**ESM Methods**

**Reagents and antibodies.** DMSO, Akt VIII inhibitor and fish gelatin were from Sigma-Aldrich (St. Louis, MO, USA). Rapamycin was from Biomol, (Plymouth-Meeting, PA, USA). PF-4708671 was from Symansis (Timaru, NZ). Insulin was from Eli Lilly (Toronto, ON, Canada). The anti-IRS1, anti-PGC1α, anti-HNF4α, anti-S6K1, anti-G6Pase and anti-PEPCK antibodies were from Santa Cruz Biotechnology Inc. (Santa Cruz Biotechnology, Paso Robles, CA, USA). The anti-phospho-IRS-1 Ser 1101 and Ser 636/9; the anti-phospho-S6K1 Thr 389, phospho-S6 Ser 235/36, phospho-MSK1 Thr581, MSK1, phospho-Ser133 CREB, S6, CREB, Foxo, eEF2, phospho-Thr172 AMPK, AMPK and the phospho-Akt Ser 473, Thr 308 were from Cell Signaling Technologies (Danvers, MA, USA). The anti-actin was from Millipore (St. Louis, MO, USA). Antibodies from Cell Signaling Technology, were used at 1:1,000 dilution. Santa Cruz Biotechnology Inc. antibody was used at 1:500 dilution. β-actin antibody was used at 1:10,000 dilution.

**Glucose uptake.** L6 cells were serum-deprived during 5 h prior to the experiments, and 100 nmol/l of insulin was used to stimulate the cells during the last hour of deprivation. L6 cells were incubated for 8 min in HEPES-buffered saline containing 10 μmol/l unlabeled 2-DG and 10 μmol/l D-2-deoxy-[3H] glucose (0.5 μCi/ml). The reaction was terminated by washing three times with ice-cold 0.9% NaCl (wt/vol). Cell-associated radioactivity was determined by lysing the cells with 0.05 N NaOH, followed by liquid scintillation counting and normalization to protein concentration.
**Glucose production.** FAO cells were incubated 16 h in serum-free medium, with or without the indicated concentration of insulin, PF-4708671 (10 µmol/l) or rapamycin (25 nmol/l). The cells were washed three times with PBS and incubated with phenol- and glucose-free DMEM medium supplemented with 20 mmol/l sodium L-lactate and 2 mMmol/l sodium pyruvate for 5 h with or without the indicated concentration of insulin, PF-4708671 (10 µmol/l) or rapamycin (25 nmol/l). Cell supernatants were collected and glucose concentration was measured with the Amplex-Red Glucose assay kit (Invitrogen, Burlington, ON, Canada) according to the manufacturer’s instructions. Cells were lysed with 50 mmol/l NaOH and protein concentration was determined using a BCA protein assay kit for normalization.

**Animal studies.** Animal handling and treatment were approved by the Animal Care and Handling Committee of Laval University. 6 weeks old male C57Bl/6 mice were purchased from Charles River Laboratories (St. Constant, QC, Canada) and housed individually in cages in a room kept at 23 ± 1°C with a 12-h light/12-h dark cycle. After 1-week adaptation, mice were matched by weight and put on standard diet (Chow) or on a high fat diet (HFD, 60 % Kcal from fat, Research Diets, D12492) for 12 weeks. HFD-fed mice were then randomly assigned to three groups: control (HF) receiving vehicle (8% (vol/vol) EtOH, 0.2% (wt/vol) carboxymethylcellulose sterile), treated with PF-4708671 (35 mg kg⁻¹ day⁻¹, i.p.) or treated with rapamycin (2 mg kg⁻¹ day⁻¹, i.p.) for 7 days while being kept on the same HFD. After the treatments, mice were fasted for 6 h and euthanized 5 min after tail-vein injection of either saline or insulin (3.8 U/kg body weight). Tissues and blood were rapidly harvested and frozen in liquid nitrogen. Dual X-
ray absorptiometry (Piximus; Lunar, Madison, WI) was used to measure total fat and lean masses as well as bone mineral content in mice anesthetized with isoflurane.

**RNA extraction and quantitative PCR analysis.** The primer sequence used for evaluating PEPCK and G6Pase expression in FAO cells: (PEPCK; 5’-TGGGTGATGACATTGCCTGG-3’), (G6Pase; 5’-CGACTCGCTACCTCCAA GTG-3’). Data are expressed as the ratio between the expression of the target gene and the housekeeping gene 36B4 (also known as ARBP). Mouse liver (PEPCK; Mm01247058_m1), (G6Pase; Mm00839363_m1) and gene expression were evaluated with primer/probes and Taqman gene expression master mix from Life Technologies.