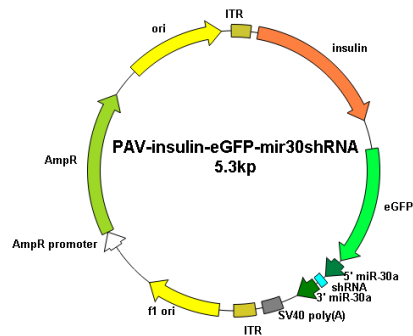


## Online supplemental information:

### Supplemental Materials:

#### 1. The vector map for AAV- $\beta$ -shSTRA6



#### 2. Apo-RBP4 preparation

Apo-RBP4, retinol-free RBP4, was prepared as previously described(1, 2). Briefly, holo-RBP4 were incubated with 40% butanol-60% diisopropyl ether at 30°C overnight and centrifuged at 5000 rpm for 5min, and the bottom phase was collected. This step was repeated twice more with 1-h incubations of 40% butanol–60% diisopropyl ether. Apo- and holo-RBP4 were measured by native polyacrylamide gel electrophoresis (PAGE) and analyzed by UV spectrum from 250 to 350 nm while the 330/280 nm peak ratio near 0.9 indicated the holo-RBP4(1-4).

#### References:

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**Supplemental Table 1. The primers used in quantitative real-time PCR**

**Supplemental Table 2. General parameters of mice injected with either AAV-β-GFP or AAV-β-shSTRA6**

**Supplemental Table 3. General parameters of mice injected with either AAV-GFP or AAV-shRBP4**

**Supplemental Figure 1.** The expression levels of RBP4 in primary islets and β cells: A. Quantitative RT-PCR analysis of RBP4 mRNA expression levels in islets isolated from C57BL/J mice and INS-1 cell line while the expression level in liver was used as positive control.

**Supplemental Figure 2.** Glucose stimulated insulin secretion levels from the primary islets after 80μg/ml apo-RBP4 treatment. A. Apo- and holo-RBP4 were measured by native polyacrylamide gel electrophoresis (PAGE). B. Apo- and holo-RBP4 were analyzed by UV spectrum from 250 to 350 nm and the 330/280 nm peak ratio near 0.9 indicated the holo-RBP4. C. 2.0mM (basal) or 16.8mM glucose induced insulin secretion levels after 80μg/ml apo-RBP4 treatment for 24h and the corresponding stimulatory index.

**Supplemental Figure 3.** The glucose homeostasis in RBP4-Tg mice. A. the mouse(left) and human(right) RBP4 mRNA expression level in the liver of WT and RBP4-Tg mice presented as  $2^{-\Delta CT}$ ; B. the mouse(left) and human(right) RBP4 levels in serum of WT and RBP4-Tg mice as measured by corresponding ELISA kits; C-D. fasting glucose levels(C) and fed glucose levels(D) in serum of WT and RBP4-Tg mice at indicated age; E-F. glucose tolerance test (E) and insulin tolerance test(F) were performed on 8-week-old(left), 12-week-old(middle) and 16-week-old (right) WT and RBP4-Tg

mice with measurement of blood glucose concentrations; G-H. fasting insulin levels(G) and fed insulin levels(H) in serum of WT and RBP4-Tg mice at indicated age.

**Supplemental Figure 4.** The glucose homeostasis and  $\beta$  cell function in the AAV-shRBP4 treated RBP4-Tg mice. A-C. Glucose tolerance test(A), GSIS level(B) and the corresponding insulinogenic index(C) in AAV-GFP or AAV-shRBP4 treated RBP4-Tg mice. D-E. GSIS level in primary islets isolated from AAV-GFP or AAV-shRBP4 treated RBP4-Tg mice (D) and the stimulatory index(E).

**Supplemental Figure 5.** A. The mRNA expression levels of pro-inflammation cytokines (*TNF $\alpha$* , *IL-1 $\beta$* , *F4/80* and *MCP-1*) and anti-inflammation cytokines (*IL-10* and *IL-4*) in islets isolated from WT and RBP4-Tg mice.

**Supplemental Figure 6.** A. STRA6 expression levels in INS-1E cells after transfected with scrambled or STRA6-targeting siRNA and then incubated with 80 $\mu$ g/ml RBP4; B. Phosphorylation levels of JAK2/STAT1 signaling cascade in INS-1E cells after transfected with scrambled or STRA6-targeting siRNA and then incubated with 80 $\mu$ g/ml RBP4 for 24h(n=3-4).

**Supplemental Figure 7.** A. Phosphorylation levels of JAK2/STAT1/ISL-1 signaling cascade in INS-1E cells after pretreated with or without 50 $\mu$ mol/L fludarabine for 12h and then incubated with 80 $\mu$ g/ml RBP4.

**Supplemental Table 1. the primers used in quantitative real-time PCR**

<b>Gene</b>	<b>Forwards primers</b>	<b>Reverse primers</b>
mouse- $\beta$ -actin	AGCCATGTACGTAGCCATCC	GTGGTGGTGAAGCTGTAGCC
rat- $\beta$ -actin	AACACCCAGCCATGTACGTAG	GAACCGCTCATTGCCGATAGT
mouse-RBP4	AGTCAAGGAGAACTTCGACAAGG	CTTGGCTGTGGCGCTCATA
rat-RBP4	ATCATCGCTGAGTTTTCTGTGG	CTTCTGTGTCTGTGAAAGTGCC
human-RBP4	AGGAGAACTTCGACAAGGCTC	GAGAACTCCGCGACGATGTT
mouse -STRA6	GGCTCTGCTCTACTATCCAGC	GGAGACTCTGCACAAGTTGTACT
rat-STRA6	ACTGGCTGGCCTCAATCCTCA	ATAATGGCTATTTGGCGGGTGC
mouse-Glut2	TCAGAAGACAAGATCACCGGA	GCTGGTGTGACTGTAAGTGGG
mouse-Gck	TGAGCCGGATGCAGAAGGA	GCAACATCTTTACTACTGGCCT
mouse-Pdh	GGACTTCGGGTGAGTGAATGC	TCTGAGAAGATTGTCGGGGA
mouse-kir6.2	CCTTTTCTCCATCGAGGTCCA	GCCCGACGATATTCTGCACA
mouse-Cav1.3	CCCAAAGAAAACGTCAGCAATAC	GAGGGATAAACAGAAAAGGGCA
mouse-Cav1.2	TCCCAGCACATCCCTACTC	ACTGACGGTAGAGATGGTTGC
mouse-Cav2.1	TTGAGGCTGGAATTAAGATCGTG	CTCAGTGTCCGTAGGTCAAAC
mouse-Cav3.2	CGTGACACTGGGCATGTTC	TCCGTCCAGAGAGTATTCCATC
mouse-Snap25	CAACTGGAACGCATTGAGGAA	GGCCACTACTCCATCCTGATTAT
mouse-Vamp2	GCTGGATGACCGTGCAGAT	GATGGCGCAGATCACTCCC
mouse-connexin36	CAGCAGCACTCCACTATGATTG	CGTACACCGTCTCCCCTACAA
mouse-Ins1	CACTTCCTACCCCTGCTGG	ACCACAAAGATGCTGTTTGACA
mouse-Ins2	TGGAGGCTCTTACCTGGTG	TCTACAATGCCACGCTTCTG
mouse-MafA	AGGAGGAGGTCATCCGACTG	CTTCTCGTCTCCAGAATGTG
mouse-Neurod1	ATGACCAAATCATAACAGCGAGAG	TCTGCCTCGTGTTCCCTCGT
mouse-Pdx1	CCCCAGTTTACAAGCTCGCT	CTCGGTTCCATTCGGGAAAGG
mouse-Is11	ATGATGGTGGTTTACAGGCTAAC	TCGATGCTACTTCACTGCCAG
mouse-Pax6	TACCAGTGTCTACCAGCCAAT	TGCACGAGTATGAGGAGGTCT
mouse-Lmx1 $\alpha$	TTCAAAGTGCGATTGAGACCTC	CAGTTTCTCGTAGTGGTACTTGC
mouse -Hnf4 $\alpha$	ATGCGACTCTCTAAAACCCTTG	ACCTTCAGATGGGGACGTGT
mouse -Nkx6.1	CTGCACAGTATGGCCGAGATG	CCGGGTTATGTGAGCCCAA
mouse -F4/80	CTTTGGCTATGGGCTTCCAGTC	GCAAGGAGGACAGAGTTTATCGTG
mouse-MCP-1	CCACTCACCTGCTGCTACTCA	TGGTGATCCTCTTGTAGCTCTCC
mouse-Interleukin1 $\beta$	GAAATGCCACTTTTGACAGTG	TGGATGCTCTCATCAGGACAG
mouse-TNF $\alpha$	ACGGCATGGATCTCAAAGAC	AGATAGCAAATCGGCTGACG
mouse-IL10	GCTCTTACTGACTGGCATGAG	CGCAGCTCTAGGAGCATGTG
mouse-IL4	GGTCTCAACCCCCAGCTAGT	GCCGATGATCTCTCTCAAGTGAT
rat-Ins1	GATCCACAATGCCACGCTTCT	ACCCAAGTCCCGTCGTGAAGT
rat-Ins2	TGTAGAAGAATCCACGCTCCC	GGCTTTTGTCAAACAGCACCT

rat-Glut2	GGGACAAACTCGGAAGGATCA	CCTGAGTGTGGTTGGAGCAA
rat-Gck	GTGGAGCCCAGTTGTTGACT	GCTCGACCCTCCACATGATA
rat-Pdh	CTGCGCTCCATGAGGAAGAT	TAGACGATGAAGGTCACATTTCTTA
rat-kir6.2	GTCAGGGGCTCAGTAAGCAA	CTTGCACCAACCTCTGGACT
rat-Cav1.3	ATCCAAGCTCAGATCGCACG	ACGGCTGTAGGGTCTGACAT
rat-Cav1.2	GAAACATGAGCATGCCACAA	CAGTAGCGGCTGAACTTGA
rat-Cav2.1	TTGCGAGTAATATCGCCCC	AGCTCCACCCTTTGCGATTT
rat-Cav3.2	CGGCGCCTGGAGAGGA	CATCCAGGGACTTGGGCTG
rat-Snap25	TGGATGAGCAAGGCGAACAA	TCCTGATTATTGCCCCAGGC
rat-Vamp2	GCCATATCTTTCAGCCCCCT	GGGTGTTAAGGACAACCGGA
rat-connexin36	CTGGGATGGCGGAAGATCAA	GAGTCCTGCCGAAATTGGGA
rat-MafA	ATTCTGGAGAGCGAGAAGTGC	ATTTCTCCTTGTACAGGTCCCCG
rat-Neurod1	AGCCCCCTAACTGATTGCAC	TCGGTGGATGGTTTCGTGTTT
rat-Pdx1	CCTTTCCCGAATGGAACCGA	TTTTCCACGCGTGAGCTTTG
rat-Is11	TGAAACCAGACCCGGATGACT	CACAAACAGCCCGAGAAGACC
rat-Lmx1 $\alpha$	TGCCAGCATTGCCACTACCAT	CCAGCGAGCCAAGATGAAGAA
rat-Hnf4 $\alpha$	GTCATGGTCAGTGTGAACGC	TGTGGTTCTTCCTCACGCTC
rat-Nkx6.1	CTGCTCTGCCGACCAAGTAA	CGAAAGAGGAGTGAGTCGGG
rat-Pax6	CAATCTGCTCCTGGGTAAAAG	AACTAAGGATGCTGAACGGAC

The primer sequences for indicated gene/protein were shown. Abbreviations: RBP4, retinol binding protein 4; STRA6, stimulated by retinoic acid 6; Glut2, glucose transport protein 2; Gck, glucokinase; Pdh, pyruvate dehydrogenase; Neurod1, neuronal differentiation 1; Pdx1, pancreatic duodenal homeobox 1; Is11, LIM-homeodomain transcriptional factor Islet-1, Hnf4 $\alpha$ , hepatocyte nuclear factor 4 $\alpha$ ; Nkx6.1, NK homeobox factor 6.1; Pax6, paired box 6.

**Supplemental Table 2. General parameters of mice injected with either AAV- $\beta$ -GFP or AAV- $\beta$ -shSTRA6**

	<b>WT+AAV-<math>\beta</math>-GFP</b>	<b>RBP4-Tg+AAV-<math>\beta</math>-GFP</b>	<b>RBP4-Tg+AAV-<math>\beta</math>-shSTRA6</b>	<b><i>p</i> value</b>	<b><i>p</i> value (WT+AAV-<math>\beta</math>-GFP vs RBP4-Tg+AAV-<math>\beta</math>-GFP)</b>	<b><i>p</i> value (RBP4-Tg+AAV-<math>\beta</math>-shSTRA6 vs RBP4-Tg+AAV-<math>\beta</math>-GFP)</b>
<b>Initial body weight</b>	25.23 $\pm$ 1.43	25.77 $\pm$ 1.23	25.39 $\pm$ 1.92	0.83	0.49	0.69
<b>Final Body weight(g)</b>	26.93 $\pm$ 1.02	27.27 $\pm$ 1.5	27.33 $\pm$ 1.4	0.85	0.65	0.95
<b>Liver weight(g)</b>	1.11 $\pm$ 0.15	1.19 $\pm$ 0.08	1.15 $\pm$ 0.09	0.46	0.26	0.42
<b>Subcutaneous fat weight (g)</b>	0.6 $\pm$ 0.15	0.63 $\pm$ 0.22	0.59 $\pm$ 0.13	0.94	0.84	0.75
<b>Epididymal fat weight(g)</b>	0.59 $\pm$ 0.23	0.8 $\pm$ 0.25	0.76 $\pm$ 0.21	0.27	0.16	0.78

All values are mean  $\pm$  SD, n = 7-10. Significant *p* values are indicated in bold.

**Supplemental Table 3. General parameters of mice injected with either AAV-GFP or AAV-shRBP4**

	<b>Control+AAV-GFP</b>	<b>db/db+AAV-GFP</b>	<b>db/db+AAV-shRBP4</b>	<b><i>p</i> value</b> (db/db+AAV-shRBP4 vs db/db+AAV-GFP)
<b>Initial body weight</b>	18.82±1.22	30.76±3.72	30.31±3.36	0.79
<b>Final Body weight(g)</b>	21.83±1.32	40.31±1.88	36.96±2.75	<b>0.01</b>
<b>Liver weight(g)</b>	0.97±0.09	2.38±0.49	2.13±0.34	0.14
<b>Subcutaneous fat weight (g)</b>	0.16±0.06	2.41±0.3	2.27±0.48	0.19
<b>Epididymal fat weight(g)</b>	0.19±0.06	1.98±0.25	1.97±0.2	0.83

All values are mean ± SD, n = 7-10. Significant *p* values are indicated in bold.