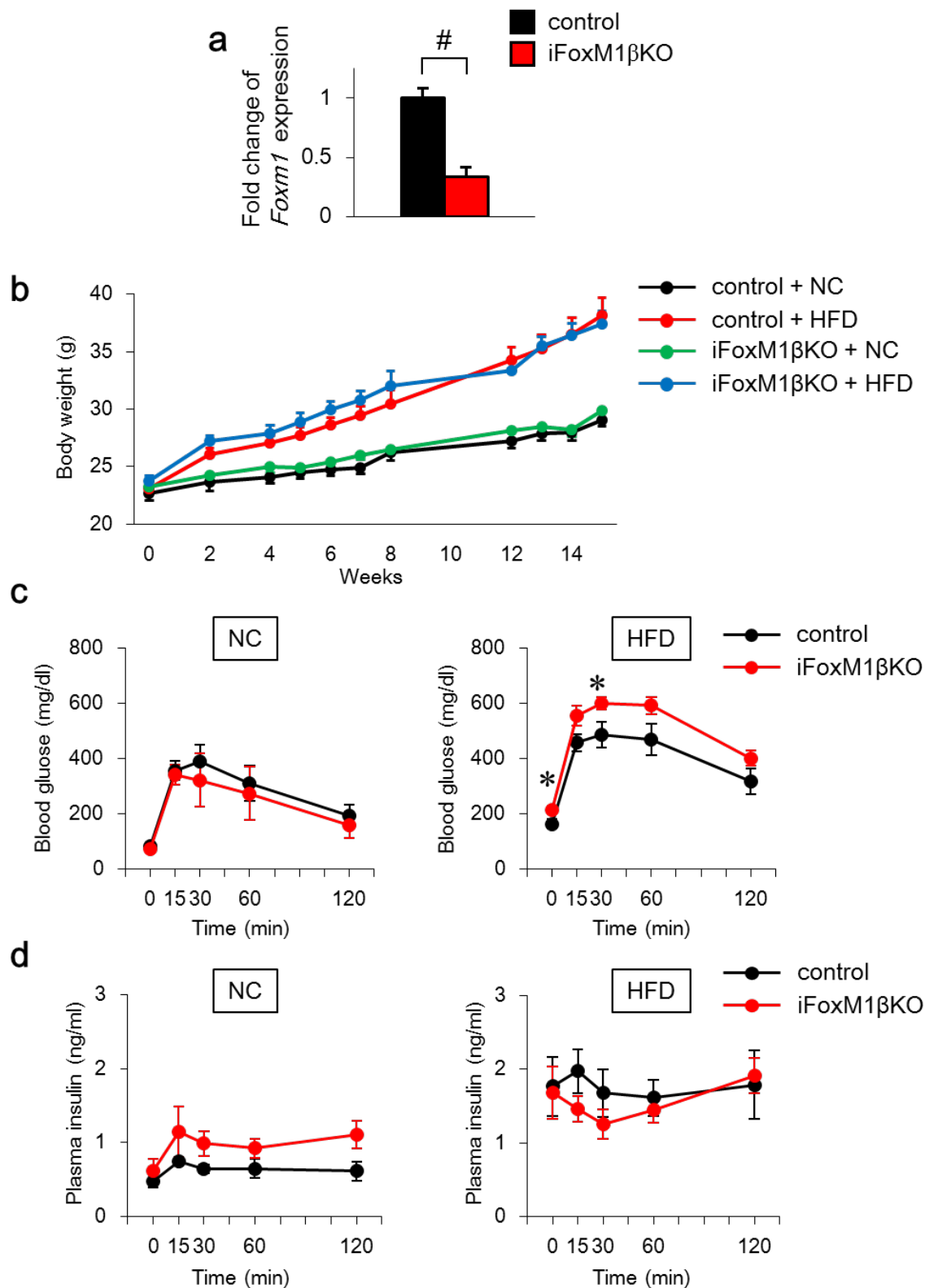


### Supplementary Figure 1

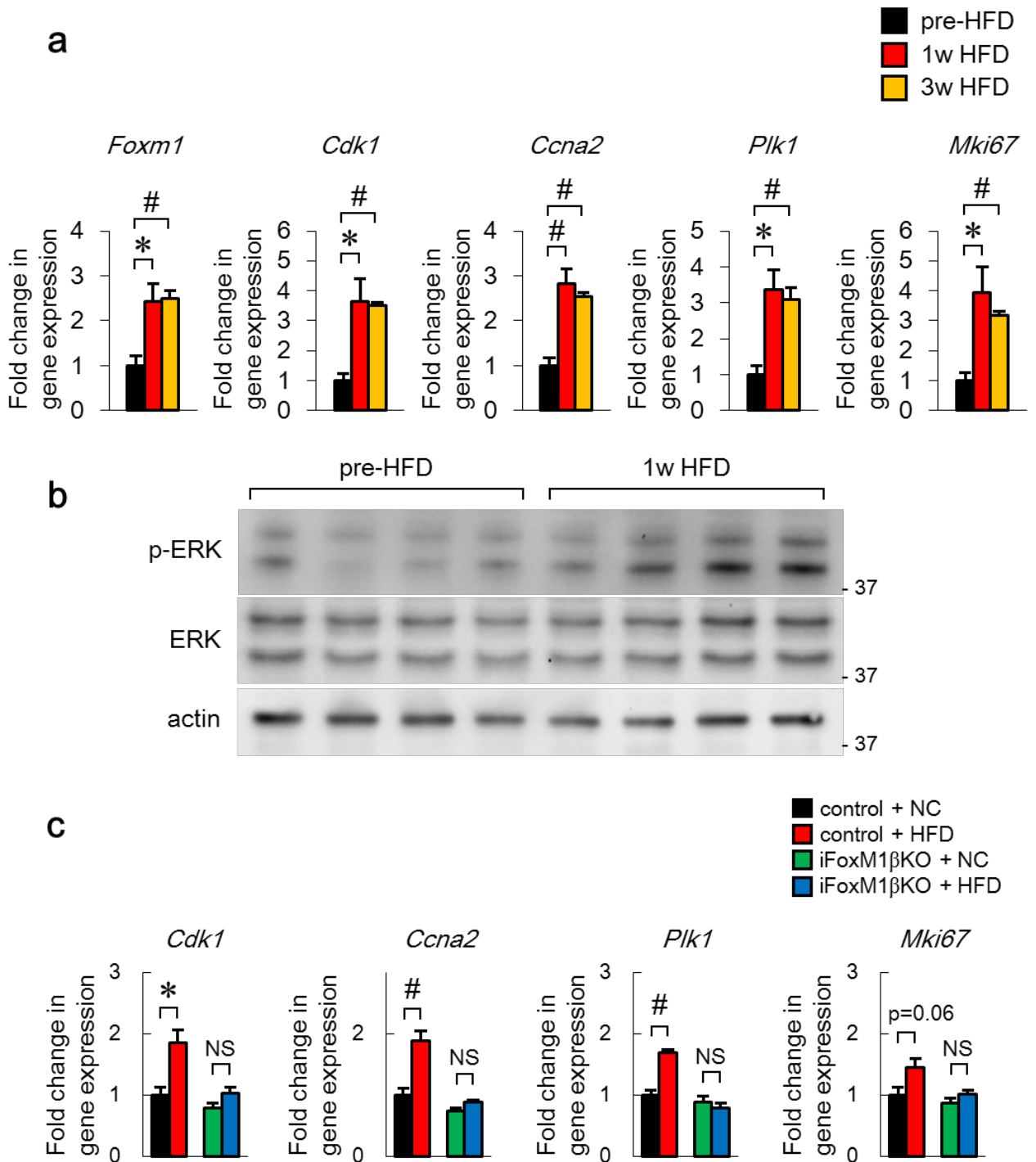
**Expressions of *Foxm1* and target genes as well as that of the *Mki67* gene are increased in islets along with hepatic ERK activation in ob/ob mice.** (a) Hepatic ERK phosphorylation of L-MEK-mice or LacZ-injected mice on day 3 after adenoviral administration. (b) Hepatic ERK phosphorylation of 6 week-old ob/ob mice or lean littermates. (c) Expressions of *Foxm1* and its target genes as well as that of the *Mki67* gene in islets of 6-week-old ob/ob mice or lean littermates are shown. Data are presented as means  $\pm$  s.e.m. \* $P < 0.05$ , assessed by unpaired t test.  $n = 4$ .

(d) Hepatic ERK phosphorylation of ob/ob mice or L-MEK-mice. The right graph shows quantitative data.  $n = 3$ . (e) Hepatic ERK phosphorylation of d/nMEK- or LacZ-injected ob/ob mice.



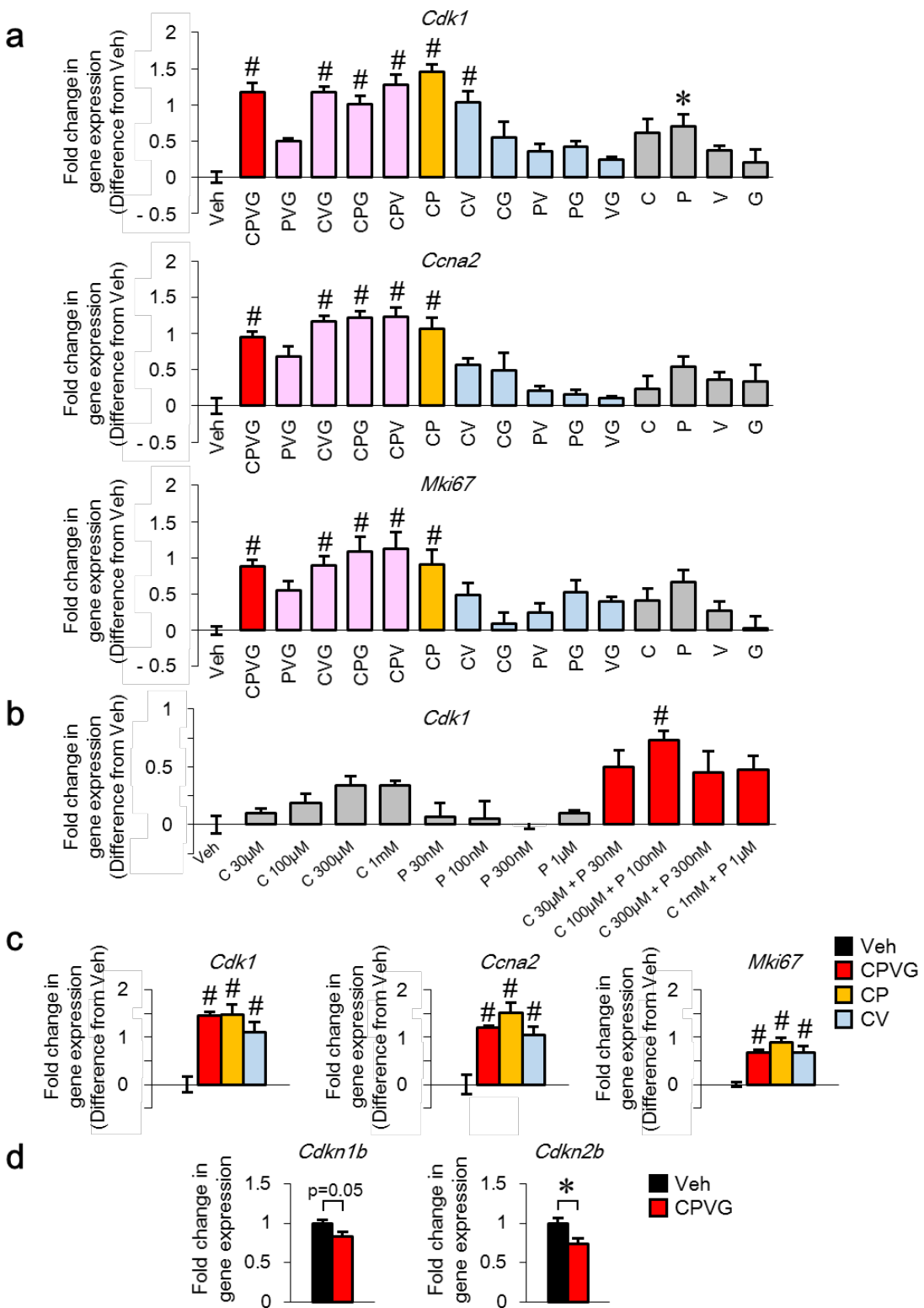
### Supplementary Figure 2

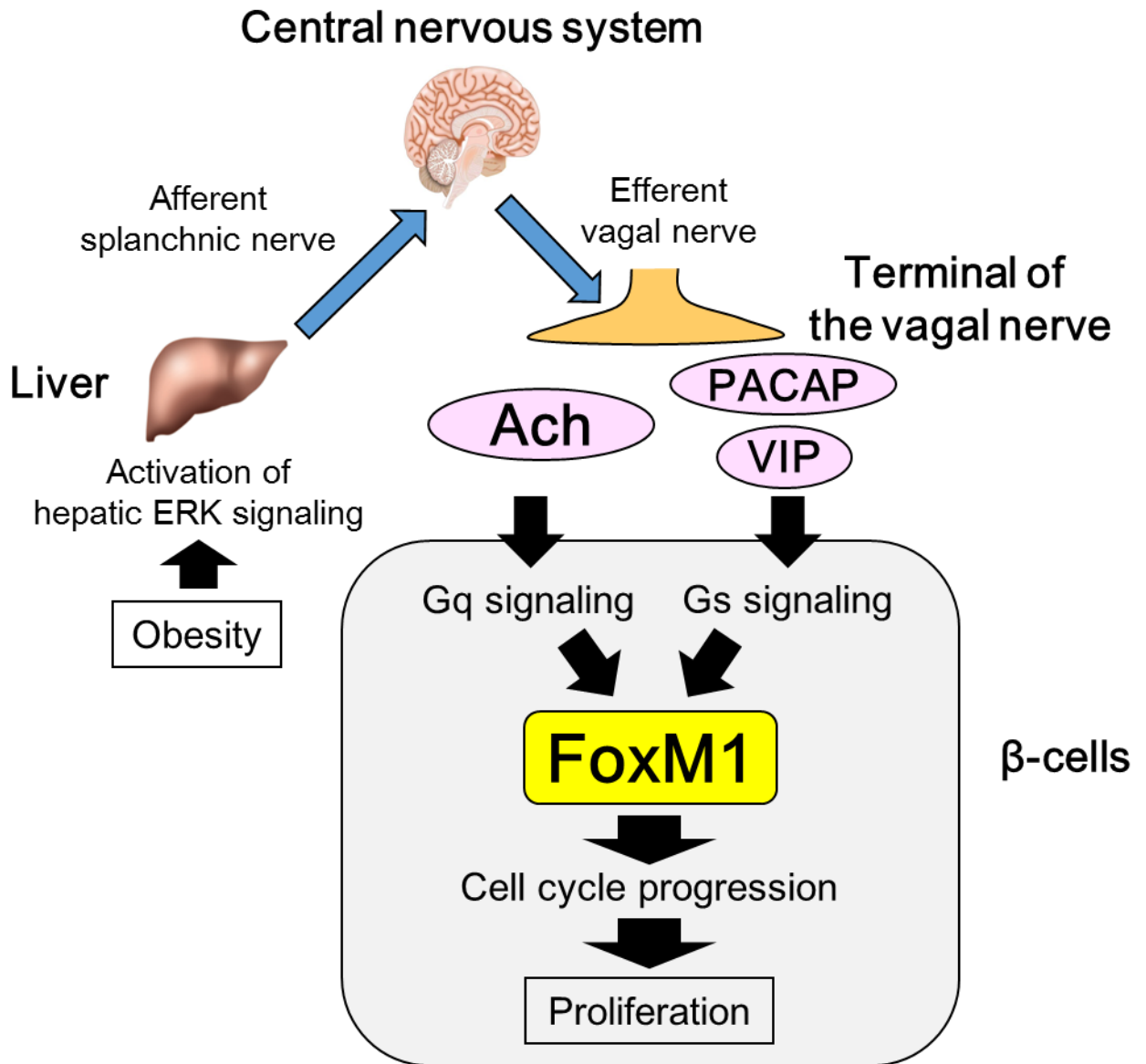
**The phenotypes of iFoxM1 $\beta$ KO mice.** (a) Knockout deficiency of *Foxm1* in islets of iFoxM1 $\beta$ KO mice, on day 7 after the completion of tamoxifen injections. (b) Body weight changes of NC- and HFD-fed iFoxM1 $\beta$ KO mice or control littermates. (c) Blood glucose levels of FoxM1 $\beta$ KO mice and control littermates, after 12 weeks of HFD or NC feeding, during the glucose tolerance test. (d) Plasma insulin levels of FoxM1 $\beta$ KO mice and control littermates, after 12 weeks of HFD or NC feeding, during the glucose tolerance test. Data are presented as means  $\pm$  s.e.m. \* $P < 0.05$ , # $P < 0.01$ , assessed by unpaired t test.  $n = 4$  (a),  $n = 4$  to 10 (b),  $n = 3$  to 6 (c, d).



### Supplementary Figure 3

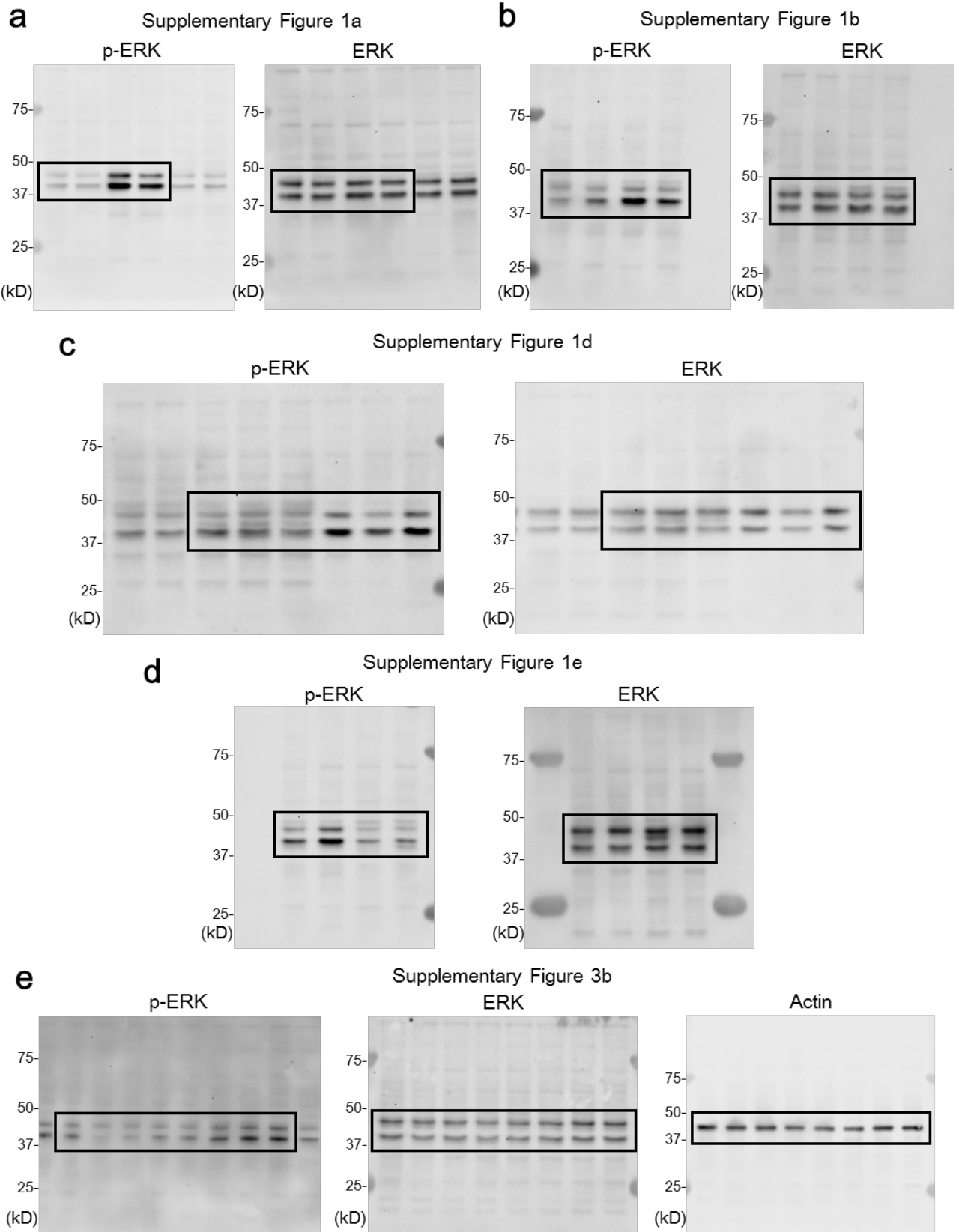
**Up-regulations of FoxM1 target genes and the *Mki67* gene in islets induced by one-week HFD feeding are blocked in iFoxM1βKO mice.** (a) Expressions of *Foxm1* and its target genes as well as that of the *Mki67* gene in islets of C57BL/6N mice after HFD feeding. (b) Hepatic ERK phosphorylation of C57BL/6N mice after one week of HFD feeding and before HFD feeding (pre-HFD). (c) Expressions of FoxM1 target genes and that of the *Mki67* gene in islets of iFoxM1βKO or control littermates, after one week of HFD or NC feeding. Data are presented as means ± s.e.m. \*P < 0.05, #P < 0.01, assessed by unpaired t test. n = 4 or 5 (a), n = 3 to 6 (c).





**Supplementary Figure 5**

**Proposed molecular mechanism of  $\beta$ -cell proliferation induced by FoxM1 activation, mediated by vagal factors via the liver-pancreas neuronal relay, during obesity development.**



**Supplementary Figure 6**

Uncropped scans of the immunoblots for Supplemental Figure 1a, 1b, 1d, 1e, and 3b.

Name of the pathway	Number of genes	p-value	Zscore
Mm_Complement_and_Coagulation_Cascades_KEGG	49	0	9.656881004
Mm_Inflammatory_Response_Pathway	26	3.30E-12	6.964324704
Mm_DNA_replication_Reactome	50	1.98E-09	5.999469842
Mm_Ribosomal_Proteins	126	2.79E-08	5.554150507
Mm_Cell_Cycle_KEGG	106	2.80E-07	5.13623703
Mm_Complement_Activation_Classical	12	6.25E-07	4.983333397
Mm_Nucleotide_GPCRs	14	1.03E-05	4.411262296
Mm_Striated_muscle_contraction	30	1.44E-05	4.337583038
Mm_Prostaglandin_synthesis_regulation	23	9.56E-05	3.901485993
Mm_Blood_Clotting_Cascade	13	1.11E-04	3.865389276
Mm_IL-3_NetPath_15	167	2.66E-04	3.646496808
Mm_Focal_adhesion_KEGG	258	4.21E-04	3.526311043
Mm_Matrix_Metalloproteinases	16	6.28E-04	3.419072674
Mm_Electron_Transport_Chain	97	8.13E-04	3.348246787
Mm_S1P_Signaling	37	1.26E-03	3.225938246
Mm_Nucleotide_Metabolism	24	2.34E-03	3.043743392
Mm_IL-9_NetPath_20	38	7.23E-03	2.685902487
Mm_Eicosanoid_Synthesis	17	8.82E-03	2.618765008
Mm_Apoptosis	117	1.01E-02	2.57272684
Mm_Triacylglyceride_Synthesis_BiGCaT	38	1.52E-02	2.427472351
Mm_GPCRDB_Class_A_Rhodopsin-like	79	2.06E-02	2.314960402
Mm_B_Cell_Receptor_NetPath_12	230	2.11E-02	2.306240141
Mm_GPCRDB_Other	51	0.02137	2.301458286
Mm_Proteasome_Degradation	121	2.24E-02	2.282873819
Mm_IL-4_NetPath_16	100	2.44E-02	2.250262541
Mm_Cell_Cycle-G1_to_S_control_Reactome	93	2.76E-02	2.202745025
Mm_Smooth_muscle_contraction	225	0.057745	1.897631754
Mm_Osteoclasts	14	6.86E-02	1.820805622
Mm_T-Cell-Receptor_NetPath_11	179	7.08E-02	1.80670769
Mm_Heme_Biosynthesis	11	0.082226	1.737914218
Mm_Integrin-mediated_cell_adhesion_KEGG	148	0.11118	1.592910329
Mm_Glycolysis_and_Gluconeogenesis	54	0.134558	1.496367613
Mm_Adipogenesis	172	0.135752	1.491796743
Mm_Glutathion_Metabolism_KEGG	21	0.143973	1.461154334
Mm_IL-7_NetPath_19	72	0.182609	1.332764218
Mm_Delta-Notch_NetPath_3	120	0.183107	1.331248014
Mm_IL-6_NetPath_18	148	0.194489	1.297414668
Mm_IL-2_NetPath_14	131	0.209363	1.255318137
Mm_Regulation_of_Actin_Cytoskeleton_KEGG	218	0.232539	1.19384523
Mm_One-carbon_metabolism	40	0.240003	1.174978832
Mm_Mitochondrial_fatty_acid_betaoxidation	20	0.261327	1.123260044
Mm_Biogenic_Amine_Synthesis	13	0.276539	1.088126299
Mm_IL-5_NetPath_17	103	0.315277	1.004209942
Mm_Androgen-Receptor_NetPath_2	178	0.345283	0.943778126
Mm_Fatty_Acid_Beta_Oxidation_1_BiGCaT	40	0.356741	0.921591967
Mm_GPCRDB_Class_B_Secretin-like	12	0.375717	0.885814606
Mm_Peptide_GPCRs	25	0.430497	0.788340805
Mm_TNF-alpha-NF-kB_NetPath_9	288	0.45166	0.752650816

Name of the pathway	Number of genes	p-value	Zscore
Mm_TGF_Beta_Signaling_Pathway	63	0.475206	0.714034194
Mm_Oxidative_Stress	34	0.48863	0.692489719
Mm_Translation_Factors	95	0.510544	0.657990517
Mm_Statin_Pathway_PharmGKB	21	0.527837	0.631310582
Mm_Selenium-metabolism_Selenoproteins	66	0.530558	0.627155055
Mm_Insulin_Signaling	237	0.555214	0.589964472
Mm_Fatty_Acid_Beta_Oxidation_Meta_BiGCaT	47	0.592474	0.535253978
Mm_Alanine_and_aspartate_metabolism_KEGG	14	0.616313	0.501081918
Mm_IL-1_NetPath_13	60	0.836666	0.206159508
Mm_Hedgehog_Netpath_10	28	0.886807	0.142345136
Mm_Alpha6-Beta4-Integrin_NetPath_1	97	0.917448	0.103648375
Mm_EGFR1_NetPath_4	272	0.920464	9.98E-02
Mm_Fas_Pathway_and_Stress_Induction_of_HSP_Regulation_Biocrta	57	0.984587	0.01931911
Mm_Calcium_regulation_in_cardiac_cells	197	0.885494	-0.14400846
Mm_Pentose_Phosphate_Pathway	10	0.874124	-0.15842222
Mm_MAPK_signaling_pathway_KEGG	215	0.860705	-0.17547663
Mm_G13_Signaling_Pathway	59	0.804017	-0.24815122
Mm_Kit-Receptor_NetPath_6	106	0.686718	-0.40331356
Mm_Fatty_Acid_Synthesis_BiGCaT	30	0.649672	-0.45421828
Mm_Wnt_NetPath_8	154	0.600842	-0.52318985
Mm_Cholesterol_Biosynthesis	31	0.597987	-0.52729767
Mm_Krebs-TCA_Cycle	46	0.59375	-0.53340927
Mm_Signaling_of_Hepatocyte_Growth_Factor_Receptor_Biocrta	58	0.589209	-0.53998291
Mm_MAPK_Cascade	53	0.587082	-0.54306884
Mm_ESC_Pluripotency_Pathways	158	0.53804	-0.61578004
Mm_Nuclear_Receptors	39	0.519718	-0.64378063
Mm_Notch_signaling_KEGG	29	0.491376	-0.68812241
Mm_Nuclear_receptors_in_lipid_metabolism_and_toxicity	21	0.474887	-0.71454955
Mm_Glycogen_Metabolism	33	0.455388	-0.74646205
Mm_p38_MAPK_signaling_pathway	48	0.44445	-0.76470101
Mm_G_Protein_Signaling	138	0.432529	-0.78487123
Mm_Tryptophane_Metabolism_KEGG	41	0.431311	-0.78695102
Mm_Fatty_Acid_Beta_Oxidation_3_BiGCaT	10	0.423721	-0.79998201
Mm_Urea_cycle_and_metabolism_of_amino_groups_KEGG	22	0.387627	-0.86392917
Mm_RNA_transcription_Reactome	62	0.36714	-0.90184441
Mm_mRNA_processing_binding_Reactome	745	0.351944	-0.930826
Mm_HSP70_and_Apoptosis	30	0.232434	-1.19411191
Mm_Ovarian_Infertility_Genes	38	0.186494	-1.32102328
Mm_Small_ligand_GPCRs	10	9.44E-02	-1.67284733
Mm_Wnt_Signaling	98	0.085966	-1.71707461
Mm_Hypertrophy_model	20	6.90E-02	-1.81861192
Mm_Acetylcholine_Synthesis	12	3.88E-02	-2.06649866
Mm_TGF-beta-Receptor_NetPath_7	227	3.05E-02	-2.16379703
Mm_Id_NetPath_5	66	6.26E-03	-2.73386594
Mm_Circadian_Exercise	85	1.12E-03	-3.25798697

## Supplementary Table 1

Results of pathway analysis of microarray data obtained from the islets of L-MEK-mice compared to that obtained from the islets of LacZ-injected mice.

	forward (5' to 3')	reverse (5' to 3')
<i>Mouse Foxm1</i>	GCTCCATAGAAATGTGACCATC	AACCTTCACTGAGGGCTGTAAC
<i>Mouse Cdk1</i>	AAGAACCTGGACGAGAACG	GTCATCAAAGTACGGGTGCT
<i>Mouse Ccna2</i>	CCTTAAGTACCTGCCTTCACTC	ACAAGGCTTAAGACTCTCCA
<i>Mouse Plk1</i>	ACGGCACC GTGCAGATTA	AGGCGGTACGTTT GGAAGTC
<i>Mouse Mki67</i>	AGTCTCTGGAGAGTCTGATGTTA	ACTTCTTGGTGCATACAATGTC
<i>Mouse Cdkn1b</i>	CGACGCCAGACGTAAACAG	CAGTGCTTATACAGGATGTCCA
<i>Mouse Cdkn2b</i>	CGCTGCCACTGGAGATTGA	CGTGCTTGCAGTCTTCCTAGATG
<i>Mouse Actb</i>	GATGCCCTGAGGCTCTT	TGTGTTGGCATAGAGGTCTTTAC
<i>Rat Cdk1</i>	CACGTCAAGAACCTGGATG	GATCTGATTGTCCAAGTCGTC
<i>Rat Ccna2</i>	GCTCTCTACACAGTCACAGGACA	GGTGAAGGTCCATGAGACAAG
<i>Rat Mki67</i>	ATCCAGATGTTAGGCGTTTGAG	ACAGTTTCACTTTTCTGGTGACTTC
<i>Rat Actb</i>	CCTAGCACCATGAAGATCAAGA	GTGTA AACGCAGCTCAGTAAC

**Supplementary Table 2**  
**Sequences of quantitative RT-PCR primers.**