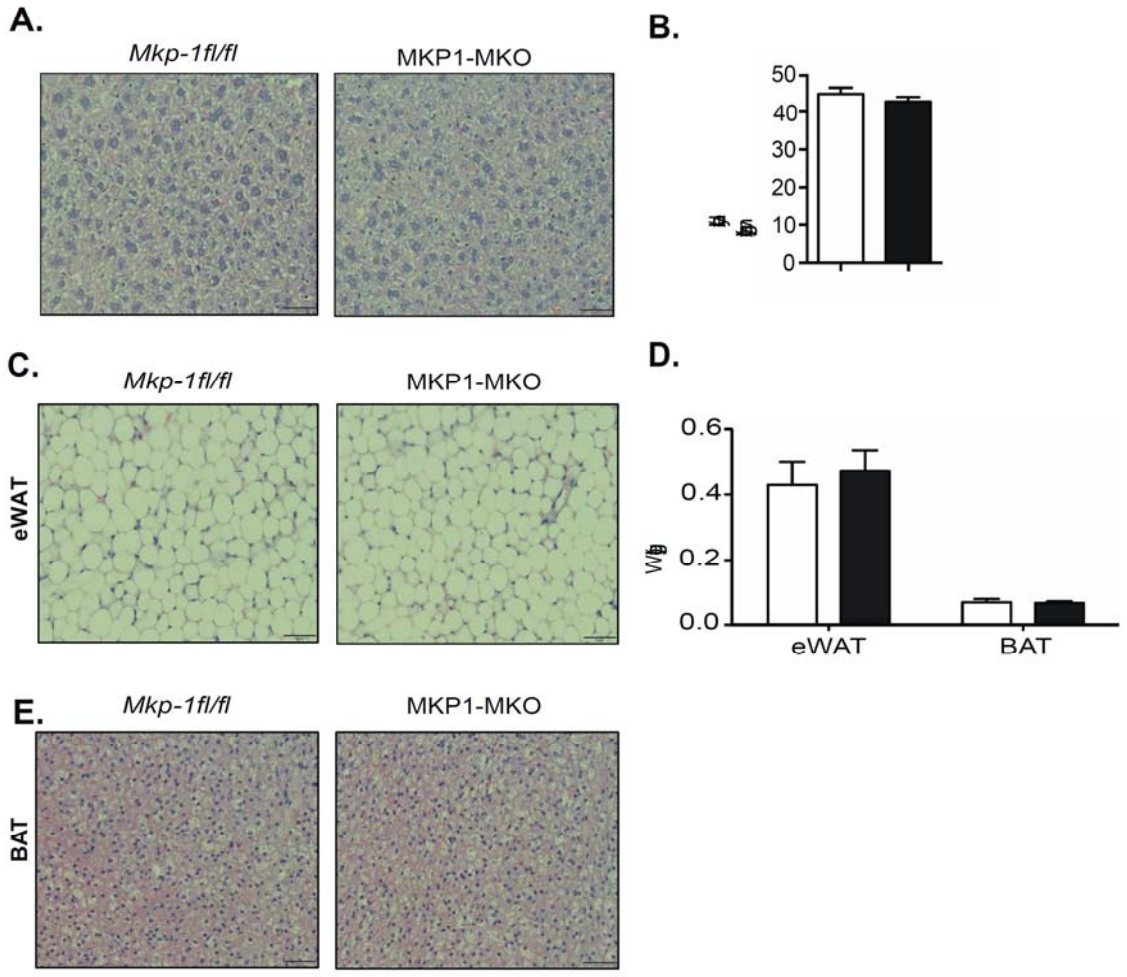
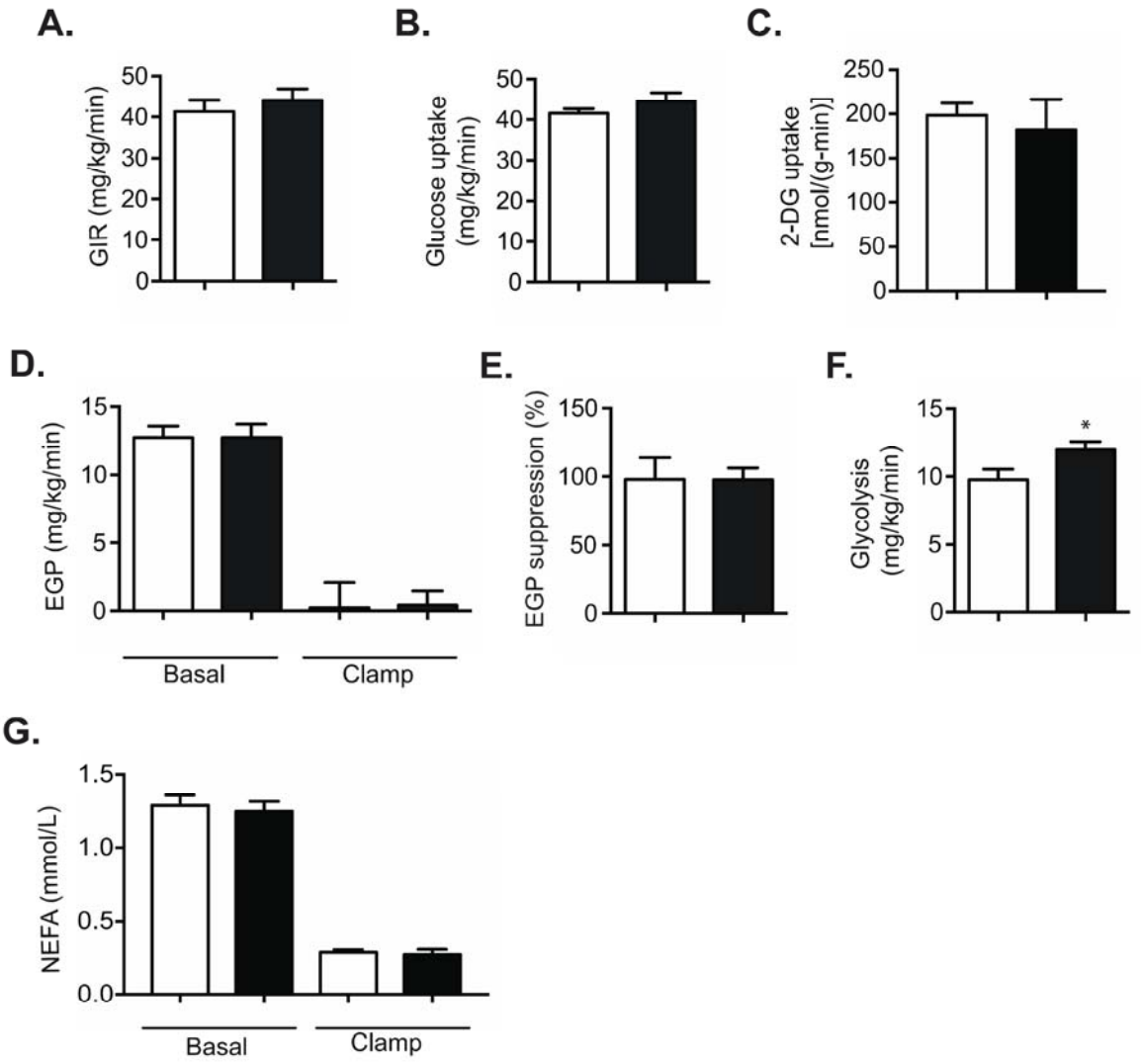
SUPPLEMENTARY DATA

Supplementary Figure 1. **Liver and adipose tissue histology in MKP1-MKO mice.** Representative hematoxylin and eosin staining from chow-fed *Mkp-1*$^{fl/fl}$ and MKP1-MKO mice of (**A**) liver, (**C**) epididymal white adipose (eWAT) and (**E**) brown adipose tissue. Quantitation of (**B**) liver and (**D**) adipose tissue weights from chow-fed *Mkp-1*$^{fl/fl}$ and MKP1-MKO mice (n = 5 per genotype). Data represent the mean ± SEM. Open bars, *Mkp-1*$^{fl/fl}$ mice; closed bars, MKP1-MKO mice.



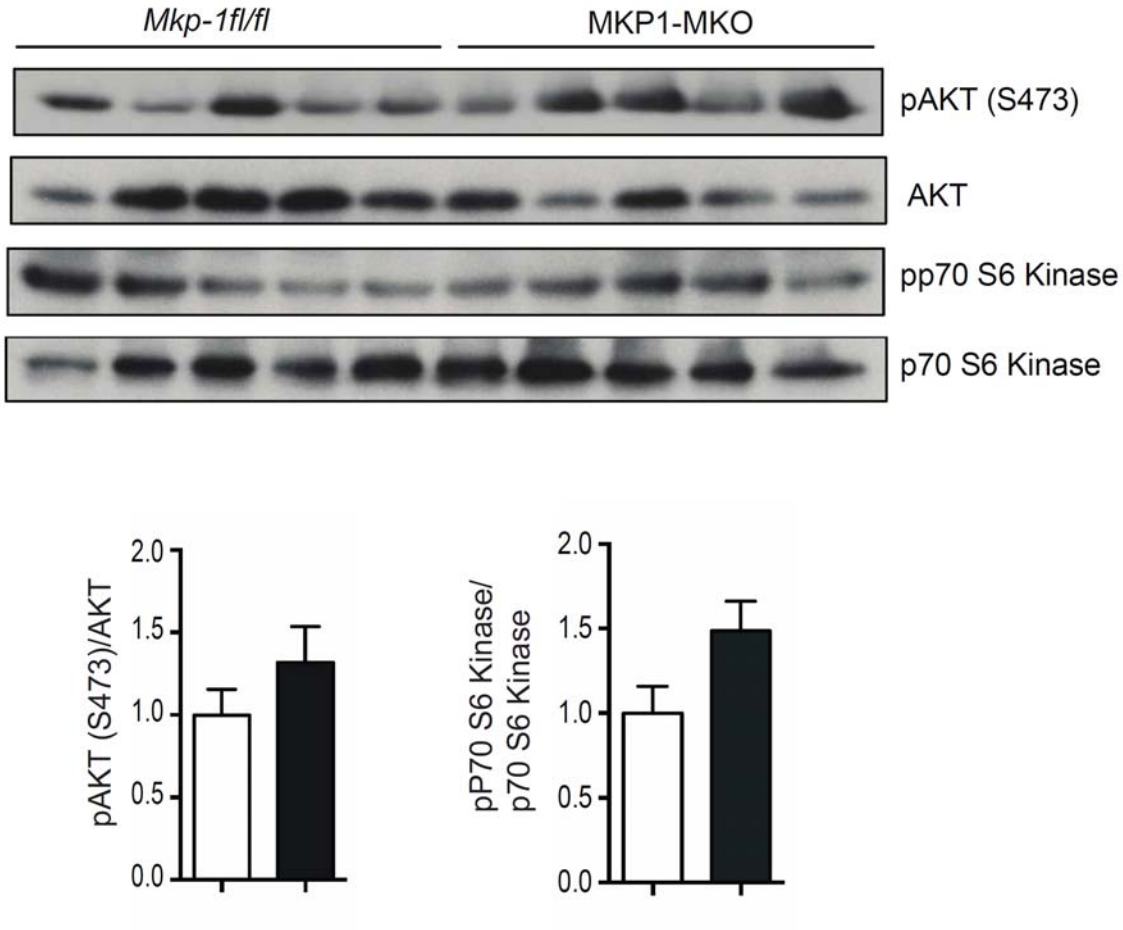
SUPPLEMENTARY DATA

Supplementary Figure 2. Glucose homeostasis in chow-fed MKP1-MKO mice. (**A-E**) Hyperinsulinemic-euglycemic clamps were performed on chow-fed *Mkp-1*$^{fl/fl}$ and MKP1-MKO mice. (**A**) glucose infusion rate (GIR), (**B**) glucose uptake, (**C**) 2-Deoxy glucose uptake, (**D**) hepatic endogenous glucose production (EGP), (**E**) hepatic insulin action (**F**) glycolysis (**G**) non-esterified free fatty acids (n = 8 per genotype). Data are represented as mean ± SEM. *; $p < 0.05$, as determined by student's t-test. Open bars, *Mkp-1*$^{fl/fl}$ mice; closed bars, MKP1-MKO mice.



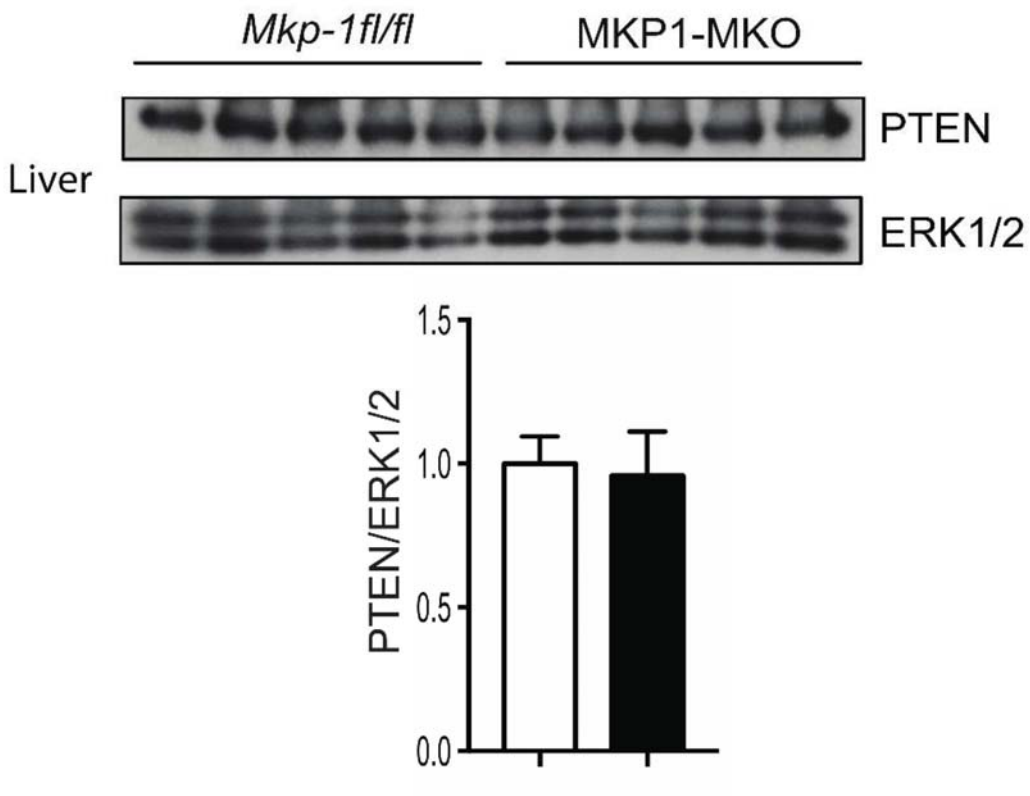
SUPPLEMENTARY DATA

Supplementary Figure 3. Akt signaling in skeletal muscle of chow-fed MKP1-MKO mice. Skeletal muscle lysates from chow-fed *Mkp-1*$^{fl/fl}$ and MKP1-MKO mice were analyzed by immunoblotting. Immunoblots were quantitated by densitometry for the levels of phospho-Akt/Akt and pp70 S6 kinase/p70 S6 kinase. Results represent n = 5 per genotype and data shown are the mean ± SEM. Open bars, *Mkp-1*$^{fl/fl}$ mice; closed bars, MKP1-MKO mice.



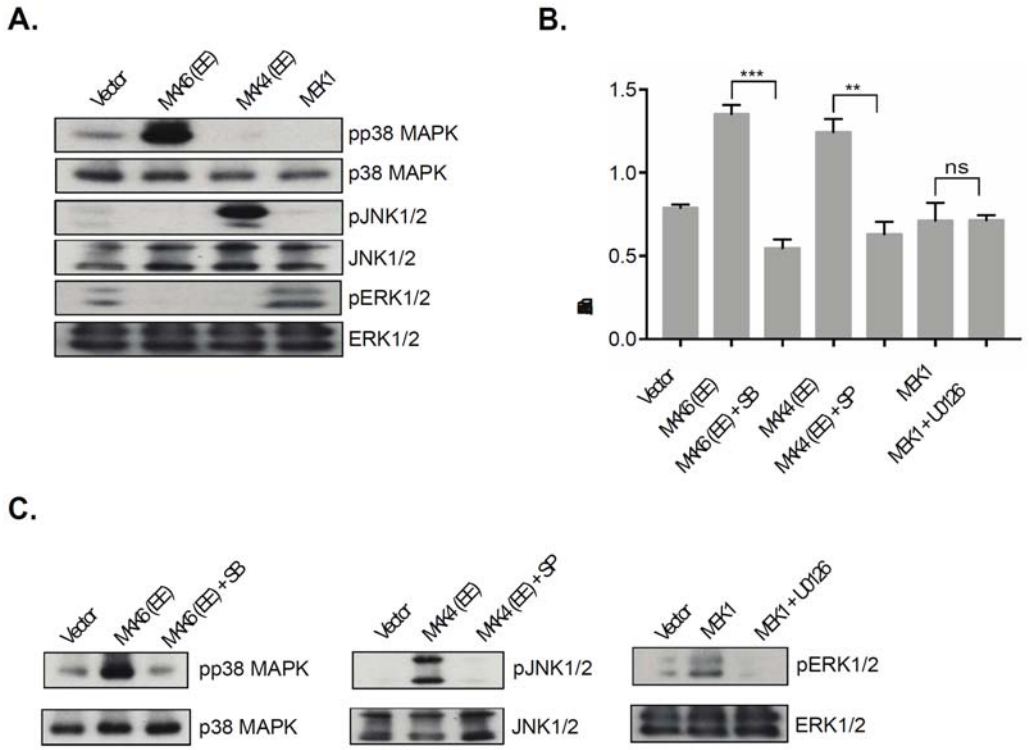
SUPPLEMENTARY DATA

Supplementary Figure 4. Hepatic expression of PTEN in MKP1-MKO mice. Immunoblots from livers of HFD-fed *Mkp-1*$^{fl/fl}$ and MKP1-MKO mice were immunoblotted for PTEN and ERK1/2 and densitometric quantitation of immunoblots. Results represent n = 5 per genotype, data shown are the mean ± SEM. Open bars, *Mkp-1*$^{fl/fl}$ mice; closed bars, MKP1-MKO mice.



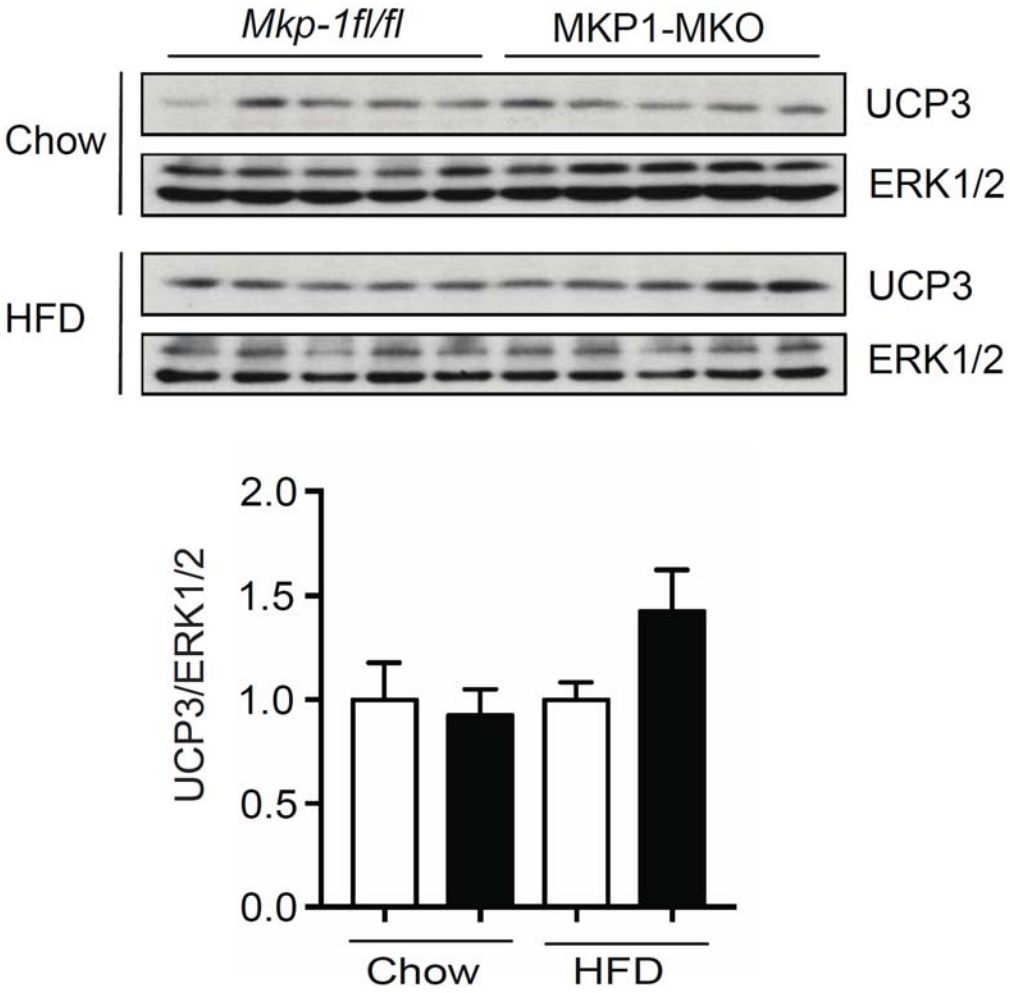
SUPPLEMENTARY DATA

Supplementary Figure 5. Effects of p38 MAPK, JNK and ERK on miR-21 expression in C2C12 myoblasts. C2C12 myoblasts were transfected with vector or constitutively active mutants of MKK6, MKK4 and MEK1. (**A**) C2C12 myoblasts transfected with MKK6EE, MKK4EE and MEK1EE were analyzed by immunoblots for phospho-p38 MAPK/p38 MAPK, phospho-JNK/JNK and phospho-ERK1/2/ERK1/2) (Representative of 3 independent experiments). C2C12 myoblasts were transfected with vector or constitutively active mutants of MKK6, MKK4 and MEK1 in the absence or presence of MAPK inhibitors of SB203580 (p38 MAPK), SP600125 (JNK) and U0126 (MEK) as indicated. Transfected C2C12 myoblasts were analyzed for (**B**) miR-21 expression and (**C**) immunoblotted for phospho-p38 MAPK/p38 MAPK, phospho-JNK/JNK and phospho-ERK1/2/ERK1/2 (Representative of 3 independent experiments).



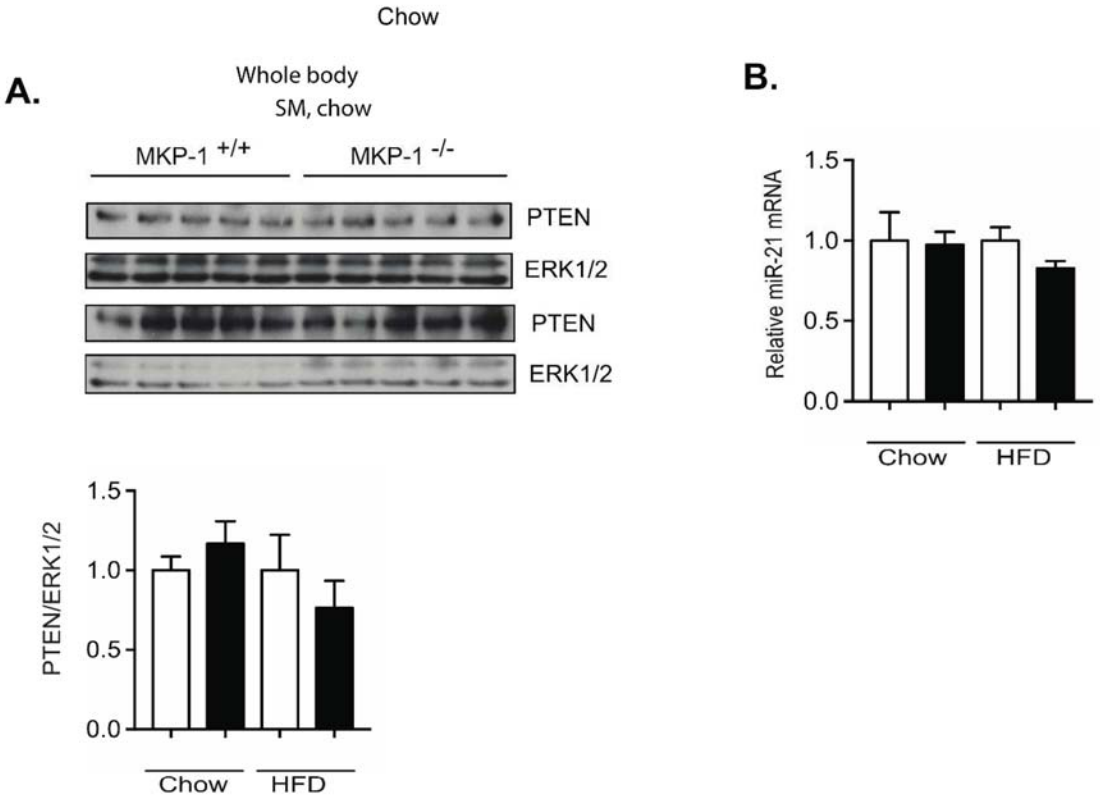
SUPPLEMENTARY DATA

Supplementary Figure 6. UCP3 expression in MKP1-MKO mice. Immunoblots from skeletal muscle of chow (upper panel) and HFD-fed (lower panel) *Mkp-1*$^{fl/fl}$ and MKP1-MKO mice were immunoblotted for UCP3 and ERK1/2. Densitometric quantitation of immunoblots shown below. Results represent n = 5 per genotype and data shown are the mean ± SEM. Open bars, *Mkp-1*$^{fl/fl}$ mice; closed bars, MKP1-MKO mice.



SUPPLEMENTARY DATA

Supplementary Figure 7. PTEN and miR-21 expression in MKP-1 whole body KO mice. (**A**) Immunoblots from skeletal muscle of chow (upper panel) and HFD-fed (lower panel) MKP-$1^{+/+}$ and MKP-$1^{-/-}$ mice were immunoblotted for PTEN and ERK1/2, and densitometric quantitation of immunoblots. (**B**) miR-21 expression. Results represent n = 5 per genotype and data shown are the mean ± SEM. Open bars, MKP-$1^{+/+}$ mice; closed bars, MKP-$1^{-/-}$ mice.



SUPPLEMENTARY DATA

Supplementary Figure 8. Model for skeletal muscle MKP-1 in obesity. Obesity results in overexpression of skeletal muscle MKP-1, which in turn down-regulates the p38 MAPK/JNK module. This promotes insulin resistance through a pathway involving skeletal muscle p38 MAPK/JNK activation of a miR-21/PTEN/Akt pathway. Skeletal muscle MKP-1 upregulation impairs mitochondrial function and promotes loss of oxidative myofibers which also contributes to the development of insulin resistance and reduced energy expenditure, leading to the onset of obesity.