Supplementary Data:

1. Expanded Methods

Animal Model: Surgical methods have been previously described [2,3]. In brief, time-dated Sprague-Dawley pregnant rats (Charles River Laboratories, Malvern, PA, USA) were individually housed under standard conditions and allowed free access to standard rat chow and water. In order to induce IUGR, on day 18 of gestation (term is 22 days) both uterine arteries were ligated, resulting in an approximately 50% reduction in blood flow [2,3]. Control animals underwent sham surgery. The rats recovered within a few hours and had free access ad libitum to food and water. The pregnant rats were allowed to deliver spontaneously, and the litter size was randomly reduced to 8 to insure uniformity of litter size between IUGR and control litters. IUGR and control pups were fostered to unoperated normal female rats and remained with their foster mothers until they were weaned.

Exendin-4 Treatment: Exendin-4 (Ex-4) was purchased from Bachem (King of Prussia, PA, USA) and prepared as either 1 μM or 10μM stock solutions in 0.9% sodium chloride and stored at -80C in single use aliquots. Just prior to injection, the aliquots were thawed and diluted in phosphate-buffered saline (PBS). Four experimental groups were studied. 1) control pups treated with vehicle (PBS); 2) control pups treated with Ex-4 (1 nmole/kg body weight injected subcutaneously for 6 days starting on day of life one; 3) IUGR pups treated with vehicle; 4) IUGR pups treated with Ex-4. All animals were treated on postnatal day 1-6. After Ex-4 or vehicle injection on day of life 6, islets were harvested from each of the 4 groups for the neonatal experiments and at age 3-12 months for the adult experiments. There were no differences in relative antibody binding over the adult age range, thus the data were analyzed as a single adult group. For the neonatal experiments, islets were harvested from 16 litters of IUGR and 16 litters of control animals. Islets were pooled from one litter for each experiment. Islets were pooled from 10 male adult animals for each treatment group. These studies were approved by the Animal Care Committee of The Children's Hospital of Philadelphia and the University of Pennsylvania.

Pdx1 mRNA: Total RNA was isolated from islets from 2 week and adult animals from each experimental group (n = 5, all from different litters, per group) using RNAzol B (Tel-Test, Friendswood, TX, USA). Quantitative PCRs were carried out using equivalent dilutions of each cDNA sample, the fluorescent indicator SYBR green, the empirically determined concentration of each primer, and the Applied Biosystems model 7700 sequence detector PCR machine (PerkinElmer Life Sciences, Waltham, MA, USA), as previously described [4]. To verify that only a single PCR product was generated for each amplified transcript, the multicomponent data for each sample were subsequently analyzed using the Dissociation Curves 1.0 program (PerkinElmer Life Sciences). To account for differences in starting material, quantitative PCR was also carried out for each cDNA sample using the Applied Biosystems rat β-Actin 20x primer and probe reagent (PerkinElmer Life Sciences). β-Actin mRNA levels in islets did not differ between the four groups. The relative abundance of the target was divided by the relative abundance of β-Actin in each sample to generate a normalized abundance. Each reaction was carried out in triplicate. Standard PCR conditions were used.

ChIP Assay: Chromatin immunoprecipitation assays were performed as previously described [14] with approximately 1000 pancreatic islets per experiment per group for the neonatal experiments and 500 islets per group for the adult experiments. In brief, pancreatic islets were isolated and trypsin digested and suspensions were fixed in phosphate-buffered saline containing 1% formaldehyde and protease inhibitor cocktail. Sonication of the islet samples was performed to yield DNA fragments ranging in size from 200-1000 bp. Soluble chromatin was diluted in IP

buffer and protease inhibitors. Supernatants were collected and cleared by incubation with protein-A-sepharose, sonicated salmon sperm DNA, and 20 μL of preimmune serum was used to monitor sonication length of the sheared chromatin. An aliquot of supernatant was collected from each experimental group and used as the total input DNA. Immunoprecipitation was carried out overnight with IgG (negative control), primary antibody to the modified histone (acetylated histone H3, H3K9me2 (Upstate/Millipore, Billerica, MA, USA), H3K4me3 (abCAM, Cambridge, MA), USF1 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), p300 (Upstate/Millipore), PCAF (Upstate Biotech/Millipore), or Dnmt1 (Upstate Biotech/Millipore) and no antibody. Cross-links were reversed and the released DNA was extracted, precipitated, and resuspended in Tris-EDTA. For each experimental group DNA sequences in the "input" and the IP samples were quantified relative to each other by real-time quantitative PCR with primers to the proximal region of the *Pdx1* promoter shown in Figure 1. (Forward: 5' AAT GGT GGC CCC AGG CTG AA 3'. Reverse: 5' AAC CAC AGG CTG GCG AGA GAC A 3') Quantitative PCR was used to measure binding of USF1, Acetylated H3, H3K4me3, H3K9me2, PCAF, p300, and DNMT1 at the promoters of *Pdx1* and β-Actin (Forward: 5'CAC GCC CTT TCT CAA TTG TCT TTC T 3' Reverse: 5' GGC CAT TTA TCA CCA GCC TCA TTA G 3' (50)). Real-time quantitative PCR was carried out using an ABI 7900HT Real-Time PCR system with SYBR Green Master Mix from Applied Biosystems. Results were expressed as IP per total input for each experimental group and normalized to the IP per total input value for the control vehicle experimental group for each antibody. Standard methods of ChIP data normalization were used to normalize individual sample immunoprecipitated DNA to both total input DNA for each experimental group and to a control sequence [24].

HAT activity: Islet HAT activity was measured from pooled islet samples from 1-week old animals, approximately 1000 islets per group, via colorimetric assay using cofactor Acetyl-CoA (Kamiya Biomedical, Seattle, WA, USA). Measurements were made at baseline and at the following time points: 1, 2 and 3 hours. Total HAT activity was computed as area under the curve and normalized to control vehicle. Experiments were performed in triplicate.

***USF1 Phosphorylation and PCAF coimmunoprecipitation*:** Islets were harvested from animals at 1 week of age and nuclear protein extracts were then prepared from islets. Nuclear extracts (10 μg of protein/reaction) were first immunoprecipitated with normal rabbit serum (negative control) or anti-USF1. Reactions were resolved by one-dimensional SDS-PAGE and electrophoretically transferred to polyvinylidene difluoride membranes. Membranes were incubated with anti-phosphoserine (1:500 dilution) or PCAF (1:500 dilution) antibody, and immunoreactive proteins were visualized by incubation with horseradish peroxidase-linked donkey anti-rabbit secondary antibody (1:5000 dilution) and the ECL Plus Western blotting system according to the manufacturer's instructions. Densitometric analyses were then performed using MacBAS, Fuji PhotoFilm Co., Ltd. and Kohshin Graphics, Inc. and values were normalized to control samples treated with vehicle. Each experiment was repeated 3 times (3 animals from 3 different litters).

Methylation analysis of the Pdx1 CpG island: Genomic DNA was extracted from 6-9 month old animals from the following groups: IUGR (n=5), IUGR Ex4 (n=5), control (n=5) and control Ex4 (n=5). Bisulfite modification was done using Zymo Research EZ Methylation Gold kit. Genomic DNA was isolated by phenoyl-chloroform-isoamyl alcohol and was collected by ethanol precipitation. Pyrosequencing analysis was performed by EpigenDx (Worchester, MA, USA). 500ng sample of genomic DNA was used for bisulfite modification followed by PCR amplification. Primer sequences are as follows:

Bisulfite Outer untreated primers:
TTAAGCTCTAATGGAGCGGTTT

GCACTTCGGGGCCGGCAGCCC

Outer bisulfite treated primers
TTAAGTTTTAATGGAGYGGTTT
ACACTTCRAAACCRACAACCC

Inner untreated primers
AGGACAGGAGAGATCAGCCTGCTGA
CTACAAGCCAGGCCTTAAGGCGCT

Inner bisulfite treated primers
AGGATAGGAGAGATTAGTTTGTTGA
CTACAAACCAAACCTTAAAACRCT

Statistical Analyses: Statistical analyses were performed using analysis of variance and the Student's unpaired t-test with unequal measures of variance. A *P* value less than 0.05 was considered significant.