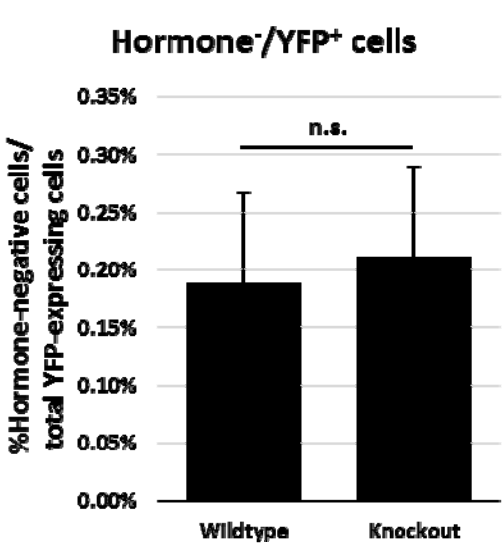
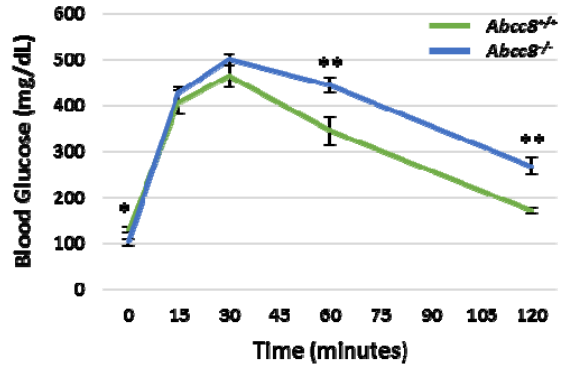


SUPPLEMENTARY DATA

Supplementary Figure 3. Blood glucose control in *Abcc8*$^{-/-}$ mice. (A) Results of intraperitoneal glucose tolerance tests on male *Abcc8*$^{+/+}$ and *Abcc8*$^{-/-}$ mice at 12 weeks of age. n=4-10 animals per genotype. Error bars represent standard error. *p<0.05, **p<0.01. **(B)** Fed blood glucose concentration in a cohort of *Abcc8*$^{+/+}$ and *Abcc8*$^{-/-}$ mice between from 4 to 8 weeks of age showing no statistically significant difference between the groups. n=5 animals per genotype. **(C)** TUNEL was used to assess β-cell death at 12 weeks of age. In *Abcc8*$^{+/+}$ islets, no insulin and TUNEL co-expressing cells were observed. In *Abcc8*$^{-/-}$ islets, one insulin and TUNEL co-expressing cell was observed.

A



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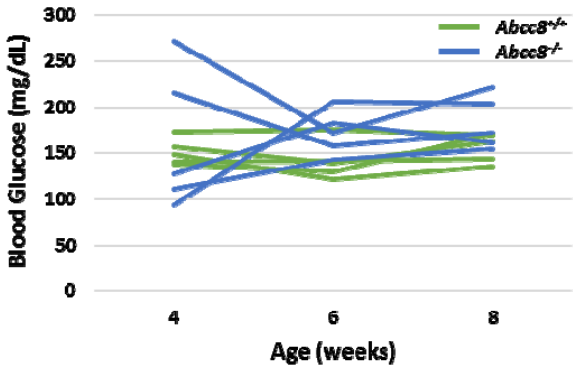
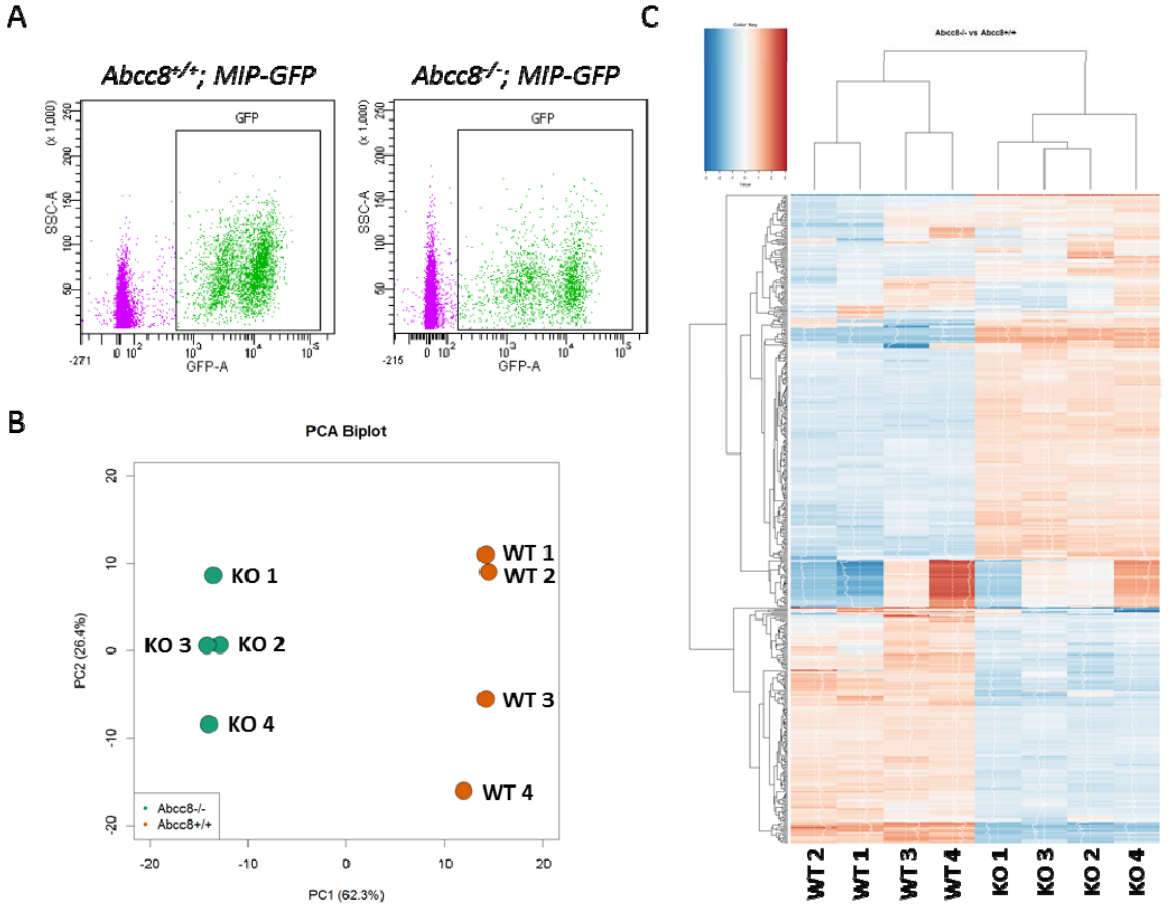


C

Genotype	Total Ins^{+} cells counted	Total Ins/TUNEL^{+} cells counted
Wildtype	3403	0
Knockout	3266	1

SUPPLEMENTARY DATA

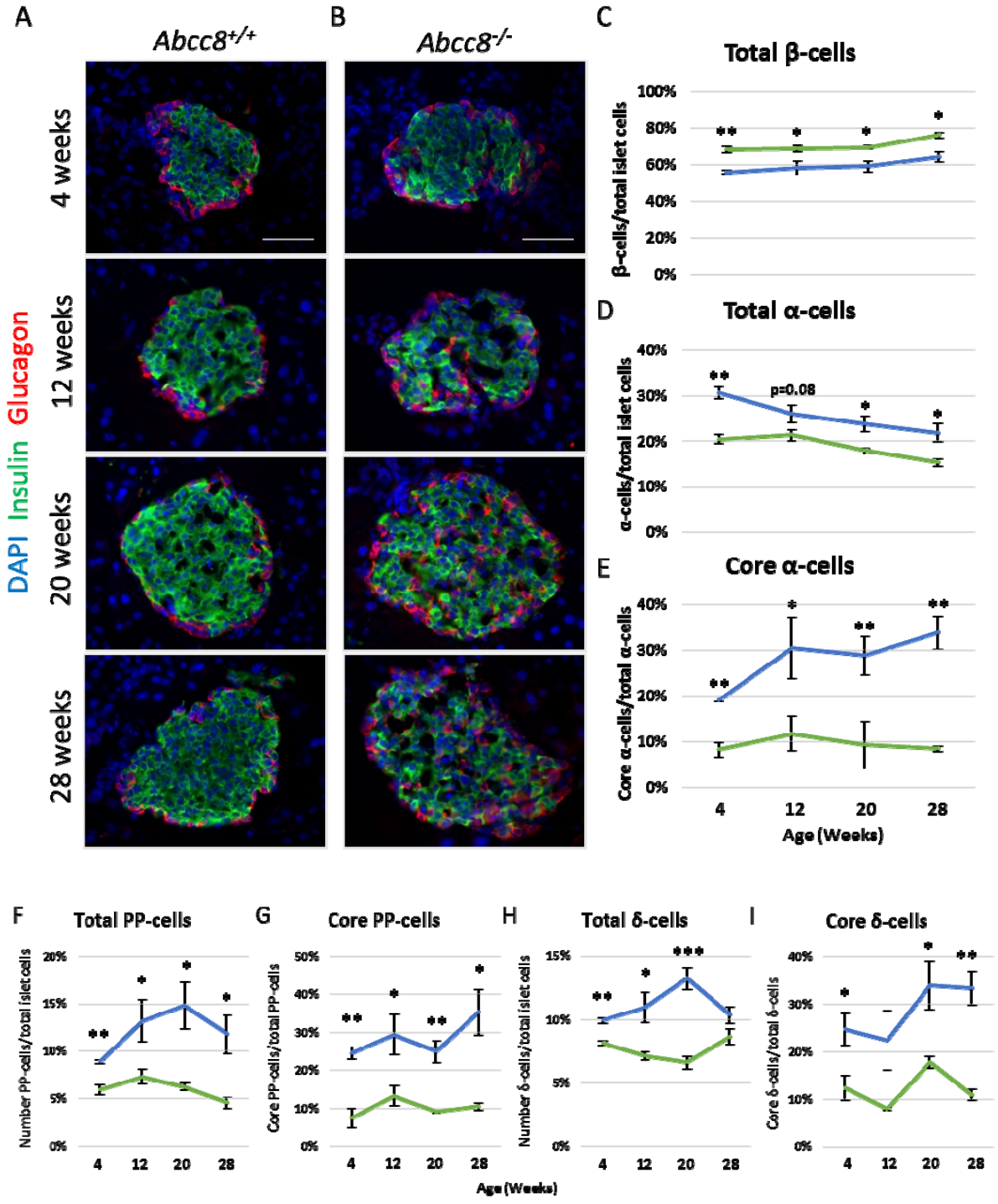
Supplementary Figure 4. Principal Component Analysis and Gene Clustering Analysis. (A) FACS profiles of sorted populations from *Abcc8*$^{+/+}$*; MIP-GFP* and *Abcc8*$^{-/-}$*; MIP-GFP* mice indicating that β-cells from both genotypes can be purified similarly. **(B)** Principal component analysis shows that the eight samples used for RNA-sequencing cluster by genotype, with some variation in the second principal component. **(C)** Heat map depicting gene clustering analysis using the top 500 differentially-expressed genes. "WT" = *Abcc8*$^{+/+}$. "KO" = *Abcc8*$^{-/-}$.



SUPPLEMENTARY DATA

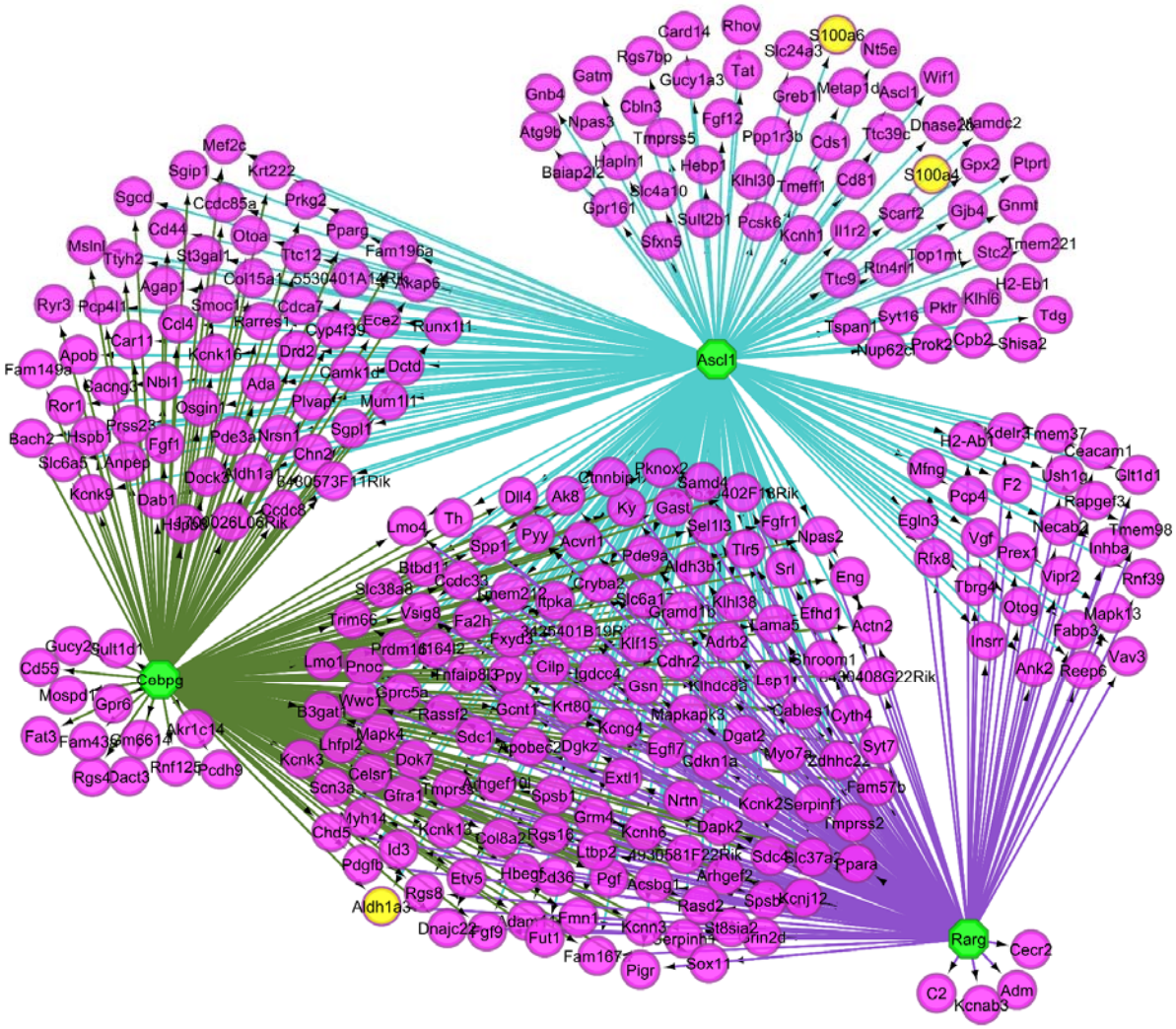
Supplementary Figure 5. *Abcc8*$^{-/-}$ islets have disrupted islet morphology. **(A)** *Abcc8*$^{+/+}$ islets maintain a clear mantle of α-cells while **(B)** *Abcc8*$^{-/-}$ islets progressively lose the boundary between mantle and core between 4 and 28 weeks of age. **(C-I)** Cell counting at 4, 12, 20, and 28 weeks of age shows that *Abcc8*$^{-/-}$ islets have fewer β-cells (C), a greater percentage of α-cells (D), PP-cells (F), and δ-cells (H), and an increasing percentage of core α-cells (E), core PP-cells (G) and core δ-cells (I). Core cells were defined as being located greater than 2 cell diameters interior from the islet boundary. Green lines represent *Abcc8*$^{+/+}$ islets. Blue lines represent *Abcc8*$^{-/-}$ islets. n=3-4 animals per genotype, 10-15 islets counted per animal. Error bars represent standard error. *p<0.05, **p<0.01, ***p<0.001. Scale bar = 50μm.

SUPPLEMENTARY DATA



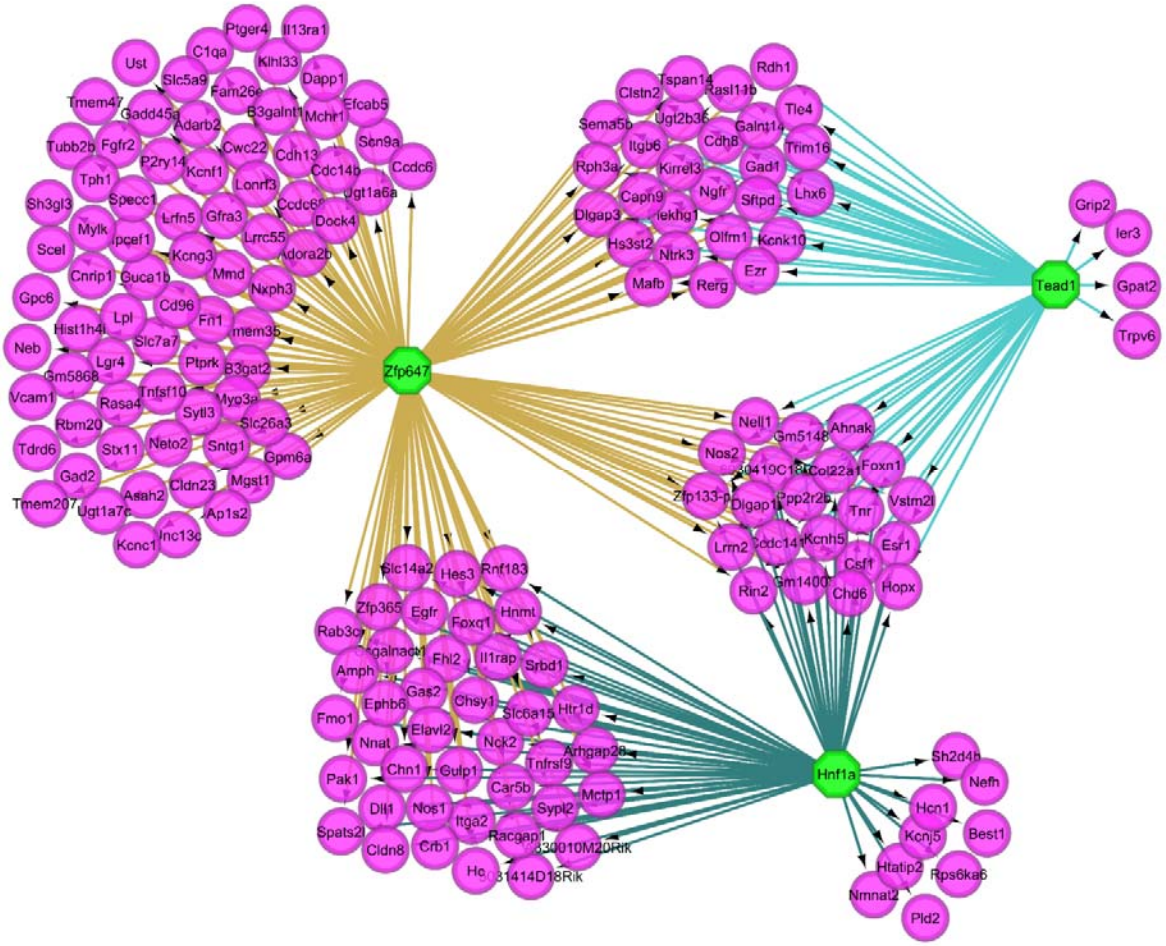
SUPPLEMENTARY DATA

Supplementary Figure 6. iRegulon-predicted network of regulators of the top 500 upregulated genes in *Abcc8*$^{-/-}$ β-cells. Map depicting the top 3 predicted regulators (green octagons) and their predicted target genes (magenta circles). A majority of the genes are predicted to be co-regulated by two or more regulators. Genes of interest (*S100a6*, *S100a4*, and *Aldh1a3*) are highlighted yellow.



SUPPLEMENTARY DATA

Supplementary Figure 7. iRegulon-predicted network of regulators of the top 500 downregulated genes in *Abcc8*$^{-/-}$ β-cells. Map depicting the top 3 predicted regulators (green octagons) and their predicted target genes (magenta circles).



SUPPLEMENTARY DATA

Supplemental Table 1. Differential expression analysis. Results of differential expression analysis using 4 *Abcc8*$^{-/-}$*; MIP-GFP* and 4 *Abcc8*$^{+/+}$*; MIP-GFP* samples. Genes are identified by MGI Symbol, Ensembl ID, and Entrez gene ID, and are categorized by MGI biotype. Log_2[Fold Change (KO vs. WT)], p-value (Wald test), and padj (p-value adjusted for Benjamini and Hochberg's False Discovery Rate), and the raw counts for each of the 8 samples are included for each gene.

Supplemental Table 2. Predicted regulators and targets of the top 500 most upregulated genes in *Abcc8*$^{-/-}$β-cells. Complete list of iRegulon-predicted target genes for each of the top 3 regulators (ASCL1, RARG, and CEBPG).

Supplemental Table 3. Predicted regulators and targets of the top 500 most downregulated genes in *Abcc8*$^{-/-}$β-cells. Complete list of iRegulon-predicted target genes for each of the top 3 regulators (TEAD1, HNF1A, and ZFP647).

SUPPLEMENTARY DATA

Link to Online Supplemental Tables

https://www.dropbox.com/sh/xxe96rmld086gyf/AADUd7WfCsQFTaI5EZvu1hSYa?dl=0