Supplemental Methods

CRISPR-Cas9 gene targeting

Zfp423$^{WT\text{-}Avi}$ and *Zfp423*$^{H1285\text{-}Avi}$ mice were generated using CRISPR-Cas9 gene editing strategy with the following gRNA and repair template sequences:
gRNA sequence: ctcatcgtgtggttctgcaaagg
Zfp423$^{WT\text{-}Avi}$ repair template sequence:
tctgcagctctctgcgtccatgccctgggtgggaggggacaggcatgctcgccattctttcgccctcatgcgtgtctcctttcttc
ggctttgcagaacaacacgatgagccagcacgcacagtgagggacctcgcgacaggacacctctccgcagaaggctt
gccggagacgccgtggggagggccatttgaacat
Zfp423$^{H1285N\text{-}Avi}$ repair template sequence:
tctgcagctctctgcgtccatgccctgggtgggaggggacaggcatgctcgccattctttcgccctcatgcgtgtctcctttcttc
ggctttgcagaacaacacgatgagccagcacgcacaatgagggacctcgcgacaggacacctctccgcagaaggctt
gccggagacgccgtggggagggccatttgaacat

Rodent diets and drug treatments

Mice were maintained on a standard rodent chow diet or chow diet containing 600 mg/kg doxycycline (DOX) (Bio-Serv, S4107). For high-fat diet studies, mice were fed a standard high-fat diet (60 kcal% fat, Research Diets, D12492i) or doxycycline-containing high fat diet (600 mg/kg dox, 60% kcal% fat, Bio-Serv, S5867) as indicated. For rosiglitazone administration, mice were orally gavaged with vehicle (1% methylcellulose) or 10 mg/kg/day of rosiglitazone (Cayman Chemical) for 4 weeks.

Proteomics

For proteomics analysis, gel fragments were reduced and alkylated with DTT (20 mM) and iodoacetamide (27.5 mM). Gel fragments were then incubated on ice with a 0.1 µg/µL solution of trypsin in 50 mM triethylammonium bicarbonate (TEAB). 50 µL of 50 mM TEAB was then added to the gel pieces for overnight digestion (Pierce). Following solid-phase extraction with an Oasis MCX µelution plate (Waters), the resulting peptides were reconstituted in 10 µL of 2% (v/v) acetonitrile (ACN) and 0.1% trifluoroacetic acid in water. 2 µL of this was injected onto an Orbitrap Fusion Lumos mass spectrometer (Thermo Electron) coupled to an Ultimate 3000 RSLC-Nano liquid chromatography systems (Dionex). Samples were injected onto a 75 µm i.d., 75-cm long EasySpray column (Thermo), and eluted with a gradient from 1-28% buffer B over 90 min. Buffer A contained 2% (v/v) ACN and 0.1% formic acid in water, and buffer B contained 80% (v/v) ACN, 10% (v/v) trifluoroethanol, and 0.1% formic acid in water. The mass spectrometer operated in positive ion mode with a source voltage of 2.4 kV and an ion transfer tube temperature of 275 °C. MS scans were acquired at 120,000 resolution in the Orbitrap and up to 10 MS/MS spectra were obtained in the ion trap for each full spectrum acquired using higher-energy collisional dissociation (HCD) for ions with charges 2-7. Dynamic exclusion was set for 25 s after an ion was selected for fragmentation.

Raw MS data files were analyzed using Proteome Discoverer v2.2 (Thermo), with peptide identification performed using Sequest HT searching against the human protein database from UniProt. Fragment and precursor tolerances of 10 ppm and 0.6 Da were

specified, and three missed cleavages were allowed. Carbamidomethylation of Cys was set as a fixed modification and oxidation of Met was set as a variable modification. The false-discovery rate (FDR) cutoff was 1% for all peptides.

Antibodies for immunoblotting

The primary antibodies and the working concentrations are as following:
Anti-FLAG: 1:1000 dilution; Sigma, #F1804
Anti-β-ACTIN: 1:10000 dilution, Sigma, #A1978
Anti-UCP1: 1:1000 dilution, Abcam, #ab155117
Anti-HISTONE H3: 1:1000 dilution, Cell Signaling Technology, #4499
Anti-BRG1: 1:1000 dilution, Abcam, #ab110641
Anti-EBF2: 1:1000 dilution, R&D Systems, #AF7006
Anti-β–TUBULIN: 1:1000 dilution, Cell Signaling Technology, #2128
Anti-CHD4: 1:1000 dilution, Abcam, #ab70469
Anti-MTA1: 1:1000 dilution, Cell Signaling Technology, #5647
Anti-HDAC1: 1:1000 dilution, Cell Signaling Technology, #5356
Anti-RBAP46: 1:1000 dilution, Cell Signaling Technology, #6882

Chromatin Immunoprecipitation (ChIP)

Fixed cells or tissue samples were lysed in Farnham lysis buffer (5 mM PIPES pH 8.0, 85 mM KCl, 0.5% NP-40, 1 mM DTT, and Protease inhibitor cocktail [Sigma, #P8340]) to obtain nuclear material. Crude nuclear pellets were collected by centrifugation and then lysed by incubation in lysis buffer containing 5 mM Tris-HCl pH 7.9, 1% SDS, 10 mM EDTA, 1mM DTT, and Protease inhibitor cocktail [Sigma, #P8340]. Chromatin fragmentation (200-500 bp length) was performed at 4 °C by Bioruptor 300 using the setting of 10 cycles of 30 seconds on and 60 seconds off. Soluble chromatin was diluted 1:10 with dilution buffer (20 mM Tris-HCl pH 7.9, 0.5% Triton X-100, 2 mM EDTA, 150 mM NaCl, 1 mM DTT, and Protease inhibitor cocktail [Sigma, #P8340]) and pre-cleared using Protein G Sepharose 4 Fast Flow (GE Healthcare Bio-sciences, #17-0618-01) for 1 hour at 4 °C. Pre-cleared samples were incubated with the indicated antibodies overnight at 4 °C. Antibody-protein-DNA complexes were captured by incubation with Protein G Sepharose 4 Fast Flow (GE Healthcare Bio-sciences, #17-0618-01) at 4 °C for 2 hours. Immunoprecipitated material was consecutively washed with low salt wash buffer (20 mM Tris-HCl pH 7.9, 2 mM EDTA, 125 mM NaCl, 0.05% SDS, 1% Triton X-100, and Protease inhibitor cocktail [Sigma, #P8340]), high salt wash buffer (20 mM Tris-HCl pH 7.9, 2mM EDTA, 500 mM NaCl, 0.05% SDS, 1% Triton X-100, and Protease inhibitor cocktail [Sigma, #P8340]), LiCl wash buffer (10 mM Tris-HCl pH 7.9, 1 mM EDTA, 250 mM LiCl, 1% NP-40, 1% sodium deoxycholate, and Protease inhibitor cocktail [Sigma, #P8340]), and 1x Tris-EDTA (TE). After elution (100 mM NaHCO3, 1% SDS), the immunoprecipitated material was digested with RNase (Roche, #11119915001) and proteinase K (ThermoFisher Scientific, #EO0491) prior to the purification and concentration of the immunoprecipitated genomic DNA by ChIP DNA Clean & Concentrator kit (Zymo Research, #D5201). ChIP-isolated DNA was subjected to qPCR (ChIP-qPCR) or library production (ChIP-seq) using NEBnext NGS DNA Library Preparation for Illumina kit (New England BioLabs, #E7645). Sequencing was performed

with Illumina NextSeq 500 Mid Output (130M) by the UT Southwestern McDermott Center Next Generation Sequencing Core.

ChIP- and ChAP-seq analysis

ChIP- and ChAP-seq analysis Trimgalore version 0.4.1 was used to remove adapter sequences and to remove reads shorter than 35bp or with phred quality scores less than 20. Trimmed reads were then aligned to the mouse reference genome (GRCm38/mm10) using default parameters in BWA version 0.7.12. The aligned reads were subsequently filtered for quality and uniquely mappable reads were retained for further analysis using Samtools version 1.3 and Sambamba version 0.6.6. Library complexity was measured using BEDTools version 2.26.0 and meets ENCODE data quality standards. Relaxed peaks were called using MACS version 2.1.0 with a p-value of 1x10-2. Gene annotation of the regions bound by indicated proteins were performed by GREAT version 3.0.0 (http://great.stanford.edu/public/html). For heatmaps and profiles of ChIP-seq intensities, we used deepTools version 2.5.0 to generate read abundance from all ChIP-seq datasets around peak center using ‘computeMatrix’. These matrices were then used to create heatmaps and profiles, using deepTools commands ‘plotHeatmap’ and ‘plotProfile’ respectively. To identify the primary motif present in ZFP423-occupied peaks, we performed motif enrichment analysis using the MEME suite version 5.3.2 (https://meme-suite.org/meme/). Differential peak calling was performed using Diffbind version 2.0.2 with FDR threshold of 5x10-2.