

SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1. (A) Body weight, (B) cumulative food intake from day 5-14 of liraglutide or saline treatment, (C) subcutaneous (SC), mesenteric (MES), perigonadal (PG) and retroperitoneal (RP) adipose depot weights, (D) total white adipose tissue (WAT) weight, (E) brown adipose tissue (BAT) weight, and (F) fasting blood glucose in saline (CTRL) or liraglutide- (LIRA) treated WT and KO mice. Data are represented as mean $\pm$ SEM. $n = 6$ per group. * $P < 0.05$ CTRL WT vs LIRA WT by Student's t-test. \$ $P < 0.05$ CTRL KO vs LIRA KO by one-tailed Student's t-test.

Supplemental Figure 2. (A) UMAP of human islet cells that were subjected to either DROP-seq or DART-seq. (B) Donor information of the human islet sample used for the study. $n = 1$.

Supplemental Figure 3. (A) Table of islet donor information. (B) Cell marker expression overlaid on the UMAP of human islets treated with CTRL or LIRA. (C) UMAP of human islets treated with either saline (CTRL) or liraglutide (LIRA). $n = 3$.

Supplemental Figure 4. (A) Table showing average log-fold change (avg_logFC) in the expression of *INS*, *IAPP*, *PCSK1* and *MAFA* upon liraglutide treatment, within the alpha-cell sub-clusters. n.s. = not significant. (B) Volcano plot showing liraglutide-induced differential gene expression in delta-cells. $n = 3$.

Supplemental Figure 5. (A) Table of islet donor information for human islets used for IHC outcomes. (B) Table of islet donor information for human islets used for active GLP-1 measures.

Supplemental Figure 6. Comparison of males vs females. (A) Body weight, (B) cumulative food intake from day 5-14 of liraglutide or saline treatment, (C) total white adipose tissue (WAT) weight,

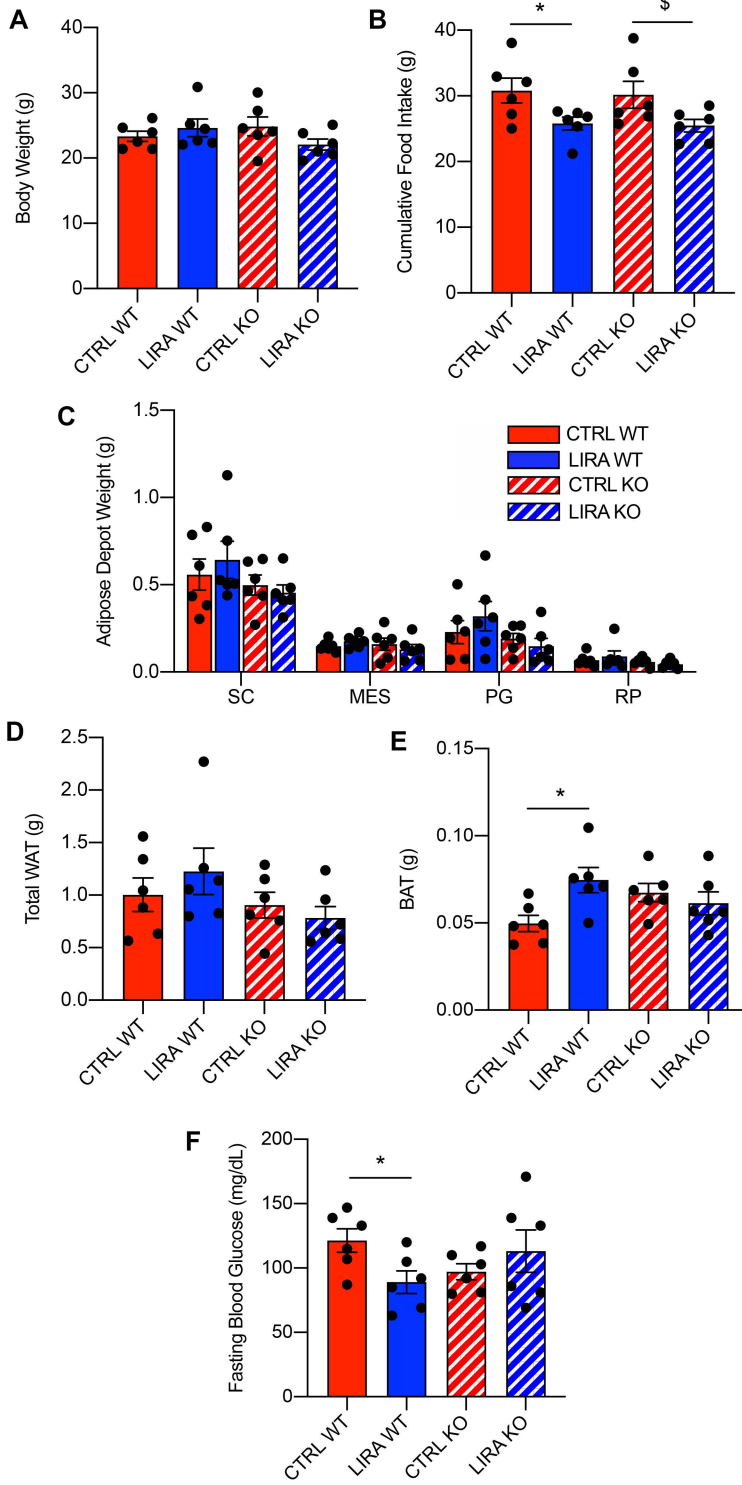
(**D**) brown adipose tissue (BAT) weight, (**E**) subcutaneous (SC), mesenteric (MES), perigonadal (PG) and retroperitoneal (RP) adipose depot weights, (**F**) fasting blood glucose in saline (CTRL) or liraglutide- (LIRA) treated WT and KO mice. (**G**) Average GLP-1 staining per islet. (**H**) PC1/3 co-localization with glucagon. (**I**) Percentage of islets with centrally located alpha-cells. (**J**) Percentage of bi-hormonal insulin⁺ glucagon⁺ positive cells per islet. (**K**) Percentage of centrally located bi-hormonal insulin⁺ glucagon⁺ positive cells per islet. Data are presented as mean $\pm$ SEM. $n = 6$ per group (3 males, 3 females). * $P < 0.05$ CTRL WT vs LIRA WT, ⁺ $P < 0.05$ CTRL KO vs LIRA KO, [#] $P < 0.05$ LIRA WT vs LIRA KO by two-factor ANOVA; ^{\$} $P < 0.05$ CTRL WT vs LIRA WT, ⁺ $P < 0.05$ CTRL WT vs CTRL KO by two-tailed Student's t-test.

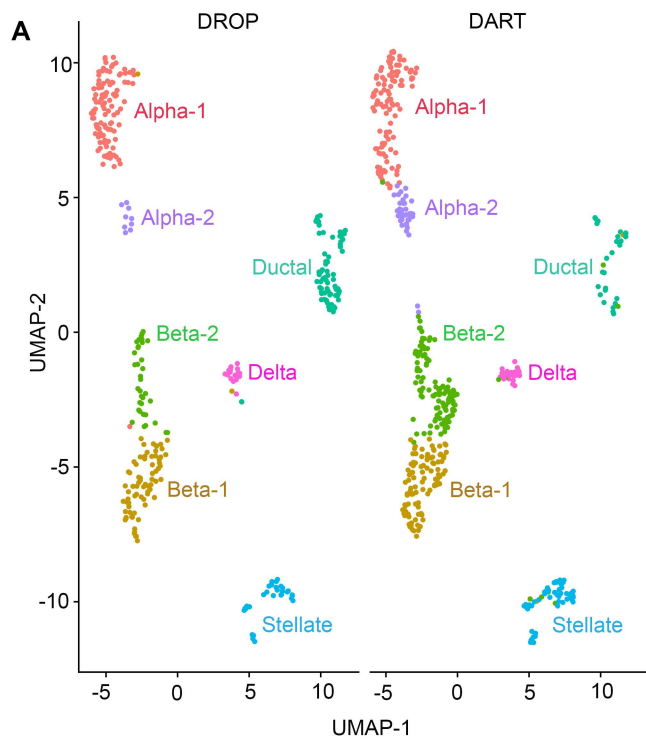
SUPPLEMENTAL TABLES

Supplemental Table 1. Sequence information of DNA primers used as the probes and toeholds for DART-seq beads. Related to Figure 2.

Name	Sequence (5'-3')
PCSK1_Probe	/5Phos/GCC GGT CGT CTC TGT GCT TG
PCSK1_Toehold	GAG ACG ACC GGC AAA AAA AAA AAA
GCG_Probe	/5Phos/TTG GTC TGA ATC AAC CAG TT
GCG_Toehold	GAT TCA GAC CAA AAA AAA AAA AAA
PCSK2_Probe	/5Phos/CTG GTC GAT GTA CGG GGC AC
PCSK2_Toehold	TAC ATC GAC CAG AAA AAA AAA AAA
PCSK1n_Probe	/5Phos/AGG CGT TTC ACA CGC AGC AG
PCSK1n_Toehold	TGT GAA ACG CCT AAA AAA AAA AAA
XBP1U_Probe	/5Phos/TCC AGG CTG GCA GGC TCT GG
XBP1U_Toehold	TGC CAG CCT GGA AAA AAA AAA AAA
XBP1s_Probe	/5Phos/TGG GTC CAA GTT GTC CAG AA
XBP1s_Toehold	AAC TTG GAC CCA AAA AAA AAA AAA
ATF6_Probe	/5Phos/CCA CAG AGG CAA CCC ACG TT
ATF6_Toehold	TTG CCT CTG TGG AAA AAA AAA AAA
ATF4_Probe	/5Phos/CAA GAC AGC AGC CAC TAG GT
ATF4_Toehold	GCT GCT GTC TTG AAA AAA AAA AAA

Supplemental Table 2. List of top 100 genes that are differentially expressed in the liraglutide-treated versus control condition for every alpha and beta sub-cluster. Related to Figure 4.



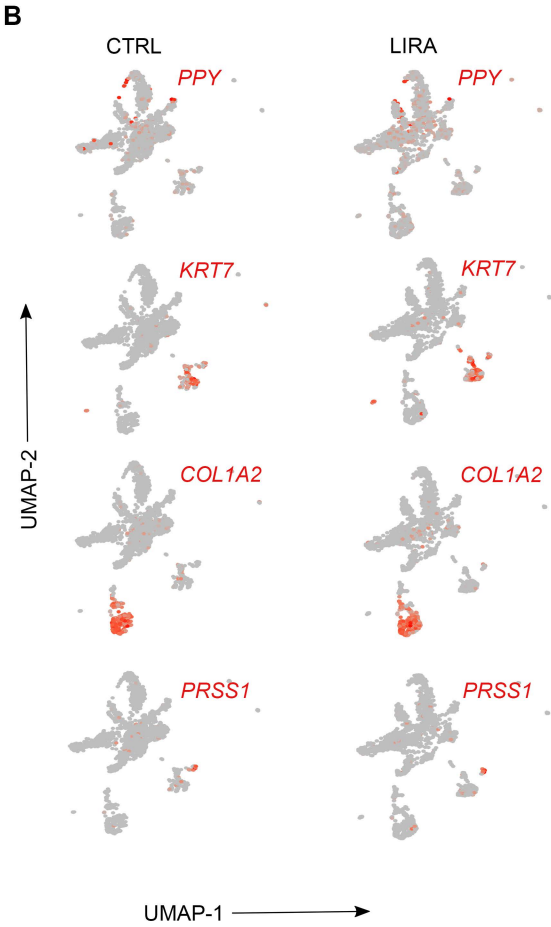
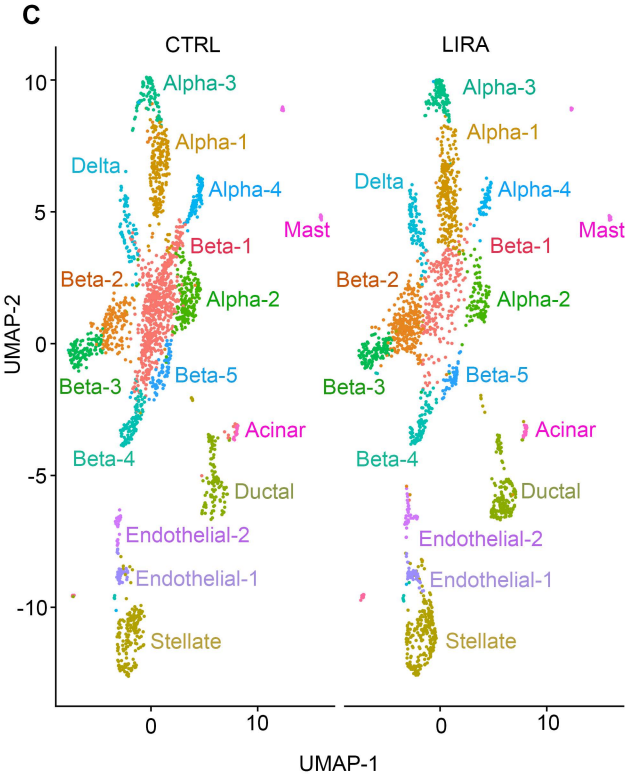


B

Age	Sex	BMI	HbA1c (%)
40	Male	30.7	5.2

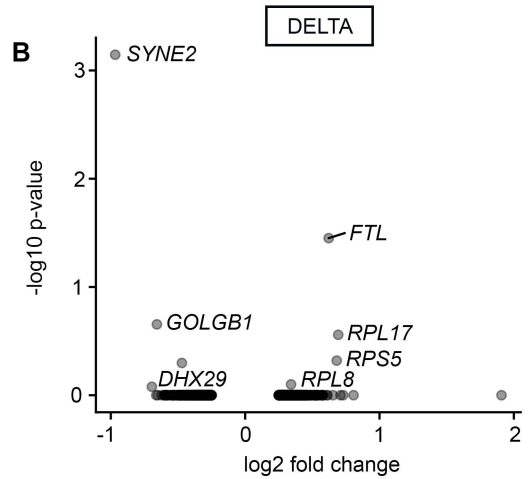
A

Donor	Age	Sex	BMI	HbA1c (%)
D1	61	Male	28.8	5.1
D2	66	Male	27.0	4.7
D3	40	Male	30.7	5.2



A

GENE	Alpha-1		Alpha-2		Alpha-3		Alpha-4	
	p-value	avg_logFC	p-value	avg_logFC	p-value	avg_logFC	p-value	avg_logFC
<i>INS</i>	9.21E-55	1.38824	1.14E-07	-0.561265	n.s.	n.s.	8.19E-08	-0.394865
<i>IAPP</i>	2.65E-51	1.66715	n.s.	n.s.	1.08E-12	1.616480	n.s.	n.s.
<i>PCSK1</i>	5.04E-46	1.63618	n.s.	n.s.	0.0111255	1.794607	n.s.	n.s.
<i>MAFA</i>	0.0005178	0.4388932	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.



A

Age	Sex	BMI	HbA1c (%)
37	Male	31.9	5.6

B

Age	Sex	BMI	HbA1c (%)
25	Male	31.3	5.9

