SUPPLEMENTARY MATERIALS:

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Fig. Captions S1, S2, S3, S4, S5, S6, S7, S8, S9, Table S1, Table S2

Figs. S1, S2, S3, S4, S5, S6, S7, S8, S9, Table S1, Table S2

SUPPLEMENTAL FIGURE CAPTIONS:

Fig. S1. Islet cell autonomous circadian clock controls rhythmic insulin secretion. (A) Schematic of *ex vivo* experimental design for insulin secretion assays in forskolin-synchronized mouse islets. **(B)** Average intracellular insulin content in WT islets stimulated with glucose at indicated time points following forskolin treatment (n=4 islet pools per time point, 3 replicates per islet pool). **(C)** Schematic of *ex vivo* tamoxifen-induced *Bmal1* ablation and insulin secretion in islets isolated from *PdxCreER;Bmal1*$^{flx/flx}$ mice. **(D)** Excision of exon 8 of the *Bmal1* gene in islets from *PdxCreER;Bmal1*$^{flx/flx}$ mice after *in vitro* tamoxifen treatment as assessed by real time PCR using primers specific to indicated exons (n=4 samples per condition). All values represent mean ± SEM. $*p<0.05$.

Fig. S2. Impaired glucose-stimulated insulin secretion in circadian mutant islets is independent of mitochondrial respiration. (A) Total oxygen consumption rates (OCR) and **(B)** mitochondrial respiration in islets in the presence of glucose, oligomycin (an ATP synthase inhibitor which inhibits mitochondrial respiration, enabling measurement of uncoupled respiration), and antimycin A (a mitochondrial toxin which enables measurement of non-mitochondrial respiration). Mitochondrial respiration is calculated by subtracting OCR value in the antimycin A condition from basal, glucose- and oligomycin-stimulated islets (n=3-4 mice per genotype, 4 replicates per mouse). All values represent mean ± SEM.

Fig. S3. Circadian control of secretory gene expression is dependent on the pancreatic clock. **(A)** Schematic showing timing of *PdxCre;Bmal1*$^{flx/flx}$ islet isolation (ZT2) for RNA-seq in relation to endogenous diurnal patterns of *in vivo* insulin secretion. **(B)** Scatterplot showing RNA expression levels in *PdxCre;Bmal1*$^{flx/flx}$ and control *Bmal1*$^{flx/flx}$ islets and volcano plot comparing FDR-adjusted p-values and fold-change among significantly differentially expressed genes (FDR-adjusted $p<0.05$). Up-regulated genes are shown in red and down-regulated genes are in green. **(C)** Breakdown of up- and down-regulated genes in *PdxCre;Bmal1*$^{flx/flx}$ islets and overlap with cycling genes identified in synchronized WT islets. **(D)** Peak phase distribution of all cycling genes with reference to timing of maximal glucose-stimulated insulin secretion and *Bmal1* and *Rev-erbα* expression. **(E)** Enrichment of KEGG terms among all RNA and cycling genes differentially expressed in *PdxCre;Bmal1*$^{flx/flx}$ islets. **(F)** Model of basic vesicular transport pathway depicting proteins involved in i) vesicle budding from the donor membrane, ii) trafficking along cytoskeletal filaments, iii) tethering to the target membrane, and iv) fusion with the target membrane.

Fig. S4. The circadian transcriptome is conserved in human islets. **(A)** Summary of human islet donor information. **(B)** RNA expression of *BMAL1* and *REV-ERBα* (top) and heatmap showing expression patterns of all cycling RNAs in human islets identified by eJTK_CYCLE analysis (bottom) (Bonferroni corrected $p<0.05$). **(C)** Overlap between cycling RNAs identified in mouse and human islets, highlighting the significant enrichment in shared genes involved in synaptic and vesicle signaling. **(D)** Expression profiles for cycling genes mapping to the "Insulin Secretion" KEGG pathway in Fig 1F. Average z-score values from the 3 donors are shown.

Fig. S5. BMAL1 and CLOCK bind distinct enhancer regulatory regions genome-wide in β-cells compared to liver. **(A)** Top known HOMER motifs enriched at BMAL1 and CLOCK binding sites from Chip-seq analysis in β-cells (top panel). Number of tandem CACGTG E-boxes allowing for 2 nucleotide mismatches within BMAL1 and CLOCK peaks at non-cycling and cycling genes. Column numbering corresponds with number of nucleotides separating sequential E-box motifs (bottom panels). **(B)** Scatter plot showing BMAL1 (x-axis) and CLOCK (y-axis) binding as $\log_2$ normalized tag count within 500bp windows surrounding BMAL1 peaks (blue) and CLOCK peaks (yellow) normalized per 10 million tags. **(C)** Venn diagram showing overlap of CLOCK/BMAL1 targets in BetaTC6 cells, cycling RNAs in wild type islets, and genes that are differentially expressed genes in *PdxCre;Bmal1*$^{flx/flx}$ compared to *Bmal1*$^{flx/flx}$ controls. **(D)** Distribution of genomic annotations of BMAL1 and CLOCK peaks from Chip-seq in β-cells. **(E)** Box and whiskers plots (whiskers represent IQR 1.5) comparing BMAL1 ChIP-seq tags normalized per 10 million tags in β-cells and liver at loci corresponding to 500bp windows surrounding BMAL1 peaks identified in either β-cells or in liver. **(F)** UCSC genome browser tracks at *Per2*, *Cry1*, and *Dbp* loci in β-cells and liver show comparable tag density in both liver and β-cells at core clock loci. Maximum BMAL1 track heights within viewable window are indicated to the right of tissue. ***p <0.0001 by Mann-Whitney non-parametric, unpaired *t*-test.

Fig. S6. Tamoxifen-induced adult-life *Bmal1* deletion is limited to pancreatic β-cells. (A) Immunofluorescent staining of BMAL1 (red), insulin (blue), and glucagon (green) in *PdxCreER;Bmal1*$^{flx/flx}$ and control islets. Scale bars, 25μm. Immunofluorescent staining of BMAL1 (red) and DAPI (blue) in **(B)** suprachiasmatic nucleus and **(C)** feeding centers in the hypothalamus of *PdxCreER;Bmal1*$^{flx/flx}$ and *Bmal1*$^{flx/flx}$ mice. SCN, suprachiasmatic nucleus. ARC, arcuate nucleus. DMH, dorsomedial hypothalamic nucleus. VMH, ventromedial hypothalamic nucleus. V3, third ventricle. Scale bars, 50μm.

Fig. S7. Adult-life pancreatic β-cell-specific loss of BMAL1 does not impact behavior, feeding, or body weight. (A) Representative actograms showing locomotor activity over a 28 day period in individually-housed *PdxCreER* and *PdxCreER;Bmal1*$^{flx/flx}$ mice post-tamoxifen treatment. **(B)** Period of activity in total darkness (DD), calculated using Chi-square periodogram for days 7-14 in DD (n=4-5 mice per genotype). **(C)** Food intake (% total) during either the light or dark periods and **(D)** total food intake (g) in *PdxCreER;Bmal1*$^{flx/flx}$ and littermate control mice before and after tamoxifen treatment (n=3-5 mice per genotype). **(E)** Body weight in *PdxCreER;Bmal1*$^{flx/flx}$ and littermate control mice before and after tamoxifen treatment (n=7-10 mice per genotype). All values represent mean ± SEM.

Fig. S8. Acute *Bmal1* deletion in adult β-cells impairs glucose homeostasis. (A) Fasting glucose in *PdxCreER;Bmal1*$^{flx/flx}$ and littermate control mice before and after tamoxifen treatment (n=7-11 mice per genotype). **(B)** Glucose tolerance and insulin secretion at ZT14 following intraperitoneal glucose administration of 2 and 3g/kg body weight, respectively, in *PdxCreER;Bmal1*$^{flx/flx}$ mice and littermate controls before and after tamoxifen treatment (n=4-10 mice per genotype). *p<0.05, **p<0.01, ***p<0.001. For B asterisks denote significance between *Bmal1*$^{flx/flx}$ and *PdxCreER;Bmal1*$^{flx/flx}$, and plus symbols denote significance between *PdxCreER* and *PdxCreER;Bmal1*$^{flx/flx}$. All values represent mean ± SEM.

Fig S9. Islet mass and glucose-stimulated calcium influx are normal in adult-life *Bmal1* knockout islet cells. **(A)** Morphometric analysis of insulin-positive area in the pancreas of *PdxCreER;Bmal1*$^{flx/flx}$ and *Bmal1*$^{flx/flx}$ control mice (n=3 mice per genotype). Scale bars, 1000μm. **(B)** Ratiometric determination of intracellular Ca^{2+} using Fura2-AM dye in islets isolated from *PdxCreER*, *Bmal1*$^{flx/flx}$, and *PdxCreER;Bmal1*$^{flx/flx}$ mice following *ex vivo* challenge with 20mM glucose, where the dashed line indicates the time when glucose was injected (left) and area under the curve (right) (n=2-4 mice per genotype). All values represent mean ± SEM.

Table S1. Enriched KEGG pathways in circadian transcriptome and cistrome.

Table S2. Signature islet gene regulation.

Figure S1

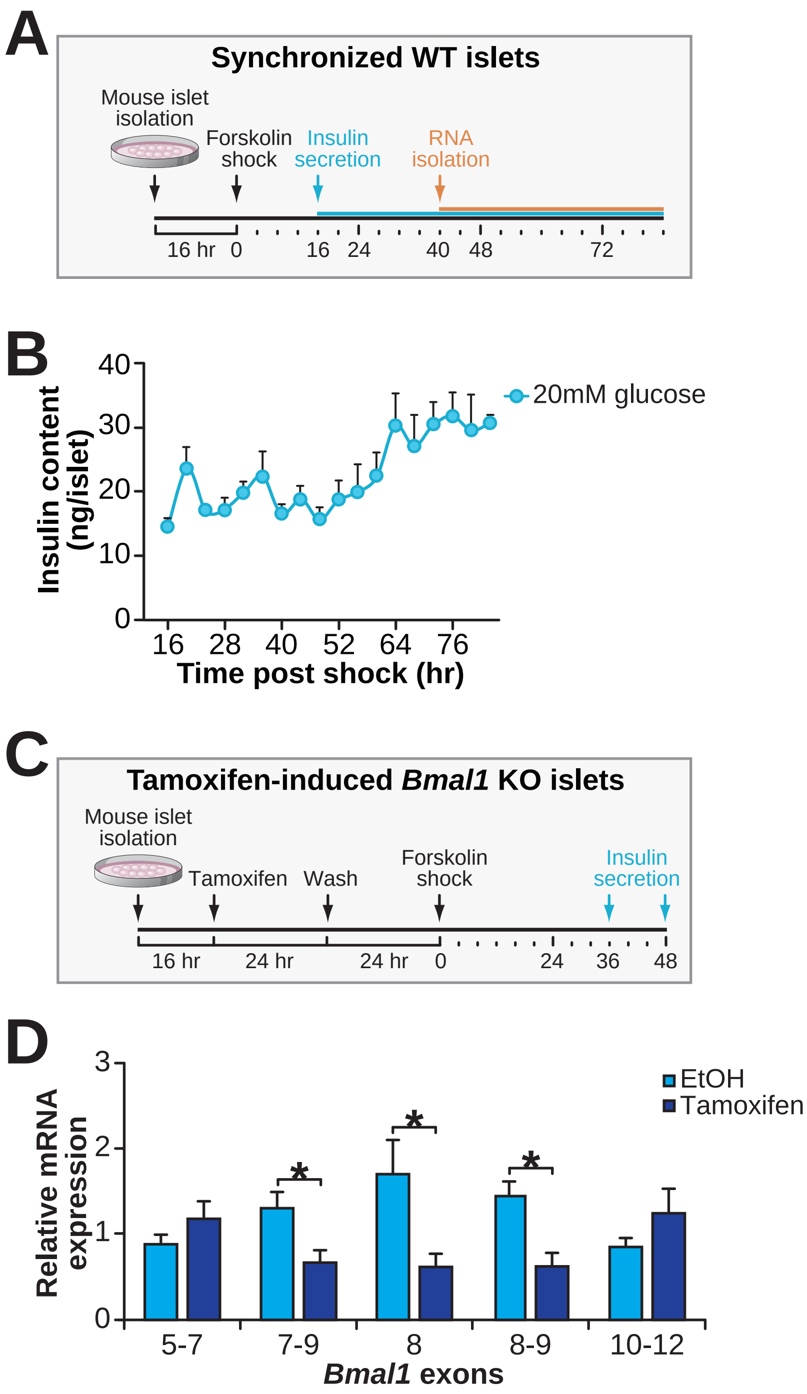

A
Synchronized WT islets
Mouse islet isolation
Forskolin shock
Insulin secretion
RNA isolation
16 hr
0
16
24
40
48
72
B
Insulin content (ng/islet)
40
30
20
10
0
16
28
40
52
64
76
Time post shock (hr)
20mM glucose
C
Tamoxifen-induced *Bmal1* KO islets
Mouse islet isolation
Tamoxifen
Wash
Forskolin shock
Insulin secretion
16 hr
24 hr
24 hr
0
24
36
48
D
Relative mRNA expression
3
2
1
0
*
*
*
5-7
7-9
8
8-9
10-12
Bmal1 exons
EtOH
Tamoxifen

Figure S2

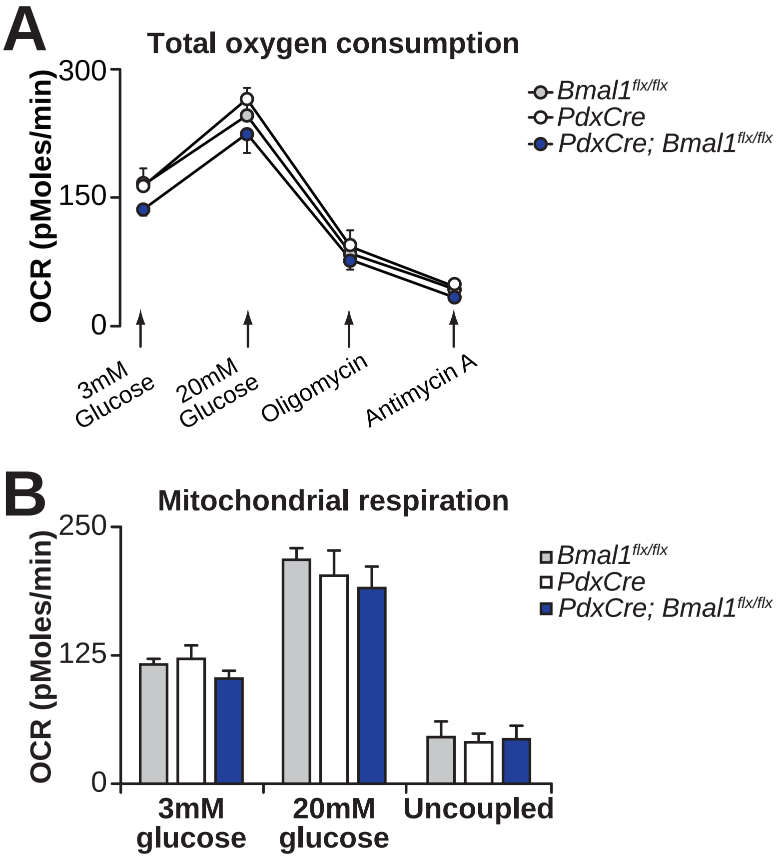

A
Total oxygen consumption
OCR (pMoles/min)
300
150
0
3mM Glucose
20mM Glucose
Oligomycin
Antimycin A
Bmal1flx/flx
PdxCre
PdxCre; Bmal1flx/flx
B
Mitochondrial respiration
OCR (pMoles/min)
250
125
0
3mM glucose
20mM glucose
Uncoupled
Bmal1flx/flx
PdxCre
PdxCre; Bmal1flx/flx

Figure S3

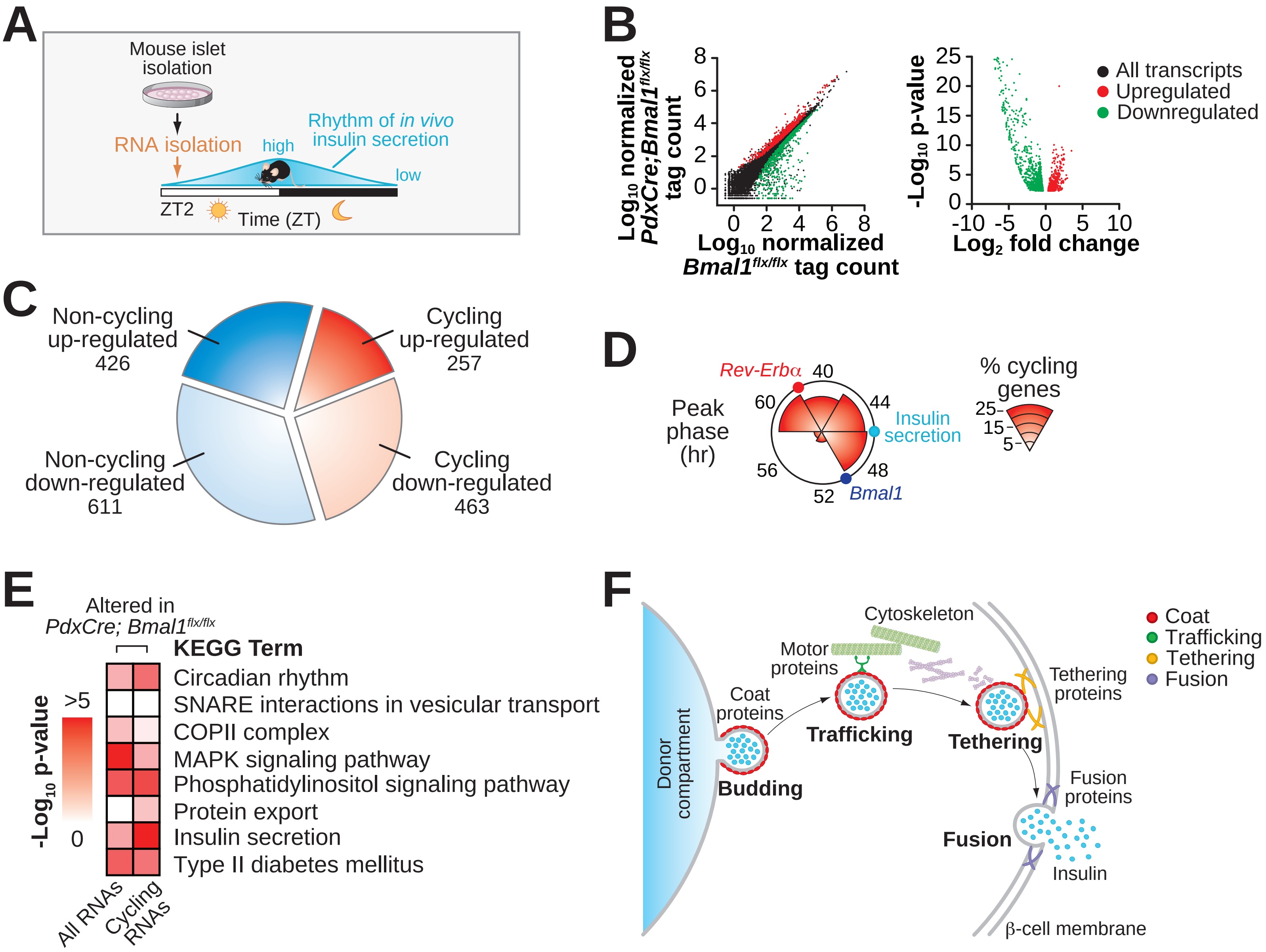
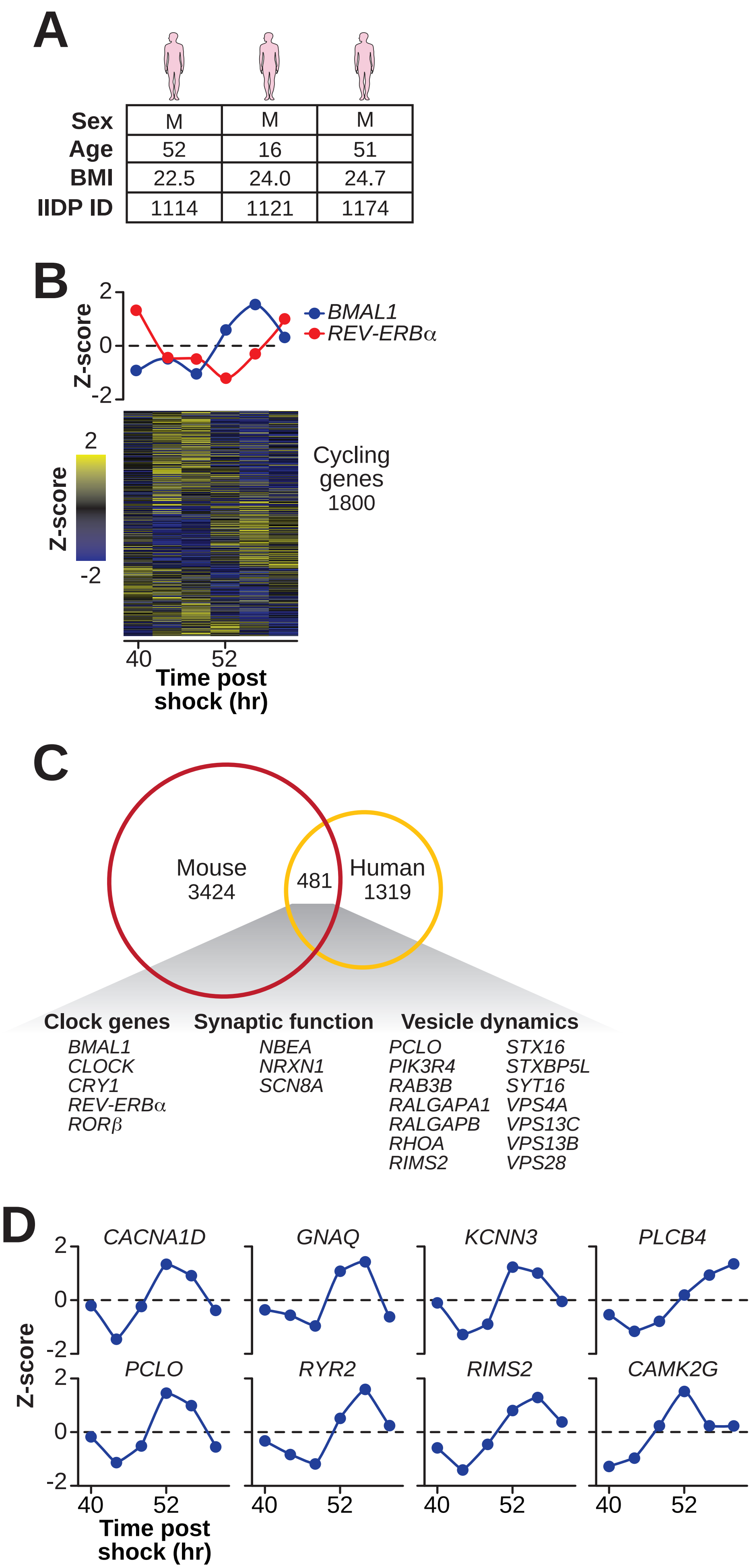

A
Mouse islet isolation
RNA isolation
high
Rhythm of *in vivo* insulin secretion
low
ZT2
Time (ZT)
B
Log$_{10}$ normalized *PdxCre;Bmal1$^{flx/flx}$* tag count
8
6
4
2
0
0 2 4 6 8
Log$_{10}$ normalized *Bmal1$^{flx/flx}$* tag count
-Log$_{10}$ p-value
25
20
15
10
5
0
-10 -5 0 5 10
Log$_2$ fold change
● All transcripts
● Upregulated
● Downregulated
C
Non-cycling up-regulated 426
Cycling up-regulated 257
Non-cycling down-regulated 611
Cycling down-regulated 463
D
Peak phase (hr)
Rev-Erbα
40
44
Insulin secretion
48
Bmal1
52
56
60
% cycling genes
25-
15-
5-
E
Altered in *PdxCre; Bmal1$^{flx/flx}$*
-Log$_{10}$ p-value
>5
0
KEGG Term
Circadian rhythm
SNARE interactions in vesicular transport
COPII complex
MAPK signaling pathway
Phosphatidylinositol signaling pathway
Protein export
Insulin secretion
Type II diabetes mellitus
All RNAs
Cycling RNAs
F
Donor compartment
Coat proteins
Budding
Motor proteins
Cytoskeleton
Trafficking
Tethering
Tethering proteins
Fusion proteins
Fusion
Insulin
β-cell membrane
● Coat
● Trafficking
● Tethering
● Fusion

Figure S4



Sex	M	M	M
Age	52	16	51
BMI	22.5	24.0	24.7
IIDP ID	1114	1121	1174

Figure S5

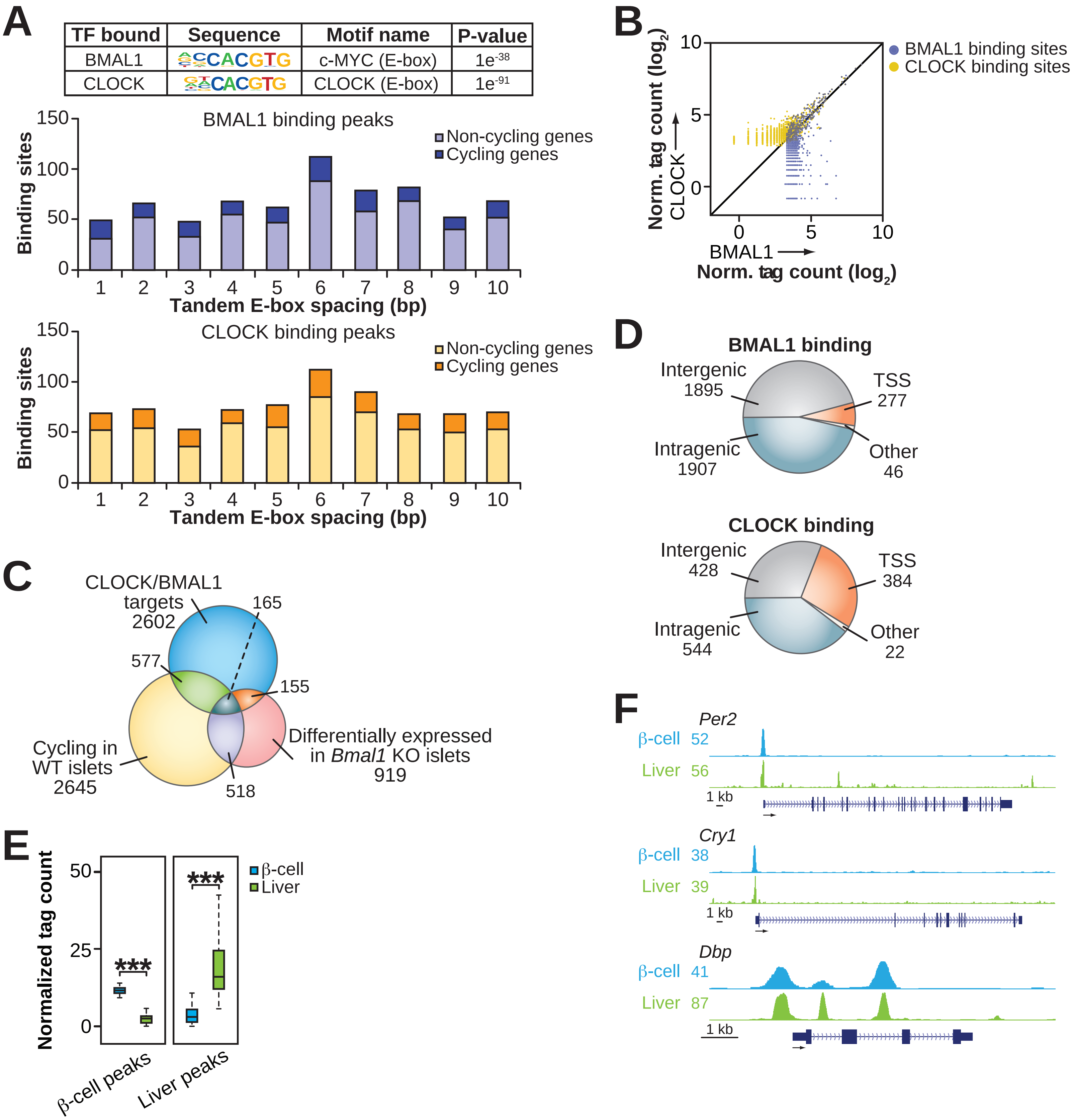
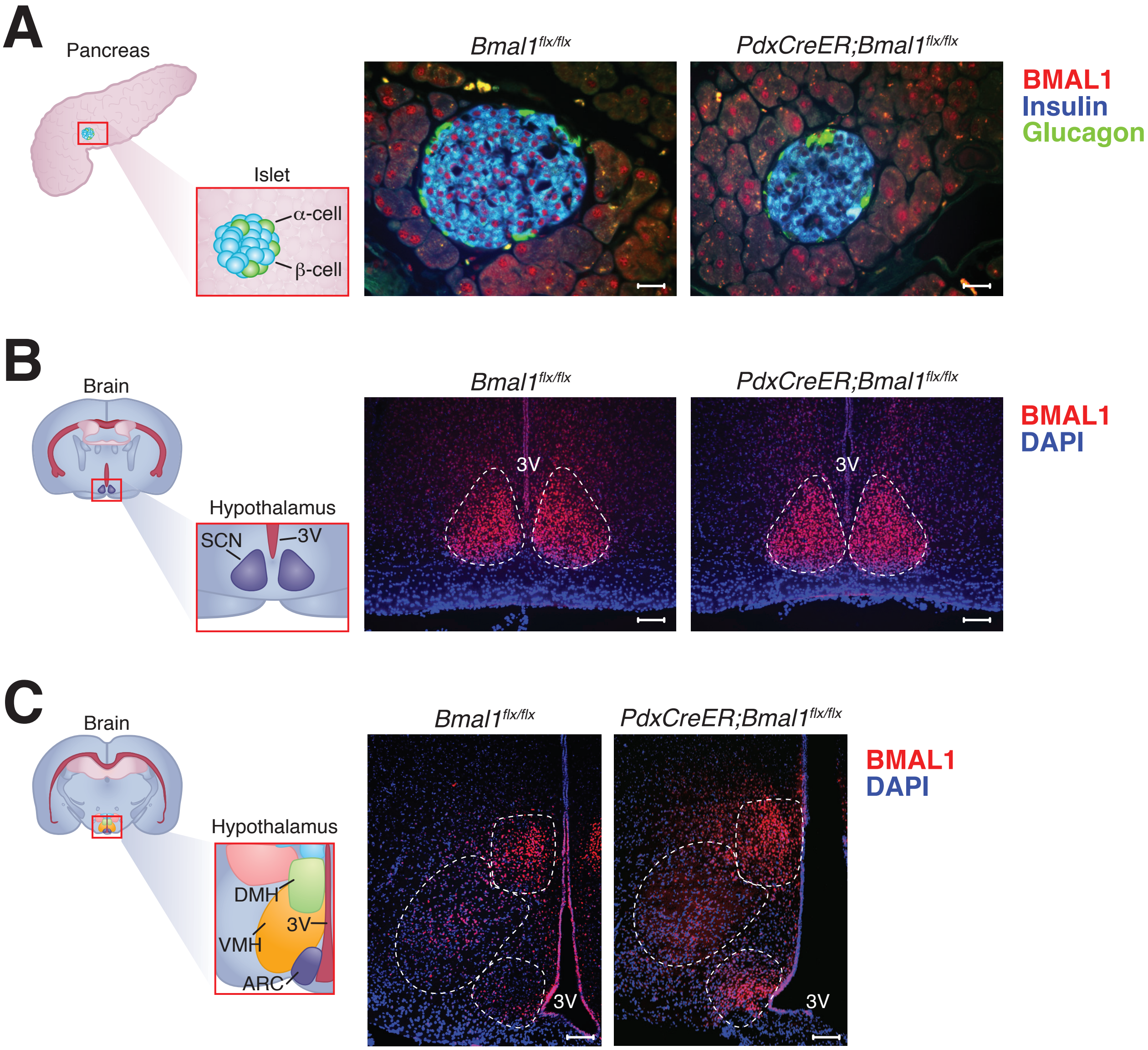

A
TF bound
Sequence
Motif name
P-value
BMAL1
CCACGTG
c-MYC (E-box)
1e-38
CLOCK
CACGTG
CLOCK (E-box)
1e-91
BMAL1 binding peaks
Non-cycling genes
Cycling genes
Binding sites
150
100
50
0
1 2 3 4 5 6 7 8 9 10
Tandem E-box spacing (bp)
CLOCK binding peaks
Non-cycling genes
Cycling genes
Binding sites
150
100
50
0
1 2 3 4 5 6 7 8 9 10
Tandem E-box spacing (bp)
B
BMAL1 binding sites
CLOCK binding sites
Norm. tag count (log2)
CLOCK
10
5
0
0
5
10
BMAL1
Norm. tag count (log2)
C
CLOCK/BMAL1 targets 2602
165
577
155
Cycling in WT islets 2645
Differentially expressed in Bmal1 KO islets 919
518
D
BMAL1 binding
Intergenic 1895
TSS 277
Intragenic 1907
Other 46
CLOCK binding
Intergenic 428
TSS 384
Intragenic 544
Other 22
E
Normalized tag count
50
25
0
***
***
β-cell
Liver
β-cell peaks
Liver peaks
F
Per2
β-cell 52
Liver 56
1 kb
Cry1
β-cell 38
Liver 39
1 kb
Dbp
β-cell 41
Liver 87
1 kb

Figure S6



A
Pancreas
Islet
α-cell
β-cell
$Bmal1^{flx/flx}$
$PdxCreER;Bmal1^{flx/flx}$
BMAL1
Insulin
Glucagon
B
Brain
Hypothalamus
SCN
3V
$Bmal1^{flx/flx}$
$PdxCreER;Bmal1^{flx/flx}$
3V
3V
BMAL1
DAPI
C
Brain
Hypothalamus
DMH
3V
VMH
ARC
$Bmal1^{flx/flx}$
$PdxCreER;Bmal1^{flx/flx}$
3V
3V
BMAL1
DAPI

Figure S7

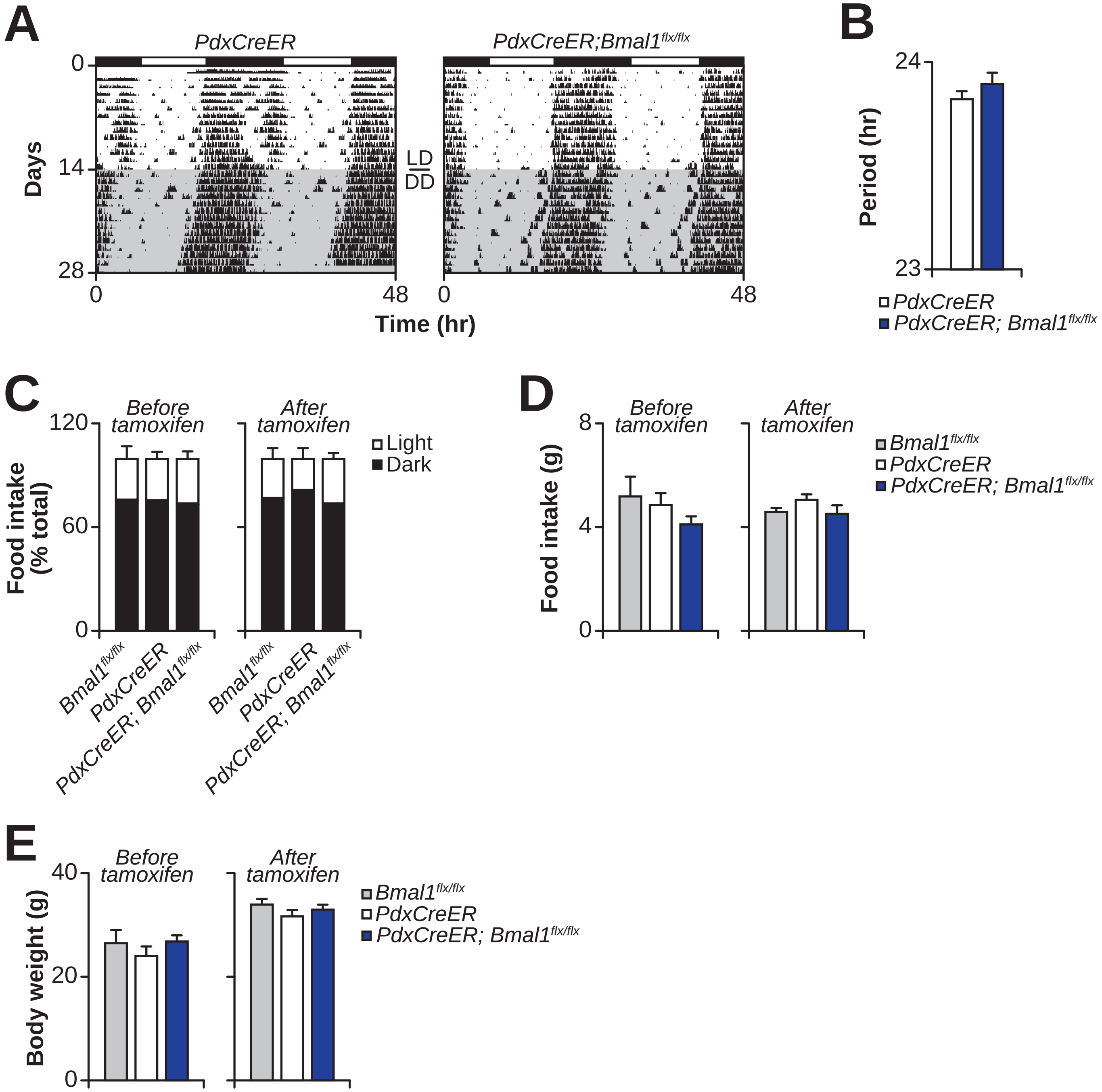

A
PdxCreER
PdxCreER;Bmal1flx/flx
Days
0
14
28
LD
DD
0
48
0
48
Time (hr)
B
Period (hr)
24
23
PdxCreER
PdxCreER; Bmal1flx/flx
C
Before tamoxifen
After tamoxifen
Food intake (% total)
120
60
0
Light
Dark
Bmal1flx/flx
PdxCreER
PdxCreER; Bmal1flx/flx
Bmal1flx/flx
PdxCreER
PdxCreER; Bmal1flx/flx
D
Before tamoxifen
After tamoxifen
Food intake (g)
8
4
0
Bmal1flx/flx
PdxCreER
PdxCreER; Bmal1flx/flx
E
Before tamoxifen
After tamoxifen
Body weight (g)
40
20
0
Bmal1flx/flx
PdxCreER
PdxCreER; Bmal1flx/flx

Figure S8

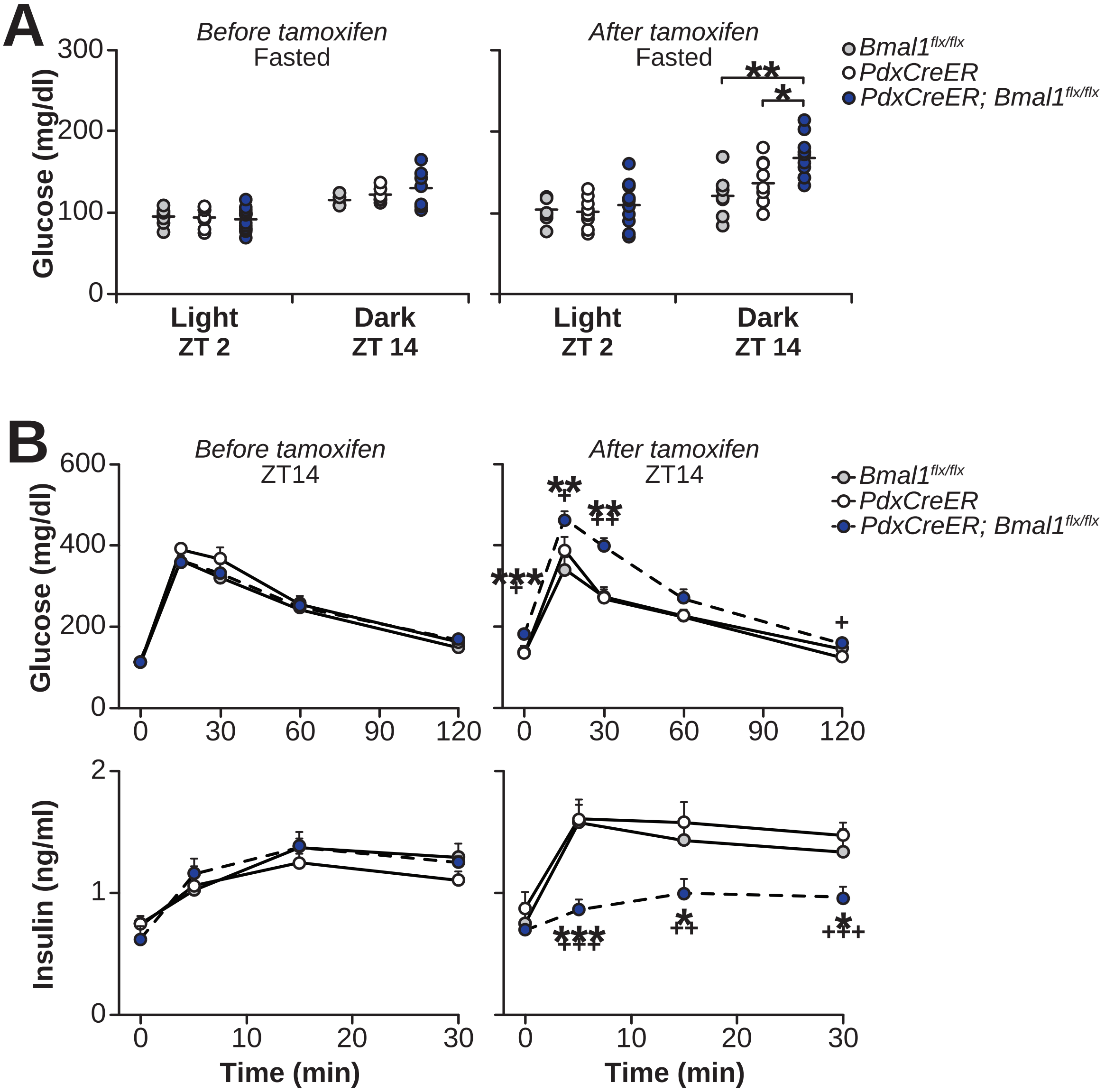

A
Before tamoxifen
Fasted
After tamoxifen
Fasted
Glucose (mg/dl)
300
200
100
0
Light
ZT 2
Dark
ZT 14
**
*
Bmal1flx/flx
PdxCreER
PdxCreER; Bmal1flx/flx
B
Before tamoxifen
ZT14
After tamoxifen
ZT14
Glucose (mg/dl)
600
400
200
0
0
30
60
90
120
***
**
**
+
‡
‡
+
Bmal1flx/flx
PdxCreER
PdxCreER; Bmal1flx/flx
Insulin (ng/ml)
2
1
0
0
10
20
30
Time (min)
***
‡‡‡
*
‡‡
*
+‡+
Time (min)

Figure S9

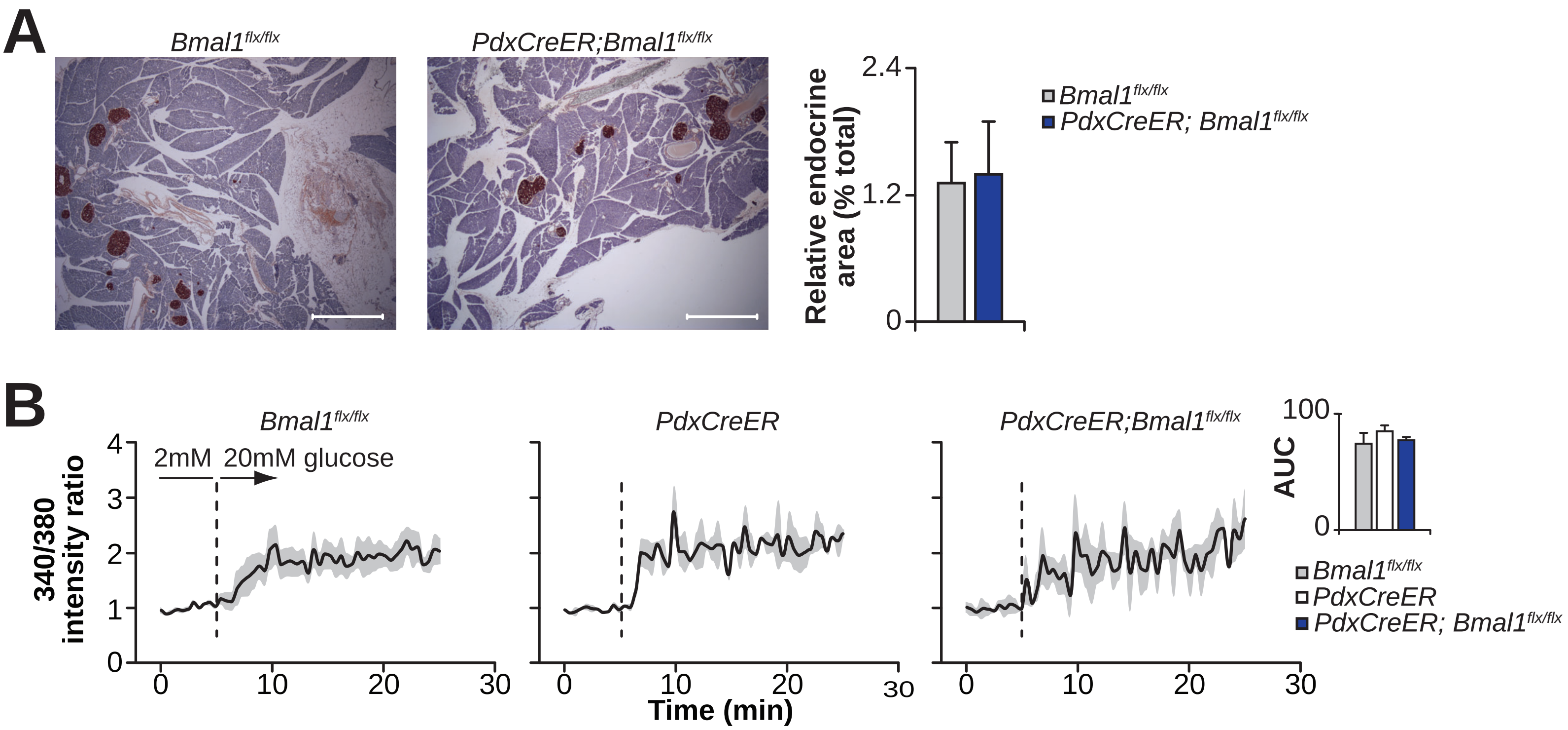

A
Bmal1flx/flx
PdxCreER;Bmal1flx/flx
Relative endocrine area (% total)
2.4
1.2
0
Bmal1flx/flx
PdxCreER; Bmal1flx/flx
B
Bmal1flx/flx
PdxCreER
PdxCreER;Bmal1flx/flx
340/380 intensity ratio
4
3
2
1
0
2mM
20mM glucose
0
10
20
30
Time (min)
AUC
100
0
Bmal1flx/flx
PdxCreER
PdxCreER; Bmal1flx/flx

Table S1

Cycling in WT Islets

KEGG Term	-log$_{10}$ P-value	Genes in Term	Target Genes in Term	Fraction of Targets	Gene Symbol
Circadian rhythm	14.2992954	30	17	0.013832384	*Nr1d1, Prkaa2, Clock, Rorc, Rbx1, Npas2, Creb1, Rorb, Fbxw11, Per2, Rora, Per3, Prkag2, Arntl, Btrc, Prkaa1, Cry1*
Insulin secretion	10.86222887	86	22	0.017900732	*Cacna1c, Atf2, Chrm3, Prkacb, Slc2a2, Atf4, Camk2g, Prkcb, Prkx, Plcb1, Prkca, Cacna1d, Kcnn4, Gnaq, Creb1, Creb3, Plcb4, Pclo, Kcnn3, Atp1b2, Rims2, Stx1a*
SNARE interactions in vesicular transport	10.86222887	33	16	0.013018714	*Sec22b, Gosr1, Vti1b, Vamp8, Vamp5, Stx8, Ykt6, Vamp1, Bnip1, Vti1a, Vamp4, Stx17, Use1, Stx16, Stx4a, Stx1a*
COPII complex	7.449579942	11	7	0.005695688	*Sar1b, Sar1a, Sec31b, Sec24b, Sec31a, Sec24a, Sec13*
Phosphatidylinositol signaling system	6.130040566	81	24	0.019528072	*Calm1, Synj2, Plcd1, Dgke, Pikfyve, Itpr2, Inpp5k, Inpp5e, Prkcb, Plcb1, Dgkh, Plcg1, Prkca, Calm2, Pi4ka, Impa2, Ocrl, Inpp4a, Pip5k1b, Itpr1, Plcb4, Plcd3, Pik3r3, Synj1*
MAPK signaling pathway	5.435454827	253	58	0.04719284	*Rps6ka4, Il1r1, Atf4, Map2k5, Pdgfa, Prkx, Prkacb, Taok1, Cacna1a, Rapgef2, Ikbkb, Cacna1d, Nr4a1, Mapk8ip3, Map3k5, Nlk, Nfkb2, Dusp10, Rap1a, Gadd45b, Mapk10, Map2k3, Stmn1, Rap1b, Dusp4, Traf6, Sos1, Mapkapk2, Taok3, Rps6ka5, Hspa8, Map2k1, Cacna1c, Atf2, Elk4, Braf, Ppm1b, Pla2g4b, Prkcb, Mapk11, Prkca, Hspb1, Mapkapk5, Elk1, Ngf, Map3k3, Cacna2d1, Tnfrsf1a, Raf1, Cacna1b, Crkl, Rps6ka3, Sos2, Mknk1, Dusp3, Mapk9, Nf1, Nfatc3*
Protein export	4.23117336	25	9	0.007323027	*Sec11c, Spcs2, Hspa5, Immp2l, Sec61b, Srp9, Spcs1, Srp14, Sec11a*
Type II diabetes mellitus	3.580764239	50	14	0.011391375	*Cacna1c, Mapk10, Cacna1b, Slc2a2, Mtor, Insr, Cacna1a, Ikbkb, Cacna1d, Pik3r3, Irs1, Mapk9, Socs4, Prkce*

Differentially Expressed in *PdxCre;*$Bmal1^{flx/flx}$ Islets

KEGG Term	-log$_{10}$ P-value	Genes in Term	Target Genes in Term	Fraction of Targets	Gene Symbol
MAPK signaling pathway	4.105230153	253	26	0.052631579	*Dusp6, Cacna1c, Elk4, Cd14, Braf, Atf4, Myc, Prkcb, Taok1, Cacna1a, Gadd45g, Chuk, Hspb1, Rasa2, Cacna2d3, Tgfbr1, Map3k2, Cacna2d1, Cacna1h, Cacna2d2, Cacna1b, Akt3, Rras2, Pdgfra, Nf1, Jund*
Type II diabetes mellitus	3.580764239	50	7	0.01417004	*Cacna1a, Cacna1c, Hkdc1, Socs2, Pklr, Cacna1b, Socs4*
Phosphatidylinositol signaling system	3.205302246	81	10	0.020242915	*Pikfyve, Prkcb, Plcb4, Itpr1, Plcb3, Itpk1, Pik3c2a, Synj11a, Dgkh, Dgkb*
Insulin secretion	2.164694745	86	9	0.018218623	*Cacna1c, Atf4, Prkcb, Plcb4, Plcb3, Pclo, Kcnn4, Atp1b3, Rims2c13*

Circadian rhythm	2.009822141	30	4	0.008097166	*Prkab2, Clock, Per2, Per3*
COPII complex	1.817835746	11	2	0.004048583	*Sec23a, Sec24a*
Protein export	0.691657973	25	2	0.004048583	*Sec11c, Srp9*
SNARE interactions in vesicular transport	4.31E-12	33	0	0	0

BMAL1 Targets Non-Cycling

KEGG Term	-log$_{10}$ P-value	Genes in Term	Target Genes in Term	Fraction of Targets	Gene Symbol
Rap1 signaling pathway	12.44593154	214	34	0.065637066	*Pdgfc, Sipa1l1, Adcy2, Plce1, Pard6b, Magi2, Bcar1, Rapgef1, Igf1r, Efna5, Akt3, P2ry1, Adcy8, Kit, Gnai1, Fgfr2, Kitl, Src, Pard6a, Vegfc, Pard6g, Itgb1, Hgf, Sipa1l2, Fgf14, Kdr, Ins1, Prkd1, Tek, Magi3, Rac1, Gnao1, Mapk1, Nras*
MAPK signaling pathway	8.881669516	253	34	0.065637066	*Cd14, Gadd45g, Ecsit, Map3k7, Mapk8, Rps6ka2, Cacng4, Dusp1, Cacna2d3, Rps6ka1, Map3k14, Jun, Akt3, Ppm1a, Rasgrf2, Tgfb2, Flnb, Fgfr2, Nfatc1, Dusp6, Ppp3ca, Casp3, Myc, Mef2c, Fgf14, Nfkb1, Rac1, Tgfbr1, Mapk1, Pla2g4a, Nras, Dusp5, Grb2, Cacnb3*
Insulin secretion	7.184122363	86	15	0.028957529	*Gcg, Atp1b1, Rab3a, Cckar, Camk2d, Kcnma1, Kcnn2, Creb3l2, Ins1, Abcc8, Adcy2, Adcy8, Pdx1, Atp1a1, Atp1a3*
Phosphatidylinositol signaling system	2.936660459	81	10	0.019305019	*Cds1, Dgkb, Dgkg, Inpp4b, Pi4kb, Pi4k2a, Plce1, Itpk1, Pten, Inpp5j*
Circadian rhythm	2.927736192	30	5	0.00965251	*Cry2, Cul1, Bhlhe40, Bhlhe41, Per1*
Type II diabetes mellitus	2.031842078	50	6	0.011583012	*Mapk1, Mapk8, Hk3, Ins1, Abcc8, Pdx1*
Protein export	1.386777127	25	3	0.005791506	*Sec63, Spcs3, Sec62*
SNARE interactions in vesicular transport	0.387042009	33	2	0.003861004	*Vamp3, Stx18*
COPII complex	1.38097E-11	11	0	0	0

CLOCK Targets Non-Cycling

KEGG Term	-log$_{10}$ P-value	Genes in Term	Target Genes in Term	Fraction of Targets	Gene Symbol
Rap1 signaling pathway	12.87814504	214	23	0.085185185	*Pard6a, Vegfc, Pard6g, Itgb1, Cdc42, Hgf, Sipa1l2, Dock4, Prkd1, Adcy2, Magi2, Mapk1, Bcar1, Pard6b, Rapgef1, Efna5, Akt2, Gnai3, Ngfr, F2rl3, Vegfb, Kit, Gnai1*
MAPK signaling pathway	7.105451517	253	20	0.074074074	*Dusp7, Dusp6, Cdc42, Map3k4, Map3k7, Tab2, Max, Mapk8, Dusp1, Mecom, Akt2, Gng12, Mapk1, Rps6ka1, Jun, Map4k2, Dusp5, Mknk2, Tgfb2, Ppp3ca*

Circadian rhythm	5.503601854	30	5	0.018518519	*Cry2, Fbxl3, Bhlhe40, Bhlhe41, Per1*
Insulin secretion	2.396637964	86	6	0.022222222	*Abcc8, Adcy2, Kcnj11, Camk2d, Kcnma1, Atp1b3*
Type II diabetes mellitus	2.241662226	50	4	0.014814815	*Mapk1, Mapk8, Abcc8, Kcnj11*
Phosphatidylinositol signaling system	0.567315545	81	3	0.011111111	*Dgkg, Inpp4b, Pten*
SNARE interactions in vesicular transport	0.34973543	33	1	0.003703704	*Gosr2*
COPII complex	1.40878E-11	11	0	0	0
Protein export	1.1483E-11	25	0	0	0

BMAL1 Targets Cycling

KEGG Term	-log$_{10}$ P-value	Genes in Term	Target Genes in Term	Fraction of Targets	Gene Symbol
Circadian rhythm	10.2035023	30	6	0.037037037	*Nr1d1, Prkag2, Prkaa2, Rbx1, Arntl, Clock*
Insulin secretion	4.527557	86	6	0.037037037	*Pclo, Chrm3, Slc2a2, Camk2g, Rims2, Gnaq*
Rap1 signaling pathway	3.138964233	214	9	0.055555556	*Rapgef6, Ngf, Magi1, Skap1, Insr, Pard3, Cnr1, Adora2b, Gnaq*
Type II diabetes mellitus	2.361287911	5	3	0.018518519	*Irs1, Slc2a2, Insr*
MAPK signaling pathway	2.306955066	253	9	0.055555556	*Ngf, Il1r1, Dusp4, Ppm1b, Mknk1, Taok1, Rps6ka3, Rps6ka5, Nfkb2*
Protein export	2.285014334	25	2	0.012345679	*Sec61b, Immp2l*
SNARE interactions in vesicular transport	1.829545138	33	2	0.012345679	*Stx17, Stx16*
COPII complex	1.537746457	11	1	0.00617284	*Sec31a*
Phosphatidylinositol signaling system	1.355737038	81	3	0.018518519	*Pikfyve, Pip5k1b, Itpr2*

CLOCK Targets Cycling

KEGG Term	-log$_{10}$ P-value	Genes in Term	Target Genes in Term	Fraction of Targets	Gene Symbol
Circadian rhythm	11.92035309	30	6	0.037037037	*Nr1d1, Rorc, Arntl, Per2, Cry1, Per3*
MAPK signaling pathway	4.899304791	253	10	0.055555556	*Cacna1c, Cacna2d1, Stmn1, Rps6ka4, Dusp4, Mknk1, Cacna1a, Prkca, Hspb1, Nfatc3*
COPII complex	4.353710244	11	2	0.00617284	*Sec31a, Sec24a*
Insulin secretion	1.828132526	86	3	0.037037037	*Cacna1c, Prkca, Chrm3*

Type II diabetes mellitus	1.649314642	50	2	0.018518519	*Cacna1a, Cacna1c*
Rap1 signaling pathway	1.339863213	214	5	0.055555556	*Prkca, Cnr1, Vegfa, Calm2, Pfn2*
Phosphatidylinositol signaling system	0.977936239	81	2	0.018518519	*Prkca, Calm2*
SNARE interactions in vesicular transport	0.878529011	33	1	0.012345679	*Stx16*
Protein export	1.66591E-11	25	0	0.012345679	0

Table S2

Signature β-Cell Genes	**Cycling**	**Differentially Expressed in *Bmal1* KO at ZT2**	**BMAL1 Target**
Glut2	Yes	No	Yes
Gck	No	No	No
Kcnj11	No	No	No
Abcc8	No	No	Yes
Pcsk1	No	No	No
Glp1r	No	No	No
Ins1	No	No	Yes
Ins2	No	No	No

Key Transcription Factors	**Cycling**	**Differentially Expressed in *Bmal1* KO at ZT2**	**BMAL1 Target**
Pdx1	No	No	Yes
Nkx2.2	No	No	No
Pax6	No	No	No
NeuroD1	No	No	No
MafA	No	No	No
Ngn3	No	No	No
Pax4	No	No	No

“Disallowed” Genes	**Cycling**	**Differentially Expressed in *Bmal1* KO at ZT2**	**BMAL1 Target**
Ldha	Yes	No	No
Slc61a1	No	No	No
Pdgfra	No	2.3 fold increase	No
Cxcl12	No	No	Yes
Maf	No	0.3 fold increase	Yes
Lmo4	No	1.8 fold increase	No
Hk1	No	No	No