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## Supplementary Materials

### Table 1. List of Primers Used for PCR

Gene	Primers
<i>Cox6a2 promoter</i>	Forward 5'-CGGGGTACCCCGACAGGCTTGATGGC-3' Reverse 5'-GAAGATCTAAGGGAGGCTAGGAATGG-3'
<i>Cox6a2 promoter mutation</i>	Forward 5'-CTCCTCCCCACTCGCAGCCAATAGAACTTTGAGCCGGCACATGGATGGCT-3' Reverse 5'-AGCCATCCATGTGCCGGCTCAAAGTTCTATTGGCTGCGAGTGGGGAGGAG-3'
<i>Cox6a2</i>	Forward 5'-CGGGATCCATGGCTCTGCCTCTTAAGGTC-3' Reverse 5'-AAGGAAAAAAGCGGCCGCTCAAGGCTGCTCGTAGCCGGT-3'
<i>Ppif (CypD)</i>	Forward 5'-CGGGATCCATGTACCCATACGACGTCCCAGACTACGCTATGCTAGCTCTGCC CTGCGGT-3' Reverse 5'-AAGGAAAAAAGCGGCCGCTTAGCTCAACTGGCCACAGTC-3'

### Table 2. List of Primers Used for Real-Time PCR

Gene	Primers
<i>Ppif (CypD)</i>	Forward 5'-CCCCTCTGTGTAAGTGG-3' Reverse 5'-TGGGATGACCCTGTGGAA-3'
<i>Cox6a2</i>	Forward 5'-TGACCTTTGTGCTGGCTCT-3' Reverse 5'-GAAGGGCTTGGTTTCGGAT-3'
<i>Gapdh</i>	Forward 5'-CCTTCATTGACCTCAACTAC-3' Reverse 5'-TCGCTCCTGGAAGATGGTGAT-3'
<i>Actin</i>	Forward 5'-GTAAAGACCTCTATGCCAACA-3'
(beta)	Reverse 5'-GGACTCATCGTACTCCTGCT-3'

### Table 3. List of Primers Used for ChIP Assay

Gene	Primers
<i>Cox6a2 promoter</i>	Forward 5'-GGGGCGTATTTCACTTTA-3' Reverse 5'-GAGGCAGAGCCATTGTTG-3'

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## Supplementary Methods

### Determination of Plasma GLP-1

Blood samples were collected from the tail vein of both GK-sham and GK-RYGB rats 2 h after feeding. The plasma GLP-1 level was determined by the Glucagon-Like Peptide-1 (Active) ELISA Kit (# EGLP-35K) according to the manufacturer's instructions.

### Supplementary Figure Legends

#### **Supplementary Figure 1.** *COX6A2 protein levels in islets and INS-1 832/13 cells.*

(A) Western blot analysis of COX6A2 protein levels in islets infected with Ad-GFP or Ad-GFP-COX6A2 adenovirus for 72 hours.  $\beta$ -actin was used as a loading control. Data are mean  $\pm$  S.E.M. n=5. \*p<0.05.

(B) COX6A2 protein expression in vector and COX6A2-overexpressing INS-1 832/13 cells.  $\beta$ -actin was used as a loading control. Data are mean  $\pm$  S.E.M. n=6. \*\* p<0.01.

(C) COX6A2 protein levels were examined in the scramble and COX6A2 knockdown INS-1 832/13 cells.  $\beta$ -actin was used as a loading control. Data are mean  $\pm$  S.E.M. n=4.

\*\* p<0.01.

#### **Supplementary Figure 2.** *Deficiency of COX6A2 attenuated STZ-induced $\beta$ -cell apoptosis.*

(A) The islets isolated from *Cox6a2*<sup>+/+</sup> and *Cox6a2*<sup>-/-</sup> mice were cultured with vehicle or 300  $\mu$ M STZ for 15 hours. Then cleaved caspase-3 levels were determined by

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western blot. Data are means  $\pm$  S.E.M of six mice per group. \*,  $p < 0.05$ .

**(B)** Cleaved caspase-3 levels were assessed in the scramble and COX6A2 knockdown INS-1 832/13 cells following treatment with vehicle or 300  $\mu$ M STZ for 15 hours. Data are means  $\pm$  S.E.M.  $n=3$ . \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ .

**Supplementary Figure 3.** *Decreased COX6A2 inhibited the activation of both caspase-3 and caspase-9 in GK rat islets.*

**(A)** COX6A2 protein expression in islets from Wistar, GK-vehicle, and GK-Cox6a2-AAV rats. Data are means  $\pm$  S.E.M of four rats per group. \*\*,  $p < 0.01$ .

**(B)** Immunofluorescence of cleaved caspase-3 (red), insulin (green), and DAPI (blue) in the pancreata of GK-vehicle and GK-Cox6a2-AAV rats. Scale bar, 20  $\mu$ m.

**(C)** Quantification of cleaved caspase-3-positive  $\beta$ -cell ratio in **(B)**. Data are means  $\pm$  S.E.M.  $n=4$  rats per group. \*\*,  $p < 0.01$ .

**(D)** The cleaved caspase-9 and caspase-9 levels in islets from Wistar, GK-vehicle, and GK-Cox6a2-AAV rats. Data are means  $\pm$  S.E.M of six rats per group. \*\*,  $p < 0.01$ .

**Supplementary Figure 4.** *Overexpression of COX6A2 does not affect CypD mRNA expression.*

The mRNA levels of CypD in vector and COX6A2-overexpressing INS-1 832/13 cells. Data are means  $\pm$  S.E.M.  $n=4$ .

**Supplementary Figure 5.** *PKA mediates the inhibition of GLP-1 signaling on COX6A2*

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*expression in  $\beta$ -cells.*

(A) Plasma GLP-1 levels in GK-sham and GK-RYGB rats. Data are means  $\pm$  S.E.M. n=3. \*, p< 0.05.

(B) Activation of PKA reduced COX6A2 protein expression. INS-1 832/13 cells were cultured in G30 medium with or without 10  $\mu$ M PKA agonist 6-Bnz-cAMP for 3 days. Data are means  $\pm$  S.E.M. n=3. \*\*, p< 0.01.

(C) PKA inhibition reversed the suppressive effect on COX6A2 mRNA expression induced by exendin-4. INS-1 832/13 cells were incubated in G30 medium in the presence or absence of 10 nM exendin-4 or 30  $\mu$ M PKA inhibitor Rp-8-Br-2'-O-MB-cAMPs (Rp-cAMP) for 3 days. Data are means  $\pm$  S.E.M. n=3. \*, p< 0.05; \*\*, p< 0.01.

**Supplementary Figure 6.** *Exendin-4 increases the  $\beta$ -cell area and improves hyperglycemia in GK rats.*

(A) Immunofluorescence of insulin (green) and DAPI (blue) in the pancreata of Wistar, GK-vehicle, and GK-exendin-4 rats. Scale bar, 200  $\mu$ m.

(B) Quantification of insulin-positive cell area in (A). Data are means  $\pm$  S.E.M. n=3 rats per group. \*, p< 0.05; \*\*, p< 0.01.

(C) Plasma glucose levels in Wistar, GK-vehicle, and GK-exendin-4 rats. Data are means  $\pm$  S.E.M. n=3. \*\*, p< 0.01 vs. GK-vehicle.