Supplemental Materials

Supplemental Figure Legends

Figure S1. LRP1 knockout impairs β-cell hyperplasia during diet-induced obesity (DIO).

As described in Figure 1, *Lrp1-βKO* and control mice were subjected to doxycycline treatment followed by HFD. (**A**) Immunofluorescence of LRP1 (red) in pancreas sections from mice after 8 months of HFD. Upper panels: LRP1 signal (red) only. Lower panels: merged with insulin (green) and DAPI (blue). (**B** and **C**) Insulin tolerance test (**B**) and body composition (**C**) on mice after 6 months of HFD. n=9 (control) and 7 (*Lrp1-βKO*). Data are presented as the mean±SEM. *P<0.05 for *Lrp1-βKO* versus control mice by two-tailed unpaired student's *t*-test. (**D**) Representative H&E stains of pancreas sections from mice after 8 months of HFD. (**E**) Pancreas sections of mice after 8 months of HFD were subjected to insulin immunostaining as described in Figure 1F. Areas of insulin-positive cells in individual islets are presented as dots.

Figure S2. Proliferation, insulin processing and endoplasmic reticulum (ER) stress in LRP1-deficient β-cells during DIO.

Pancreatic islets were isolated from *Lrp1-βKO* and control mice after doxycycline treatment and 8 months of HFD and subjected to RT-qPCR of cell cycle regulator (**A**), insulin processing (**B**) and ER stress (**C**) genes. *Xbp1t*: both unspliced (*Xbp1u*) and spliced (*Xbp1s*) mRNAs. n=3-4 mice per genotype. Data are presented as the mean±SEM. *P<0.05 for *Lrp1-βKO* versus control mice by two-tailed unpaired student's *t*-test.

Figure S3. LRP1 regulates insulin signaling in β-cells during DIO.

Pancreatic islets were isolated from mice 8 months after doxycycline treatment and subjected to Western blotting. (**A** to **D**) Quantitation of Western blots of insulin signaling molecules related to Figure 4B. n=2-6 mice per condition. (**E** and **F**) Representative Western blots (**E**) and quantitation (**F**) of CREB signaling molecules. n=2 or 4 mice per condition. Data are presented as the mean±SEM. *P<0.05 for *Lrp1-βKO* versus control mice, ##P<0.01 for RD versus HFD by two-tailed unpaired student's *t*-test.

Figure S4. LRP1 regulates mTORC1 signaling in β-cells during DIO.

From mice 8 months after doxycycline treatment, (**A** and **B**) Immunofluorescence of phosphorylated S6K1 (pS6K1) on pancreas sections. (**A**) Representative images. Upper panels: pS6K1 signal (red) only. Lower panels: merged with insulin (green) and DAPI (blue). (**B**) pS6K1 signal intensity in insulin-positive cells is quantitated in individual mice (3 20X sections per mouse). (**C** to **F**) Quantitation of Western blots of mTORC1 and Erk signaling molecules related to Figure 5, A and B. n=3-5 mice per condition. Data are presented as the mean±SEM. *P<0.05 for *Lrp1-βKO* versus control mice, ##P<0.01 for RD versus HFD by two-tailed unpaired student's *t*-test.

Figure S5. Glucose-dependent activation of Erk and mTORC1 signaling in β-cells during DIO.

Quantitation of Western blots of Erk and mTORC1 signaling molecules related to Figure 5C. n=2-3 samples per condition. Data are presented as the mean±SEM. #P<0.05 for RD

versus HFD by two-tailed unpaired student's *t*-test.

Figure S6. LRP1 regulates insulin signaling in β-cells during DIO.

(**A**) Quantitation of IRS-2 Western blots related to Figure 5D. n=2 samples per condition. (**B** to **F**) As described in Figure 5C, overnight cultured islets from mice after 4 months of HFD were first quiesced in secretion assay buffer with 3 mM glucose, and then treated with glucose, insulin and EGTA at indicated concentrations for 15 min. These islets were subjected to Western blotting of insulin signaling molecules as indicated. (**B**) Representative blots. (**C** to **F**) Quantitation of blots. n=2-3 samples per condition. Data are presented as the mean±SEM. #P<0.05 for RD versus HFD by two-tailed unpaired student's *t*-test.

Figure S7. PDGFRβ and ApoE in *Lrp1-βKO* islets.

From mice 8 months after doxycycline treatment, (**A** to **C**) Representative Western blots (**A**) and quantitation (**B** and **C**) of PDGFRβ and ApoE with isolated pancreatic islets. n=1-3 mice per condition. (**D** and **E**) Immunofluorescence of ApoE on pancreas sections. (**D**) Representative images. Upper panels: ApoE signal (red) only. Lower panels: merged with insulin (green). (**E**) ApoE signal intensity in insulin-positive cells is quantitated in individual mice (3-5 20X sections per mouse). Data are presented as the mean±SEM.

Figure S8. Sphingomyelins and sphingoid bases in *Lrp1-βKO* islets during DIO.

As described in Figure 6, pancreatic islets from mice after doxycycline treatment and 8 months of HFD were assayed for sphingomyelins (**A**) and sphingoid bases (**B**) and

normalized against the protein content of islet samples. n=6 (control) and 4 (*Lrp1-βKO*) samples with 50 islets per sample. In every panel, the first group of columns from the left represent the sums of the following species. Data are presented as the mean±SEM. *P<0.05, **P<0.01 for *Lrp1-βKO* versus control by two-tailed unpaired student's *t*-test. N.D.: not detected.

Figure S9. PPARγ2 overexpression inhibits β-cell function during DIO.

As described in Figure 8, after 4 months of HFD, *Pparg2-βOE* and control mice were switched to doxycycline HFD for 2 weeks. (**A**) Body weights and (**B**) areas under plasma insulin curve (Figure 8C) of individual mice before and after doxycycline treatment are presented as line-connected dot pairs. n=4 (control) and 7 (*Pparg2-βOE*). ##P<0.01 by two-tailed paired student's *t*-test. (**C**) Pancreas sections of mice after doxycycline treatment were immunostained for insulin, and the stained areas (brown) were normalized against total pancreas area in individual mice. Data are presented as the mean±SEM.

Figure S10. PPARγ2 overexpression inhibits β-cell insulin signaling during DIO.

Quantitation of Western blots of PPARγ isoforms and insulin signaling molecules related to Figure 8D. n=3 mice per condition. Data are presented as the mean±SEM. *P<0.05, **P<0.01 for *Pparg2-βOE* versus control by two-tailed unpaired student's *t*-test.

Figure S11. *Apbb2* knockout does not change LRP1 protein level in islets.

Western blotting of LRP1 in isolated islets from *Apbb2*$^{+/+}$ and *Apbb2*$^{-/-}$ mice.

Figure S12. The role of LRP1 in β-cells during DIO.

Insulin signaling is essential for β-cell adaptation to DIO, by promoting β-cell proliferation and insulin production. (**A**) LRP1 in β-cells serves as a suppressor of PPARγ2, the key transcription factor for lipid metabolism, and the glucose-induced, Ca^{2+}-dependent activation of Erk and p85 S6K1. (**B**) In the absence of LRP1, overactivation of PPARγ2 and p85 S6K1 diminshes insulin signaling, β-cell hyperplasia and GSIS.

Table S1. Primers for RT-qPCR.

Supplemental Methods

Genotyping PCR

Approximately 3 mm of mouse tail tip was incubated in 80 µL 50 mM NaOH at 95°C for 1.5 hr. 8 µL 1M Tris-HCl (pH 8.0) was added for neutralization. After vortexing and a short spin down, 0.5-1 µL of supernatant was used as PCR template. Primer pairs for genotyping PCR were: 5'-GCAGGGCACACATAGCATGCTTAAGG-3' and 5'-AAGCTCTCCTGCTCAGACCTGGATCAC-3' for *Lrp1* floxed and wild-type alleles; 5'-CACCTGGAGACCTTAATGGGCCAAAC-3' and 5'-CGATTGGCAGGGCATCGAGC-3' for *MIP-rtTA*; 5'-GATTTCGACCAGGTTCGTTCACTCA-3' and 5'-GCTAACCAGCGTTTTCGTTCTGCCA-3' for *TRE-Cre*; 5'-AGCTCGTTTAGTGAACCGTCAGATCG-3' and 5'-CCATGCTCTGGGTCAACAGGAGAATC -3' for *TRE-Pparg2*; 5'-GCGTTTGTTCTTACAATCTTCAGTTAGCAGTGG-3' and 5'-TGGGAGGAACGGAGATTGAGGTGTG-3' for *Apbb2* knockout allele; 5'-GCGTTTGTTCTTACAATCTTCAGTTAGCAGTGG-3' and 5'-TGTGGGAGGAACGGAGATTGAGGGTAT-3' for *Apbb2* wild-type allele. The PCR program was: 95°C for 5 min, followed by 35 cycles of 95°C for 15 sec, 62°C for 30 sec, and 72°C for 30 sec, ended with 72°C for 3 min.

Insulin tolerance test

Mice were fasted for 4-6 hr and subjected to an i.p. injection of insulin (1 mU/g body weight). Tail blood was measured for glucose at 0, 30, 60, 120, 150 and 180 min with a Contour glucose meter (Bayer #82486543).

Figure S1

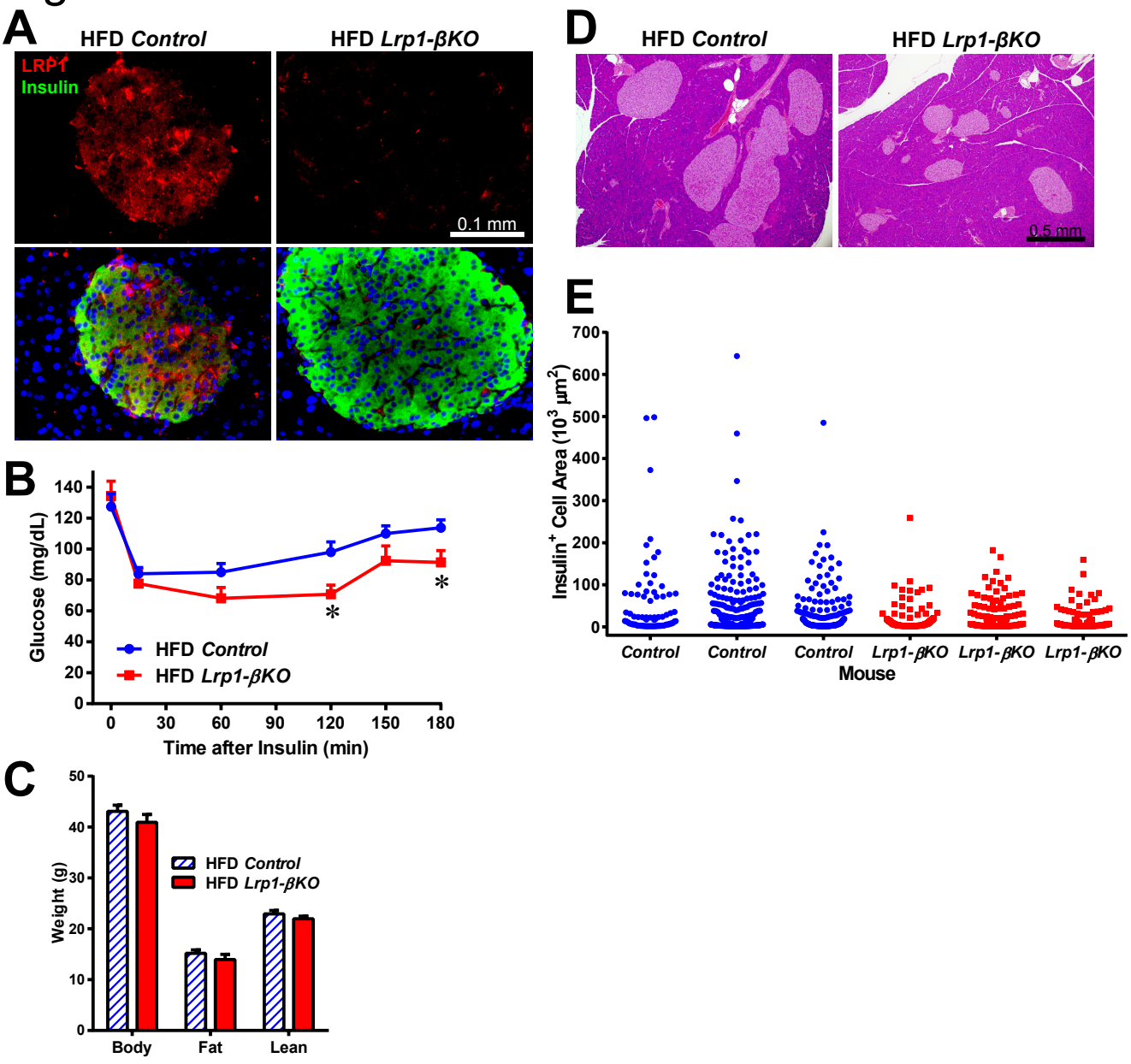

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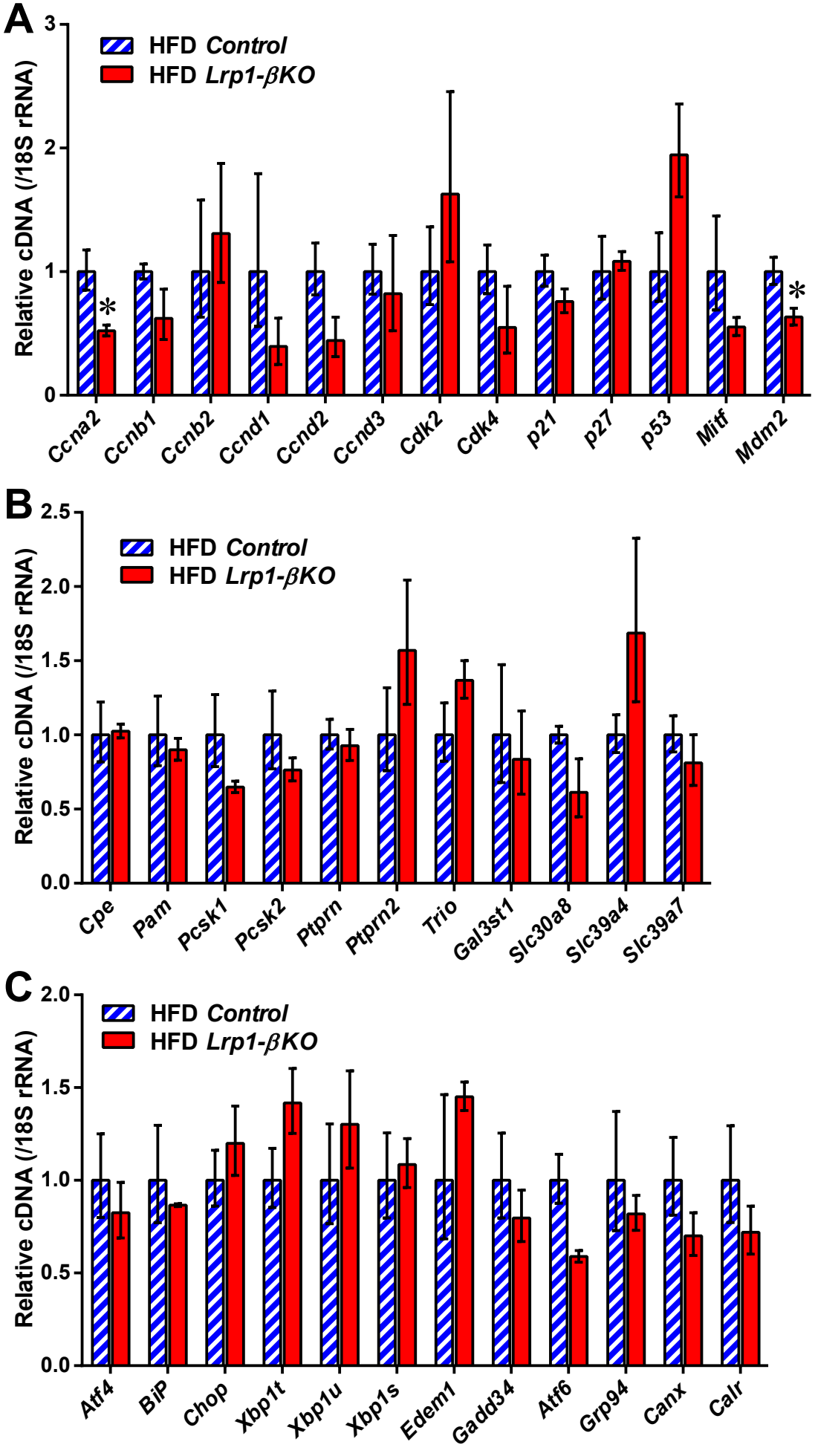
Figure S2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HFD Lrp1-βKO
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2
3
*
*
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Ccnd1
Ccnd2
Ccnd3
Cdk2
Cdk4
p21
p27
p53
Mitf
Mdm2
B
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HFD Lrp1-βKO
Relative cDNA (/18S rRNA)
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0.5
1.0
1.5
2.0
2.5
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Pcsk2
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Xbp1u
Xbp1s
Edem1
Gadd34
Atf6
Grp94
Canx
Calr

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Figure S3

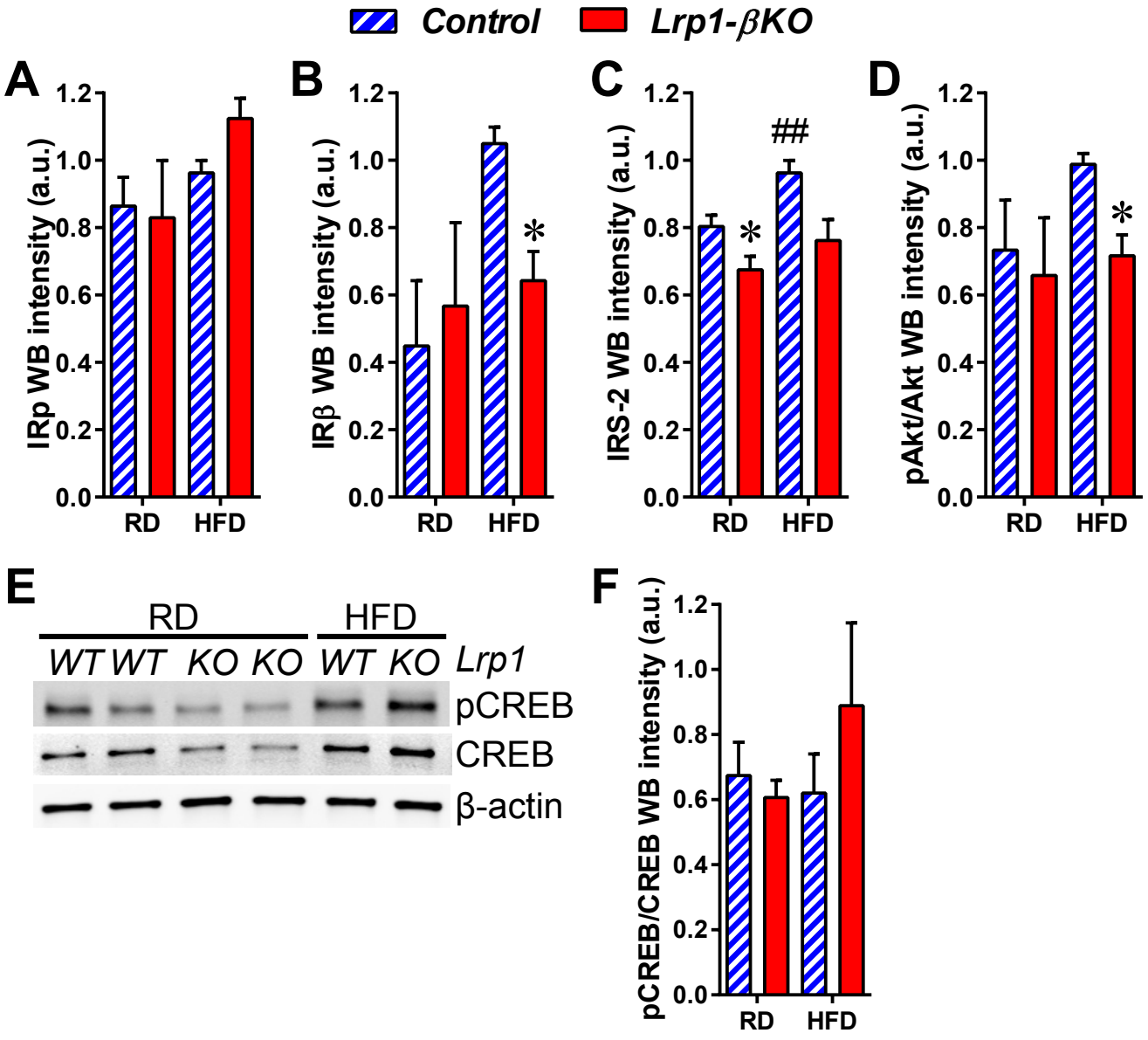

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Figure S4

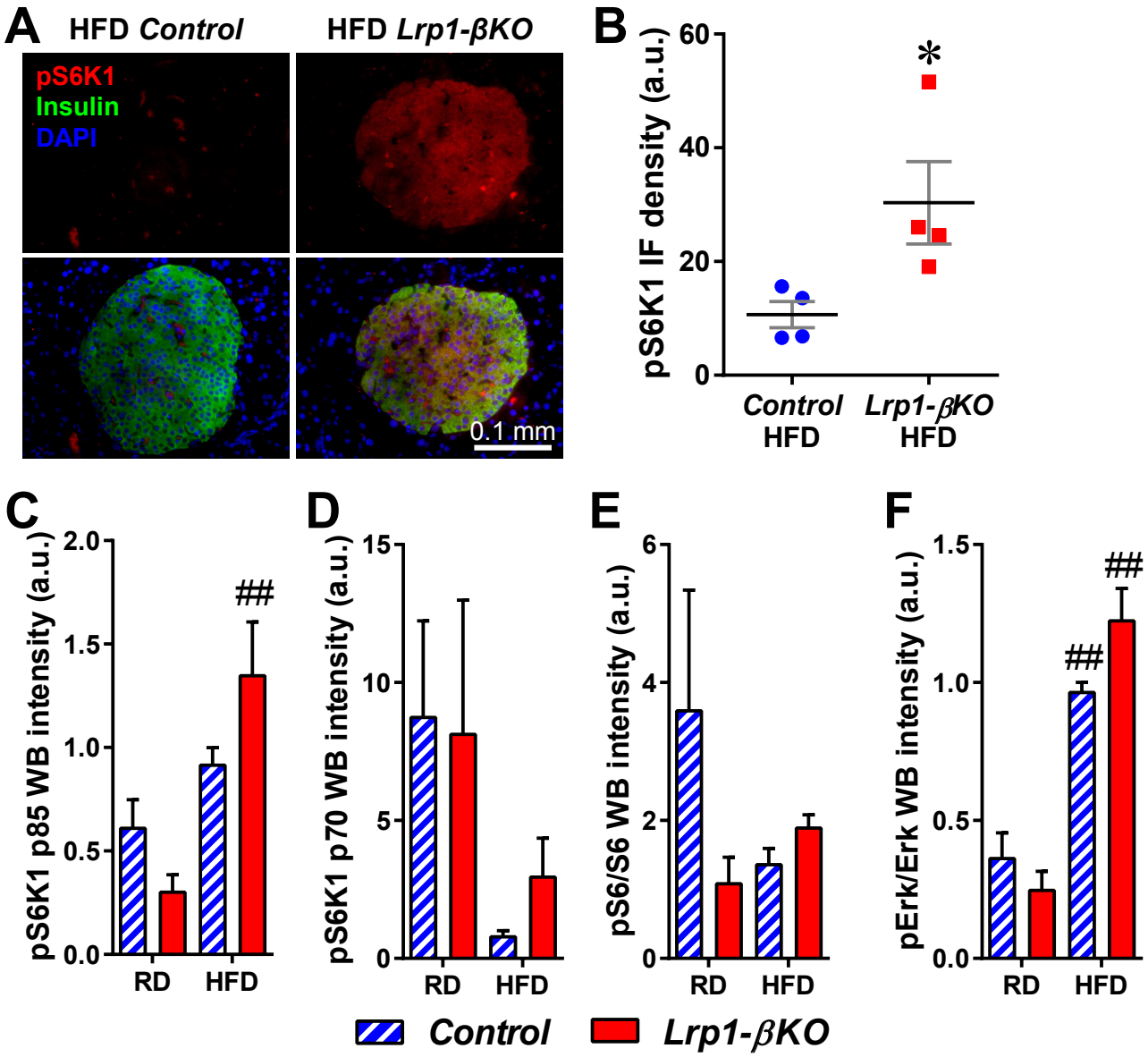

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Figure S5

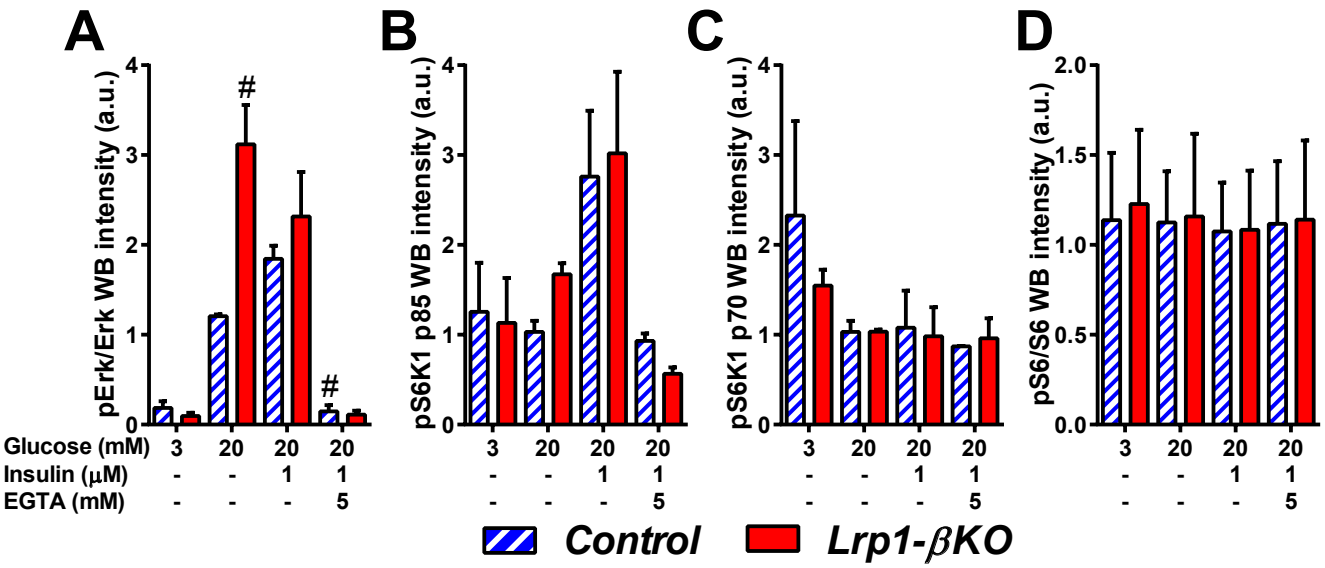
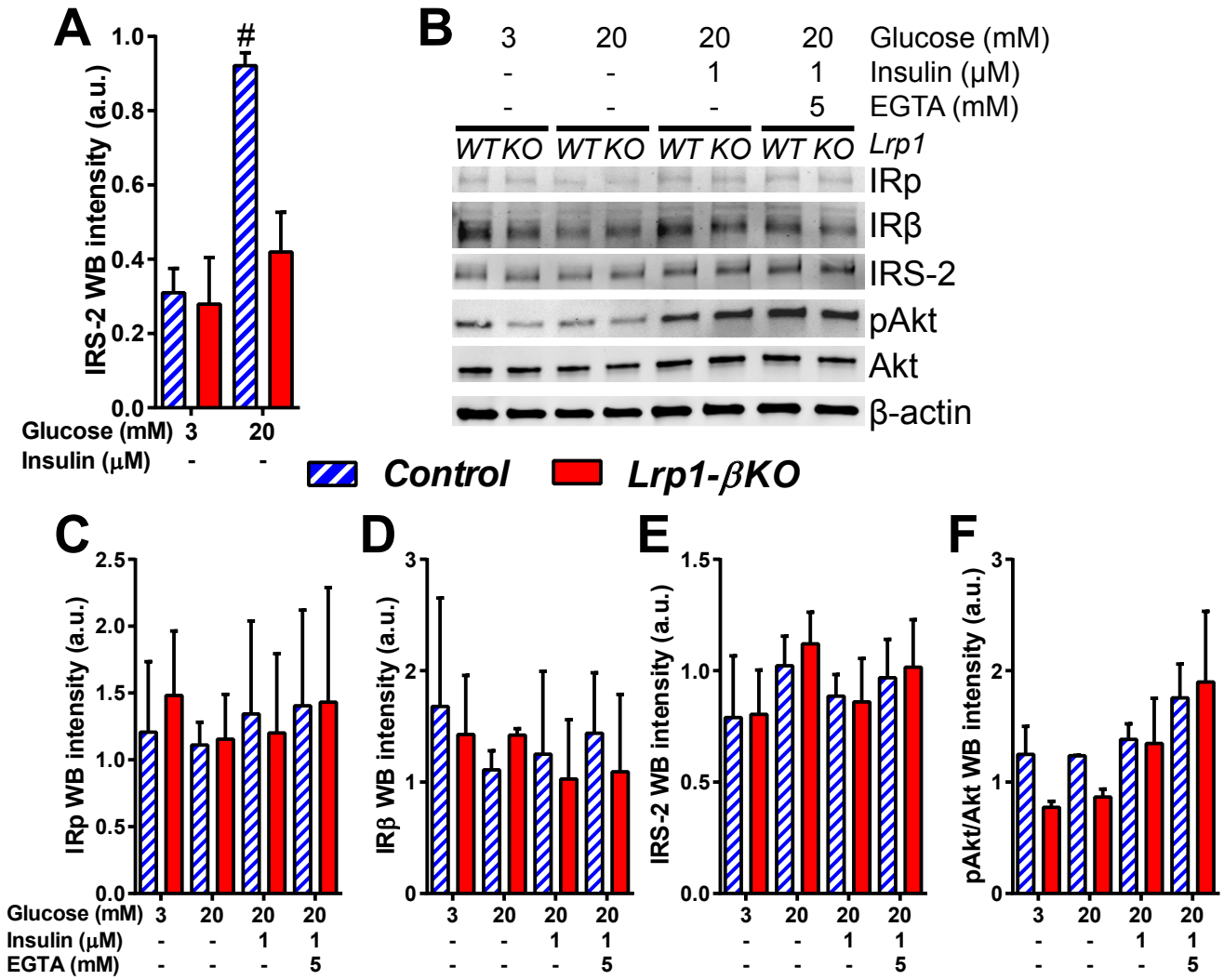


Figure S5. Glucose-dependent activation of Erk and mTORC1 signaling in β-cells during DIO.

Quantitation of Western blots of Erk and mTORC1 signaling molecules related to Figure 5C. n=2-3 samples per condition. Data are presented as the mean±SEM. #P<0.05 for RD versus HFD by two-tailed unpaired student's *t*-test.

Figure S6



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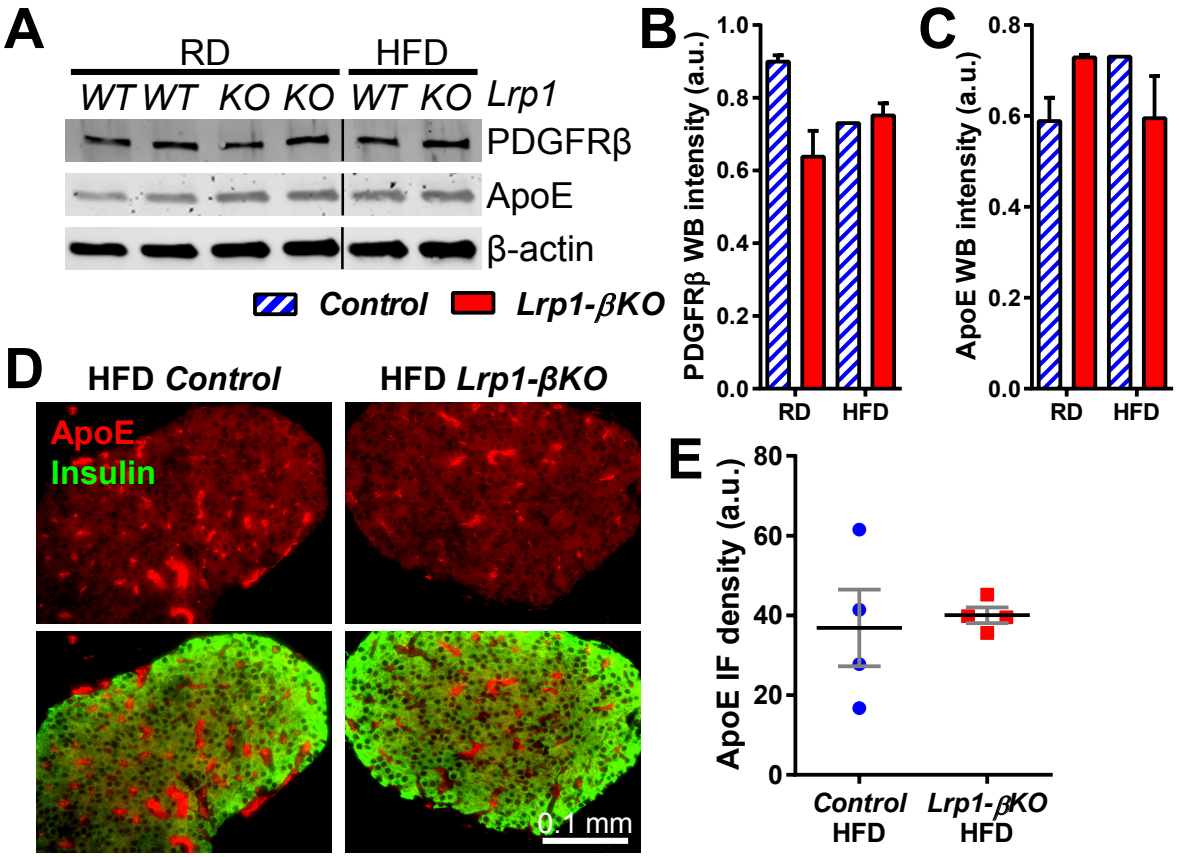

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Figure S8

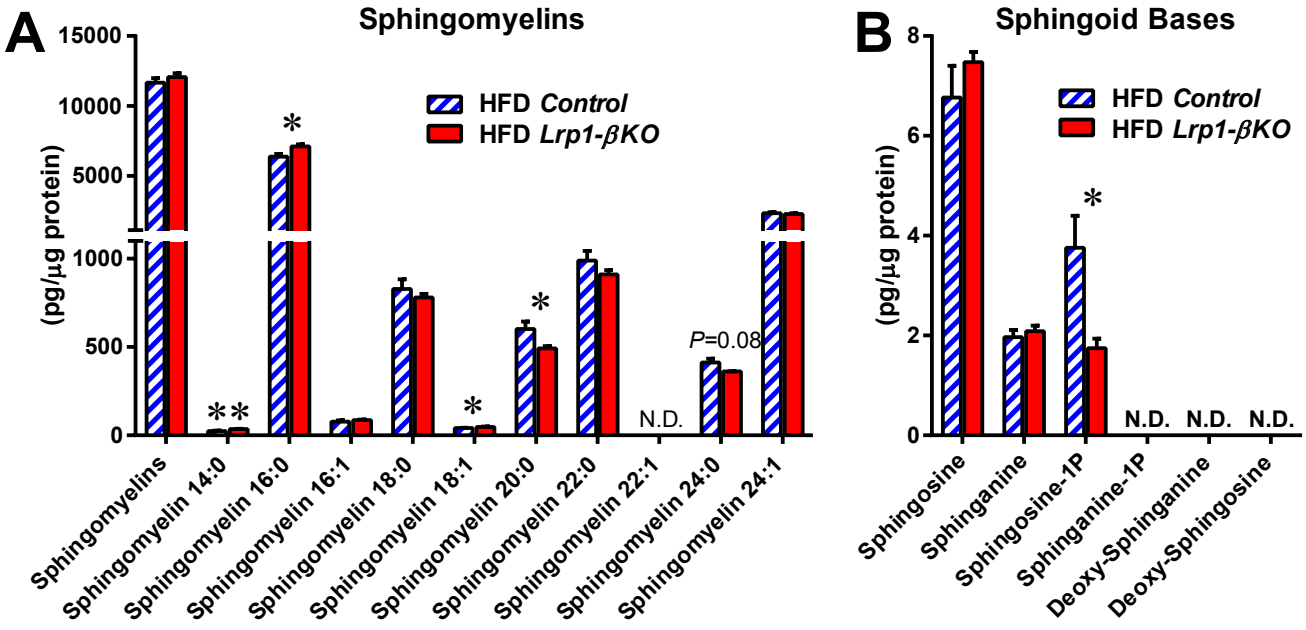

Figure S8. Sphingomyelins and sphingoid bases in *Lrp1-βKO* islets during DIO. As described in Figure 6, pancreatic islets from mice after doxycycline treatment and 8 months of HFD were assayed for sphingomyelins (**A**) and sphingoid bases (**B**) and normalized against the protein content of islet samples. n=6 (control) and 4 (*Lrp1-βKO*) samples with 50 islets per sample. In every panel, the first group of columns from the left represent the sums of the following species. Data are presented as the mean±SEM. *P<0.05, **P<0.01 for *Lrp1-βKO* versus control by two-tailed unpaired student's *t*-test. N.D.: not detected.

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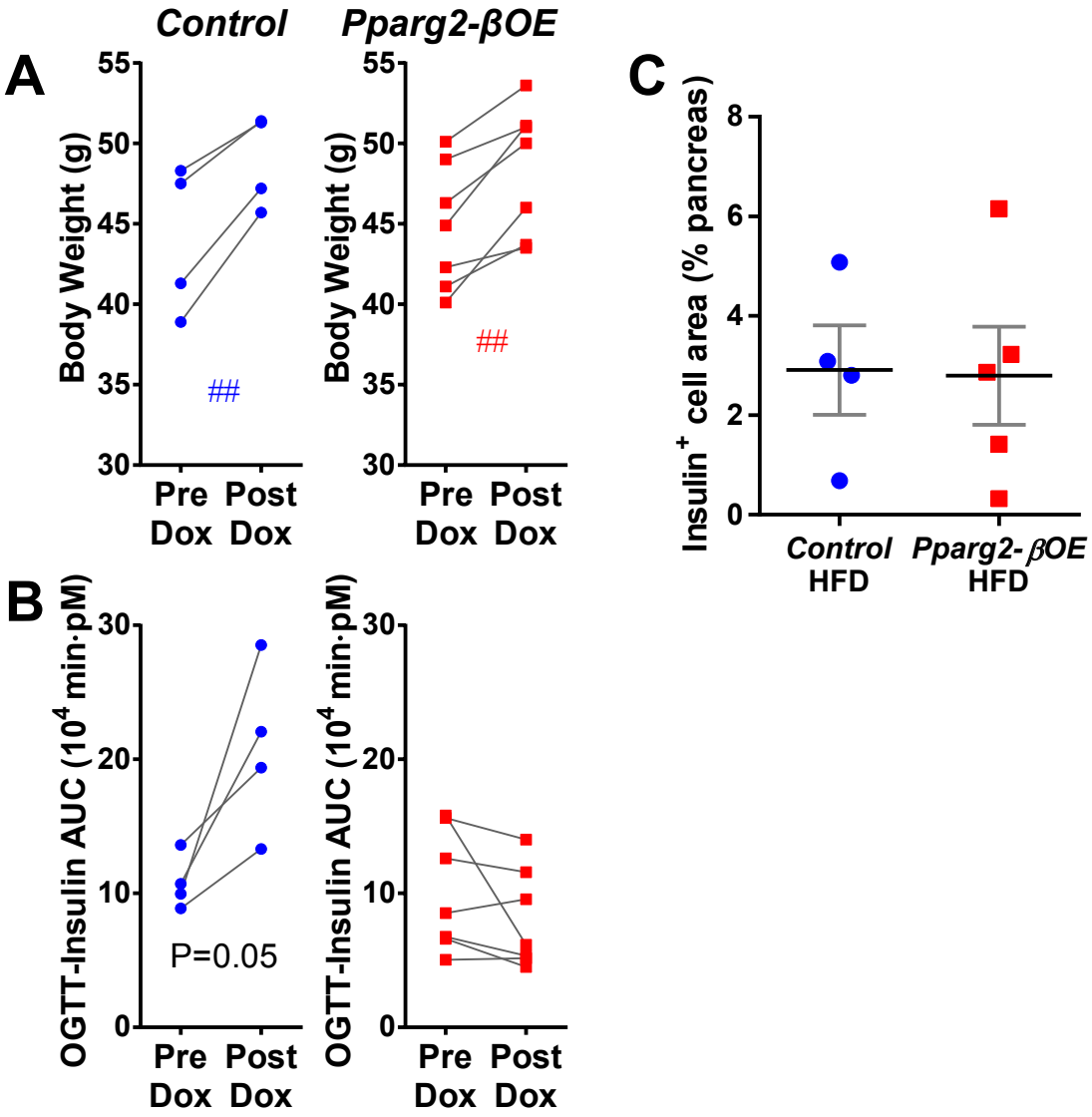

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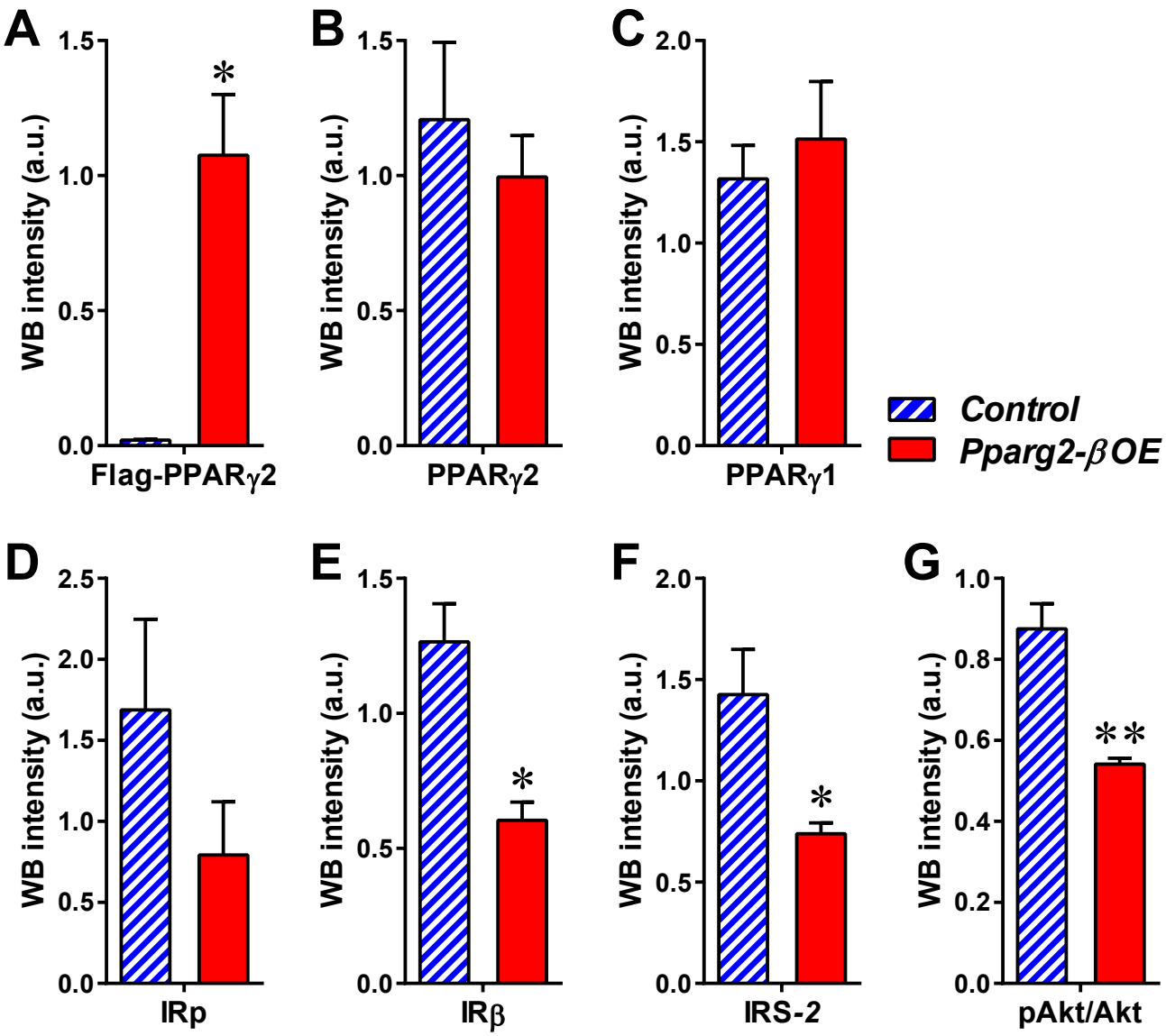

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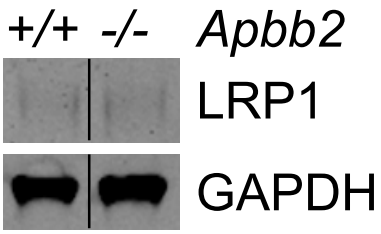

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Figure S12

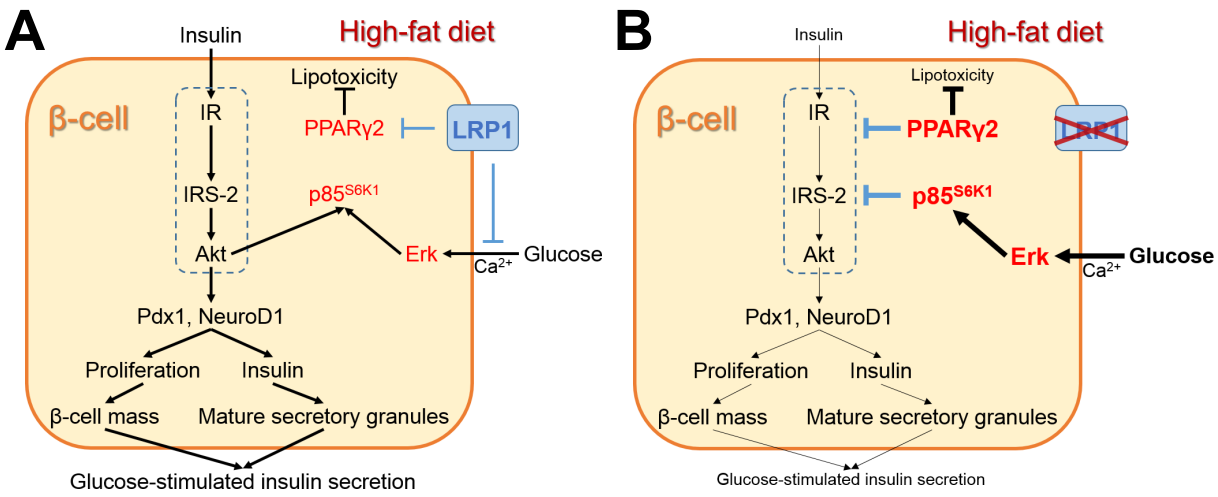

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Table S1. Primers for RT-qPCR

Transcript	Forward Primer	Reverse Primer
18S rRNA	5'-GGAGAGGGAGCCTGAGAAACG-3'	5'-CGCTCCCAAGATCCAACTACG-3'
Lrp1	5'-CTGCCGCTGCTTTCAGCTC-3'	5'-TGGGCTTTACTCTGTGGACAGATCTC-3'
Ccna2	5'-GCTCAAGACTCGACGGGTTGC-3'	5'-CACTTTAGGTTTACATTTAACCTCCATTTCC-3'
Ccnb1	5'-AAGAGTGCCTCTGAAAAGGGAAGC-3'	5'-GGTCTAACTGACTGCTCTTCCTCCAG-3'
Ccnb2	5'-GGGCCAAGGAAAATGGAATTTGAAG-3'	5'-CTTCAGGAGTCTGCTGCTGGCATAC-3'
Ccnd1	5'-GCACAGACCTTTGTGGCCCTC-3'	5'-CGGAGGCAGTCCGGGTCA-3'
Ccnd2	5'-CCTTCATCGCTCTGTGCGCTAC-3'	5'-GCAGGCTTTGAGACAATCCACATC-3'
Ccnd3	5'-CGGACCAGGCTGTGGCTC-3'	5'-GGATACATCGCAAAGGTGTAATCTGTAGC-3'
Cdk2	5'-TCACCCTAATATCGTCAAGCTGCTG-3'	5'-GGTACCACAGGGTCACCACCTC-3'
Cdk4	5'-CAGTTGGGGAAAATCTTTGATCTCAT-3'	5'-CGGAAGGCAGAGATTCGCTTATG-3'
Cdkn1a (p21)	5'-GACGACCTGGGAGGGGACAAG-3'	5'-GCGCTTGGAGTGATAGAAATCTGTCAG-3'
Cdkn1b (p27)	5'-GCCTTTAATTGGGTCTCAGGCAAAC-3'	5'-CTTTTGTTTTGCGAAGAAGAATCTTCTG-3'
Tp53 (p53)	5'-GCATTCTGGGACAGCCAAGTCTGTG-3'	5'-GGAGGGGCCAGACCATCGC-3'
Mitf	5'-TGCAAATGGCAAATACGTTACCC-3'	5'-TCCACCGCATGTCTGGATCA-3'
Mdm2	5'-CCCTCGCATCAGGATCTTGAC-3'	5'-TGAGGTACACTTCCAATAGTCAGCTAAGG-3'
Ins1	5'-GACCATCAGCAAGCAGGTCATTG-3'	5'-GGACTTGGGTGTGTAGAAGAAGCCAC-3'
Ins2	5'-ATGGCCCTGTGGATGCGCTT-3'	5'-CAGCTCCAGTTGTGCCACTTGTG-3'
Tcf7l2	5'-CGGAAAGGGATTTAGCCGATG-3'	5'-CCTCTTGGCCGCTTCTTCC-3'
Isl1	5'-GCGATCCACCAAAAAAAAAACG-3'	5'-GCACTTGGCGCATTTGATCC-3'
Pdx1	5'-GGCCAGTGGGCAGGAGG-3'	5'-TGGAACCAGATTTTGATGTGTCTCTC-3'
MafA	5'-CTTCCGGGGTCAGAGCTTCGC-3'	5'-GCCGCTTCTGTTTCAGTCGGATG-3'
Neurod1	5'-TCACTATTCAGAACCTTTTAACAACAGGAAGT-3'	5'-CGTGTTCCTCGTCCTGAGAACTG-3'
Nkx6.1	5'-CGCTTCAGCAGCCTGAGCCC-3'	5'-GTGTGTTTTCTCTTCCCATCTTTGTCCA-3'
Cpe	5'-ACCATGATGTCACCTCGGCTAAG-3'	5'-TCCTTCCTTTCAGAGAAAGACTCAAGC-3'
Pam	5'-AACCAGTTCGCAAGCACTTTGAC-3'	5'-CAACTGCCTCGGCTTTGATTTC-3'
Pcsk1	5'-AATCCTGTAGGCACCTGGACATTG-3'	5'-TGTGTGGGCCGCTTCTCC-3'
Pcsk2	5'-GGCGTGTTTGCATTAGCTTTGG-3'	5'-CGGTGGGTGGTATTTTTTCAGGG-3'
Ptprn	5'-GCTGGACTTCCGCAGGAAAG-3'	5'-GCAAACTCAAACTGGTCCTTAGAACG-3'
Ptprn2	5'-ACTCCTGGATTTCCGCAGAAAAG-3'	5'-CGCAAACTCAAACTGCTCCTTTGTC-3'
Trio	5'-GCAGAAGGGGAGGAGGGATG-3'	5'-GTCAGCTCGCAGCCACCAG-3'
Gal3st1	5'-CAACATGGCCTTCACGACCTC-3'	5'-CGAAGCGGAACAGGATGTTGAG-3'
Slc30a8	5'-GGGGATGTATTTCAGAGCATCAGTG-3'	5'-CAGGCCCTTTGGAACACCTTC-3'
Slc39a4	5'-TGTTCTGTCATGAGCTGCCCC-3'	5'-CATGGCTGGGAGCATGTCAC-3'
Slc39a7	5'-GAAGAAGAAAAAGCAGGCTCAGACC-3'	5'-GCAGTCACGAGTTGCAGACGC-3'
Atf4	5'-AGACACCGGCAAGGAGGATG-3'	5'-GATGGCCAATTGGGTTCACTG-3'
BiP	5'-AGGCTGGTGTCCTCTCTGGTG-3'	5'-TGTTAGGGGTCGTTCACCTTCATAG-3'
Chop	5'-CCCCAGGAAACGAAGAGGAAG-3'	5'-CTCTGACTGGAATCTGGAGAGCG-3'
Xbp1t (unspliced & spliced)	5'-CGAGGTTCCAGAGGTGGAGGC-3'	5'-AGAATGCCCAAAAGGATATCAGACTCAG-3'
Xbp1u (unspliced)	5'-CGAGGTTCCAGAGGTGGAGGC-3'	5'-GCCTGCACCTGCTGCAGAG-3'
Xbp1s (spliced)	5'-CGAGGTTCCAGAGGTGGAGGC-3'	5'-CCTGCACCTGCTGCGGAC-3'
Edem1	5'-CACATATCTCCTCTACCAGGCAACC-3'	5'-CGTGATGCAGCGTAGCATATCC-3'
Gadd34	5'-CCTTGGGCTGCACCTAAGCTG-3'	5'-TTCTCAGCGAAGTGTACCTTCCG-3'
Atf6	5'-CAGTACACAGAAACCACTAGCATCAGTAGG-3'	5'-CCTGCCCATTGATCACATTATCATTTA-3'
Grp94	5'-ACCCACTGATCAGAGACATGTTGC-3'	5'-GGTTCTTCCTCCACCTGTGCTTC-3'
Canx	5'-AGAGGAAGAAGAGGAGAAGCTTGAAGAG-3'	5'-CTTTCTGTTTCTTGGCGATCTGTTC-3'
Calr	5'-CAAAATCCTGAATACAAGGGCGAG-3'	5'-TCTGCTTCTCTGCAGCCTTGG-3'
Irs1	5'-GGGGGTTTGGAGAAGAGTCTTAACTACATAG-3'	5'-GGTCATTTAGGTCTTCATTCTGCTGTG-3'
Irs2	5'-GGAGCCGGACCCGTAGCC-3'	5'-TGGTAGCGCTTCACTCTTTCACG-3'
Gck	5'-GAGATGGATGTGGTGGCAAT-3'	5'-ACCAGCTCCACATTCTGCAT-3'
Glut2	5'-TTGCTGGACGAAGTGTATCAGGAC-3'	5'-AAGCTGAGGCCAGCAATCTGAC-3'
Igf1r	5'-CACTACTCATTCTGATGTCTGGTCCTTC-3'	5'-TGCCAGCACATGCGCATAAG-3'
Pid1	5'-AGCGCCTGCAGCACTTCC-3'	5'-GCCTGTGGTAGAGACTTTTCCCAGATAG-3'
Apoa1	5'-CTCCGGGGAGGTCACCCAC-3'	5'-CAGTTTTCCAGGAGATTCAGGTTCAGC-3'

Apob	5'-TGGTCTATTTAAAGGACTTTGGGACTGGC-3'	5'-CTCCTTGTACCTCCACTCAGTTTTGAATATGC-3'
Apoc1	5'-CATGACCTTGGAAGGCCCAGC-3'	5'-ACTTTGCCAAATGCCTCTGAGAACC-3'
Apoc2	5'-ATCCTGATGTTGGGAAATGAGGTCC-3'	5'-CATGGCCGCCGAGCTTTTG-3'
Apoc4	5'-ATCAGTCTCCCTTTCTGTGCTGTTCTTG-3'	5'-CAGCTCCAGGGCCCCAGAAC-3'
Apoe	5'-CTGTGGGCCGTGCTGTTGG-3'	5'-TCCTCCATCAGTGCCGTCAGTTC-3'
Apom	5'-CTACCAGCGCTTTCTCCTCTACAATCG-3'	5'-CACTTGCTGGACAGCGGGC-3'
Abca1	5'-CCAACATCTGAAAAACAGGTTTGGAG-3'	5'-ACTTTGGTCCTTGGCAAAGTTCAC-3'
Cd36	5'-GCAAATGCAAAGAAGGAAAGCCTG-3'	5'-GGTCCCAGTCTCATTTAGCCACAGTATAGG-3'
Fabp4	5'-CACCGCAGACGACAGGAAGG-3'	5'-GCCTTTCATAACACATTCCACCACC-3'
Slc27a2	5'-CTGTGCAACACACCGCAGAAAC-3'	5'-TCAGCTCATACCTTGCAACTTTTCTTTG-3'
Lrp8	5'-TGCTGTCATTGGGGTCATCG-3'	5'-TGCTGATTGCTGCGGGG-3'
Cyp2c29	5'-CTGCCTCATGCAGTGACCTGTGAC-3'	5'-CTCCAGCACAAATCCGTTTTCCTGT-3'
Cyp2c67	5'-AGAAACTACTTCATCCCCAAGGGAACAC-3'	5'-GGGCAAGGCTCTCTCCCACAC-3'
Cyp2c70	5'-TCCTTCACCTCGTAAGACAACGCAG-3'	5'-TCTCCAATACAAGCTCTTCTTCCTGCTG-3'
Cyp2d9	5'-ACATTGTTCCAGTGAATTTGCCACG-3'	5'-CATGATCTGCGGCCTGCTGA-3'
Cyp2d26	5'-GCTTTGCAGACATCGTCCCAAC-3'	5'-CATGATCTGCGGCCTGCTGA-3'
Cyp3a25	5'-GAAATCCTGAGTACTGGCCAGAGCCT-3'	5'-GCTGATCTTCAGGGGGATCTGTGTC-3'
Lpl	5'-CCGGAGAGACTCAGAAAAAGGTCATC-3'	5'-ACCCACTTTCAAACACCCAAACAAG-3'
Scd1	5'-GCTGGTGATGTTCCAGAGGAGGTACTAC-3'	5'-TAGTTGTGGAAGCCCTCGCCC-3'
Acsl1	5'-ATGAAGGCTACGGACAGACCGAGTG-3'	5'-CTCACCCTCGCCCTTGGATGC-3'
Acox1	5'-GGGCACGGCTATTCTCACAGCAG-3'	5'-ATACGCTGGCTCGGCAGGTCATT-3'
Cpt1a	5'-CTTTGGGCCGGTTGCTGATG-3'	5'-CATGGCTTGTCTCAAGTGCTTCCC-3'
Dgat2	5'-TGCGCCATGGAGCTGATCTG-3'	5'-GCTCCAGCTTGGGGACAGTGATG-3'
Lpin1	5'-TCCGCCTTGCACAGAGAAGTG-3'	5'-CAGAGCCGCACGTACGAGC-3'
Lpin2	5'-CTCTGCCTTCCACAGGGAAGTG-3'	5'-CACTCAGCCTGTGATACGATGATTTG-3'
Fasn	5'-ATAAAGCAGTTTCTTGATGTGGAACACAGC-3'	5'-CCCGTCACACACCTGGGAGAG-3'
Cebpa	5'-GGCGGGAACGCAACAACATC-3'	5'-GCGTGTCCAGTTCACGGCTCAG-3'
Pparg (1 & 2)	5'-GCCGAGTCTGTGGGGATAAAGC-3'	5'-CCCAAACCTGATGGCATTGTG-3'
Pparg2	5'-GCTGATGCACTGCCTATGAGCAC-3'	5'-GCAACCATTGGGTCAGCTCTTG-3'
Cebpb	5'-CAAGCTGAGCGACGAGTACAAGATG-3'	5'-CAGCTGCTTGAACAAGTTCCGC-3'
FoxO1	5'-GCGACAGCAACAGCTCGGC-3'	5'-TCTCCGGGGTGATTTTCCGC-3'
Hnf4a	5'-GCATGGCCAAGATTGACAACCTG-3'	5'-CTCGGGAGTGGCTGCCTGC-3'
Nr4a1	5'-GGGCTTCTTCAAGCGCACAG-3'	5'-CAGCACCAGTTCCTGGAACTTG-3'
Nr4a2	5'-AAAGCCGACCAGGACCTGC-3'	5'-TGAGCCCGTGTCTCTCTGTGAC-3'
Nr4a3	5'-GGGCTTCTTCAAGAGAACGGTG-3'	5'-GTCGGTGGGACAGTATCTGGAA-3'