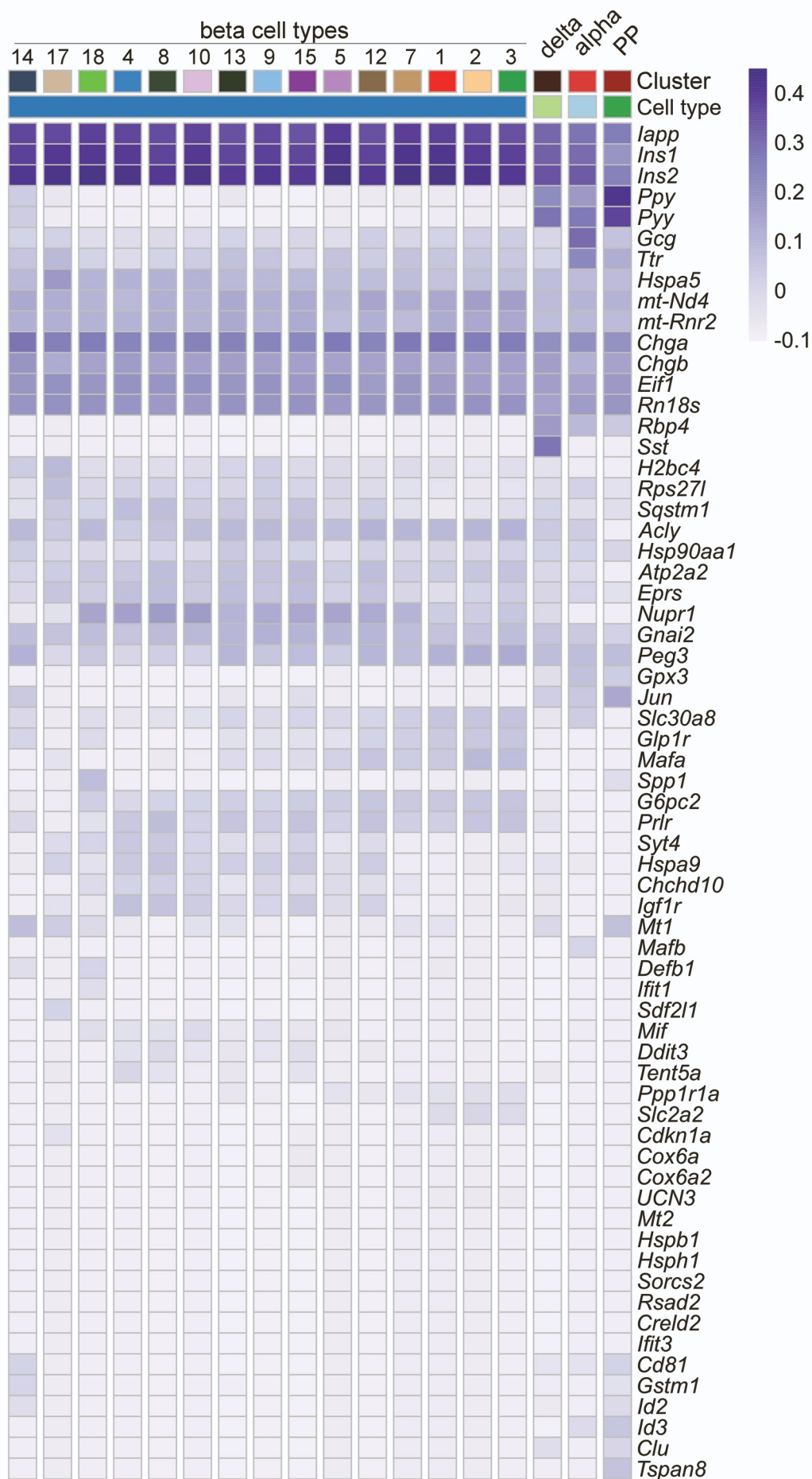


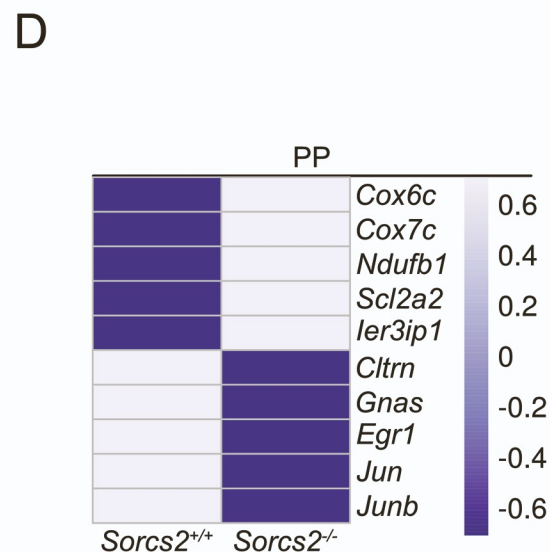
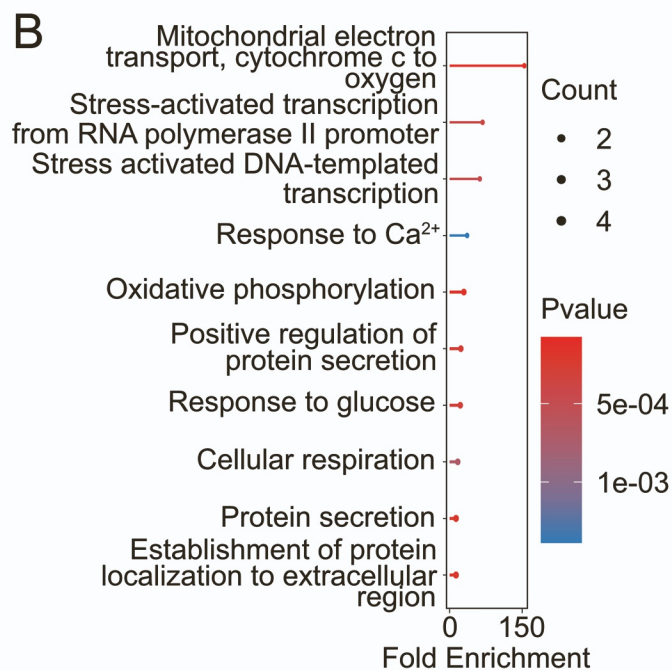
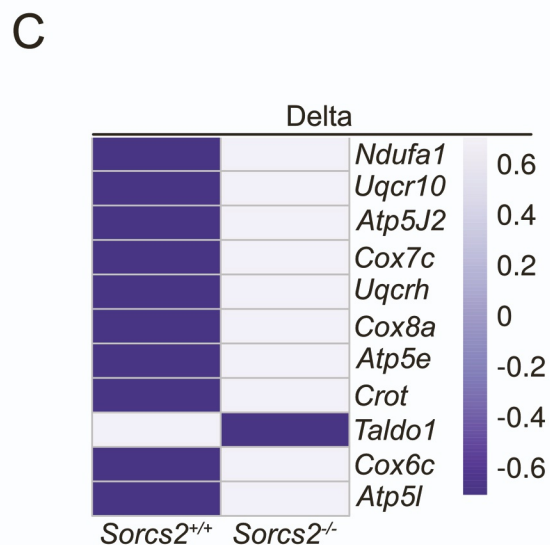
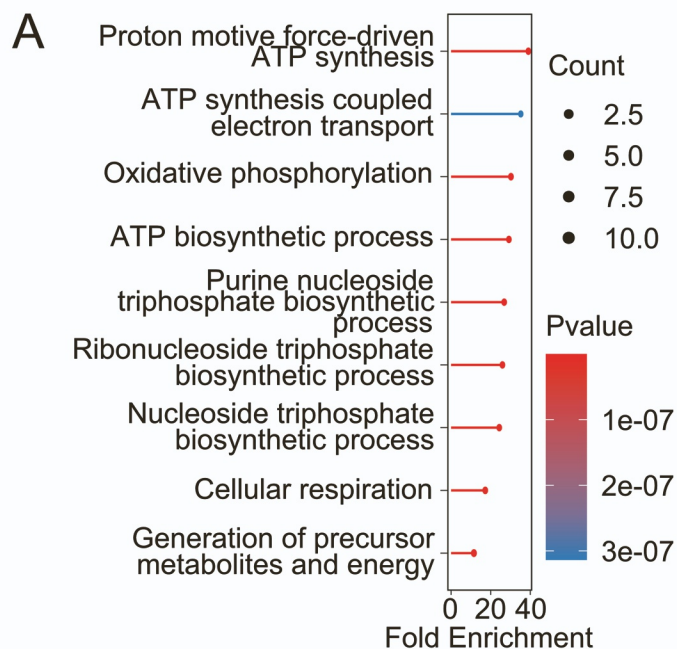
Supplemental information

**SORCS2 activity in pancreatic α -cells safeguards
insulin granule formation and release
from glucose-stressed β -cells**

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SUPPLEMENTARY INFORMATION





Kalnytska et al., Figure S2

SUPPLEMENTARY FIGURES

Figure S1, related to figure 6. Annotation of islet cell types from single-cell RNA sequencing

Heatmap showing the top 20 most unique identifiers per cluster according to the adjusted p-value calculated with linear models for microarray data (Limma) moderated t-statistics for all 18 cell clusters identified by single-cell RNA sequencing of *Sorcs2*^{+/+} and *Sorcs2*^{-/-} islets.

Figure S2, related to figure 8. Effect of SORCS2 deficiency on gene expression in pancreatic islet delta and PP cell types

(**A-B**) Graphs representing biological processes impacted in delta (A) and PP (B) cells of *Sorcs2*^{+/+} versus *Sorcs2*^{-/-} islets. (**C, D**) Heatmaps of normalized levels of DEGs associated with biological processes in GO analysis in delta (C) and PP (D) cell populations of pancreatic islets from *Sorcs2*^{+/+} and *Sorcs2*^{-/-} animals. Gene ontology analysis was performed using clusterProfiler R package¹ and visualized with Genekitr (<https://genekitr.top/genekitr/>). Benjamini-Hochberg (BH) test was applied to calculate adjusted p value of GO terms. Significance of DEGs was determined using Limma moderated t-statistics.

Table S1, related to figure 3. Plasma levels of pancreatic hormones in wildtype and SORCS2-deficient mice

Plasma hormone levels were determined by ELISA under basal conditions (basal) or 30 minutes after intraperitoneal injection of 2 g/kg body weight of glucose. Data are given as mean \pm standard deviation (SD). Significance of data was evaluated using two-way ANOVA followed by Sidak's or Tukey's multiple comparisons tests. n, number of animals; n.s., not significant.

	<i>Sorcs2</i> ^{+/+}			<i>Sorcs2</i> ^{-/-}					
	basal	glucose	n	basal	glucose	n	Interaction	<i>p</i>	
	mean \pm SD	mean \pm SD		mean \pm SD	mean \pm SD			Condition	Genotype
Glucagon (pg/ml)	7.88 \pm 3.72	5.53 \pm 2.29	8	7.41 \pm 3.36	5.22 \pm 4.21	6	n.s.	< 0.05	n.s.
GLP-1 (μ g/ml)	661 \pm 632	733 \pm 762	12	887 \pm 1164	861 \pm 1035	10	n.s.	n.s.	n.s.
GIP (pg/ml)	1.03 \pm 0.048	0.99 \pm 0.022	8	1.05 \pm 0.07	1.001 \pm 0.029	8	n.s.	< 0.001	n.s.
Somatostatin (ng/ml)	1.16 \pm 0.139	1.28 \pm 0.27	8	1.23 \pm 0.17	1.24 \pm 0.11	8	n.s.	n.s.	n.s.
Somatostatin-28 (pg/ml)	181.3 \pm 37.1	244.1 \pm 78.2	8	160.2 \pm 24.5	185.7 \pm 25.1	5	n.s.	n.s.	n.s.
NPY (ng/ml)	1.37 \pm 0.21	1.73 \pm 0.1	10	1.76 \pm 0.19	1.78 \pm 0.18	10	< 0.001	< 0.001	< 0.01
PYY (ng/ml)	1.18 \pm 0.15	1.42 \pm 0.53	10	1.09 \pm 0.13	0.95 \pm 0.09	10	< 0.05	n.s.	< 0.01

Table S2, related to figure 4. Total hormone content in isolated wildtype and SORCS2-deficient islets

Hormone levels were determined by ELISA in lysates of isolated pancreatic islets from *Sorcs2*^{+/+} and *Sorcs2*^{-/-} mice kept overnight in culture medium. Data are given as mean ± standard deviation (SD). Significance of data was determined using unpaired Student's t-test or Mann-Whitney U test. n, number of animals; n.s. not significant.

	<i>Sorcs2</i> ^{+/+}		<i>Sorcs2</i> ^{-/-}		
	mean ± SD	n	mean ± SD	n	p
Glucagon (ng/mg protein)	576.6 ± 439.3	12	653.2 ± 337.6	12	n.s.
GLP-1 (mg/mg protein)	11.74 ± 5.12	11	15.06 ± 5.26	12	< 0.05
Total somatostatin (ng/mg protein)	403.5 ± 315.5	13	462.8 ± 386	13	n.s.
Somatostatin-28 (ng/mg protein)	20.78 ± 9.63	11	26.74 ± 11.59	11	n.s.
NPY (ng/mg protein)	1.20 ± 0.19	8	1.36 ± 0.37	8	n.s.
PYY (ng/mg protein)	1.62 ± 0.55	8	0.99 ± 0.16	8	< 0.01

Table S3, related to figure 4. Levels of hormones released from wildtype and SORCS2-deficient pancreatic islets

Isolated pancreatic islets from *Sorcs2*^{+/+} and *Sorcs2*^{-/-} mice were treated for 1 hour with 1.6 mM or 16 mM glucose in Krebs-Ringer-Bicarbonate Hepes buffer. Levels of indicated hormones released into the supernatant were determined by ELISA thereafter. Data are given as mean ± standard deviation (SD). Significance of data was evaluated using two-way ANOVA followed by Sidak's or Tukey's multiple comparisons tests. n, number of animals; n.s., not significant.

	<i>Sorcs2</i> ^{+/+}			<i>Sorcs2</i> ^{-/-}					
	1.6 mM	16 mM	n	1.6 mM	16 mM	n	<i>p</i>		
	mean ± SD	mean ± SD		mean ± SD	mean ± SD		Interaction	Treatment	Genotype
Glucagon (ng/mg protein)	1.59 ± 1.24	1.87 ± 1.71	23	1.47 ± 1.15	2.27 ± 3.69	23	n.s.	n.s.	n.s.
GLP-1 (μg/mg protein)	512 ± 317	590 ± 443	21	471 ± 196	531 ± 332	21	n.s.	n.s.	n.s.
Somatostatin (ng/mg protein)	0.81 ± 0.49	1.18 ± 0.51	16	0.81 ± 0.51	1.316 ± 0.54	16	n.s.	< 0.0001	n.s.
Somatostatin-28 (pg/mg protein)	580.9 ± 131.42	858.3 ± 353.56	7	475.4 ± 453.61	1306 ± 1218.63	7	n.s.	< 0.01	n.s.
NPY (ng/mg protein)	0.03 ± 0.03	0.07 ± 0.05	12	0.06 ± 0.05	0.111 ± 0.09	13	n.s.	< 0.0001	n.s.
PYY (ng/mg protein)	0.64 ± 0.26	0.46 ± 0.21	18	0.76 ± 0.41	0.574 ± 0.28	18	n.s.	≤ 0.001	n.s.

SUPPLEMENTAL REFERENCES

- 1 Yu, G., Wang, L.G., Han, Y., and He, Q.Y. (2012). clusterProfiler: an R package for comparing biological themes among gene clusters. OMICS 16, 284-287. 10.1089/omi.2011.0118.