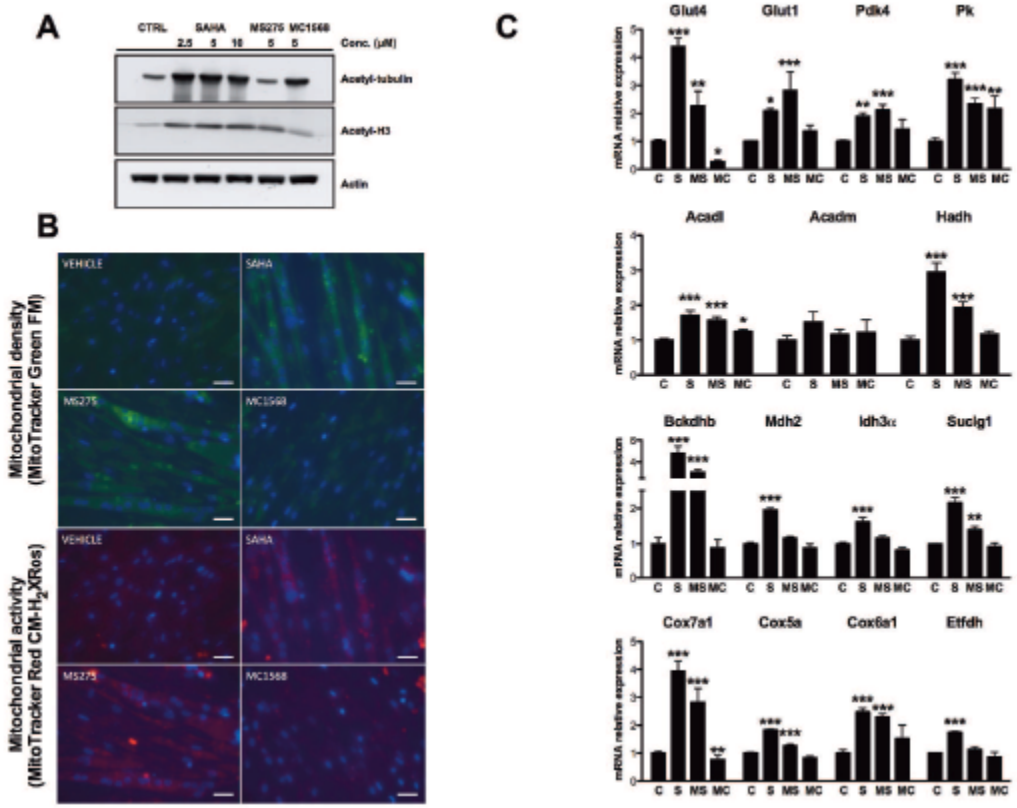
SUPPLEMENTARY DATA

Supplementary Table 1. Expression of genes involved in brown fat differentiation in WAT of *db/db* mice treated with HDAC inhibitors. Data are expressed as fold change (FC) versus control.

symbol	FC SAHA	FC MS275
Acrp30	0.97	1.82
Adrb1	1.17	1.03
Adrb2	1.01	1.04
Adrb3	1.33	7.63
Aldh6a1	0.92	1.75
Arl4a	0.93	2.18
Bnip3	0.96	1.99
Cebpa	0.97	2.20
Cebpb	1.08	1.19
Ero1l	0.95	1.07
Fabp4	0.96	1.44
Itga6	0.93	1.59
Lama4	0.98	1.96
Lamb3	1.06	0.31
Lrg1	1.23	1.86
Mb	0.88	0.80
Mrap	1.03	2.32
Nudt7	0.94	2.19
Pex11a	0.81	1.24
Pparg	1.06	2.05
Prdm16	1.10	0.94
Ptgs2	1.21	0.13
Rarres2	0.86	2.32
Rgs2	1.49	0.44
Scd1	1.01	1.22
Selenbp1	1.11	1.34
Sh2b2	0.93	2.38
Slc2a4	0.94	2.66
Ucp1	1.61	1.60

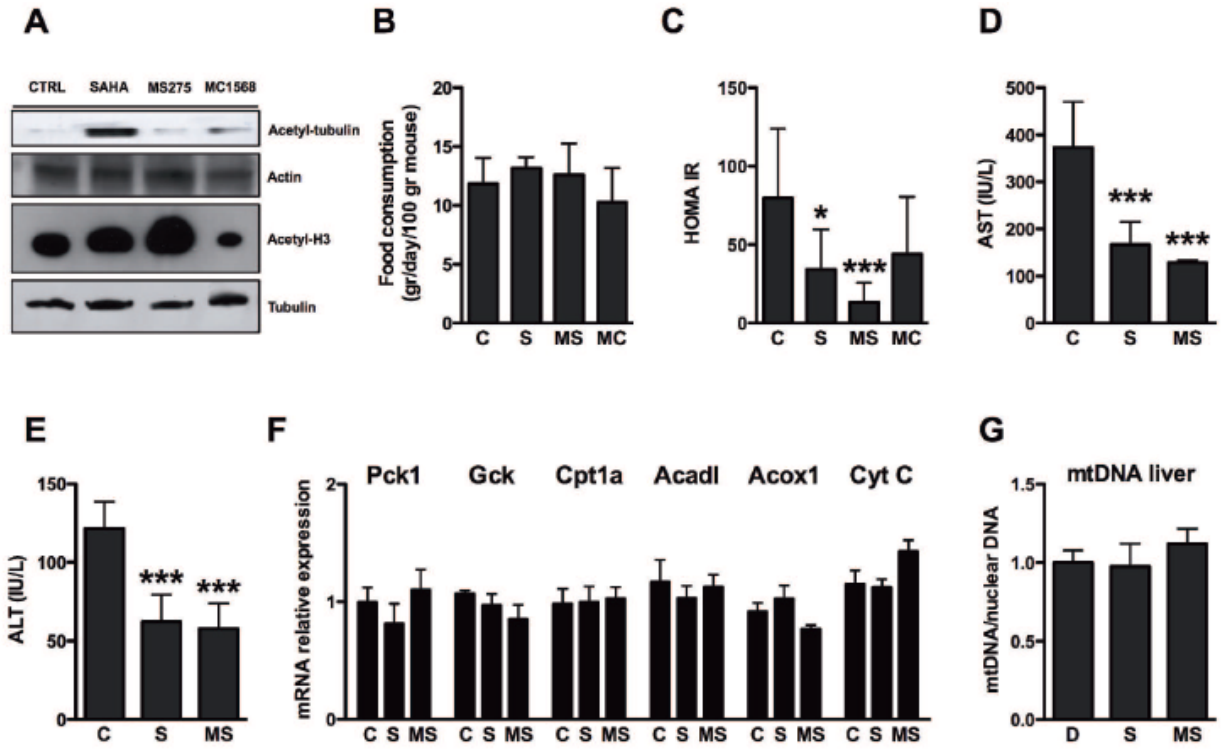
SUPPLEMENTARY DATA

Supplementary Figure 1. Effect of class-selective HDAC inhibitors in cultured myotubes.
(A) Western blot analysis of acetyl-histone H3 and acetyl-α-tubulin in C2C12 myotubes treated with vehicle, 5 μM SAHA, 5 μM MS275, or 5 μM MC1568 for 24 hr. (B) Mitochondrial density (green) and activity (red) in C2C12 myotubes after 60 hr of treatment with HDAC inhibitors (bar = 60 μm). (C) Expression of genes associated with glucose and fatty acid metabolism, TCA cycle, and OXPHOS. C= control, S= SAHA, MS= MS275, MC=MC1568. Data are presented as mean ± SD. *p<0.05, **p<0.01, ***p<0.001 versus control.



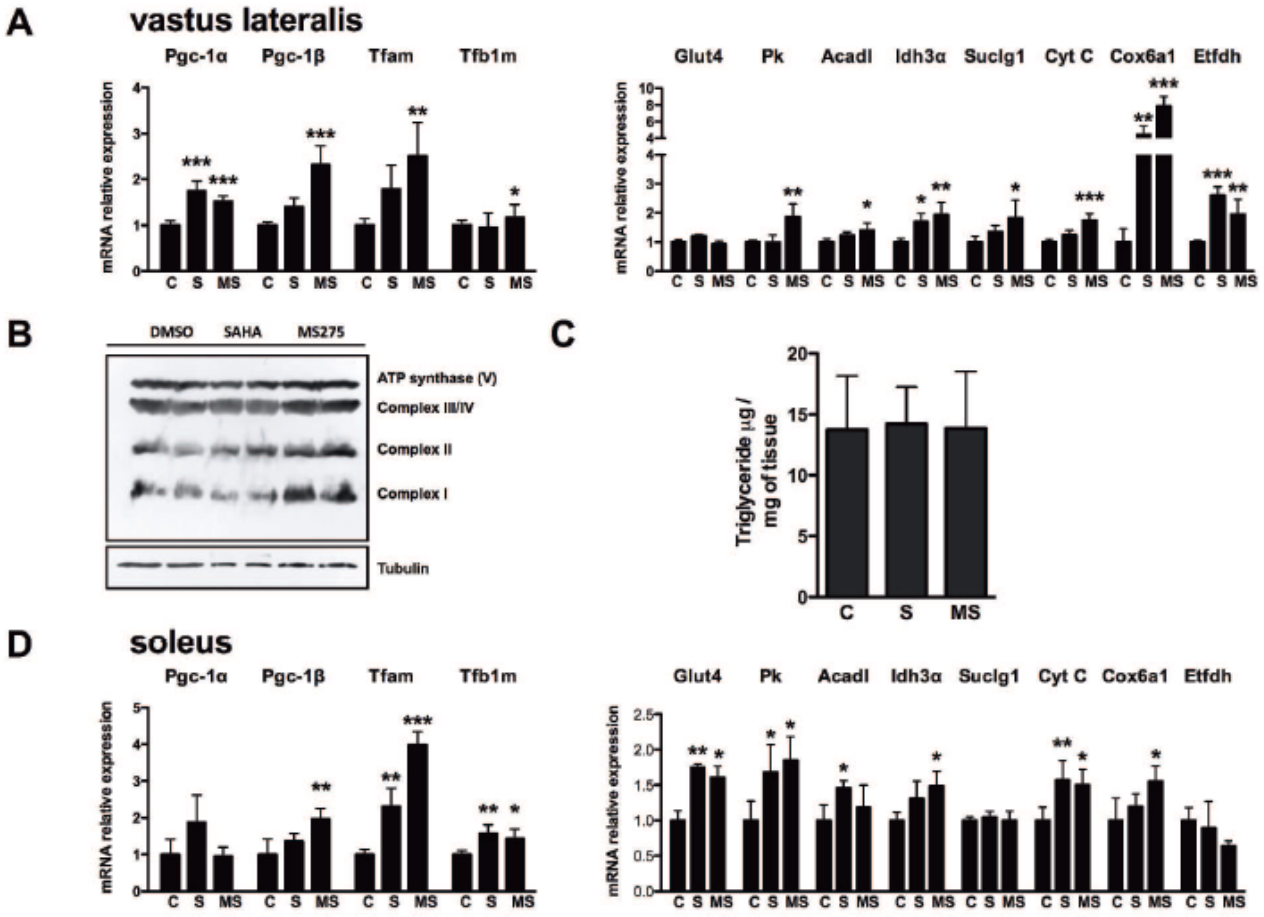
SUPPLEMENTARY DATA

Supplementary Figure 2. Class I HDAC inhibitors improve metabolic syndrome in *db/db* mice.
(A) Western blot analysis of acetyl-histone H3 and acetyl-α-tubulin in skeletal muscle of *db/db* mice treated with vehicle, SAHA, MS275, or MC1568 for 23 days. (B) Food consumption of *db/db* mice treated with HDAC inhibitors. (C) HOMA index of *db/db* mice after 3 weeks of treatment with SAHA, MS275, or MC1568 (n=10 per group). (D) ALT and AST plasma levels show the absence of toxic effects of HDAC inhibitors and improvement of hepatic function. (E) Gene expression analysis of liver of *db/db* mice treated with HDAC inhibitors. Data are presented as mean ± SD. C= control, S= SAHA, MS= MS275, MC=MC1568. *p<0.05, **p<0.01, ***p<0.001 versus control.



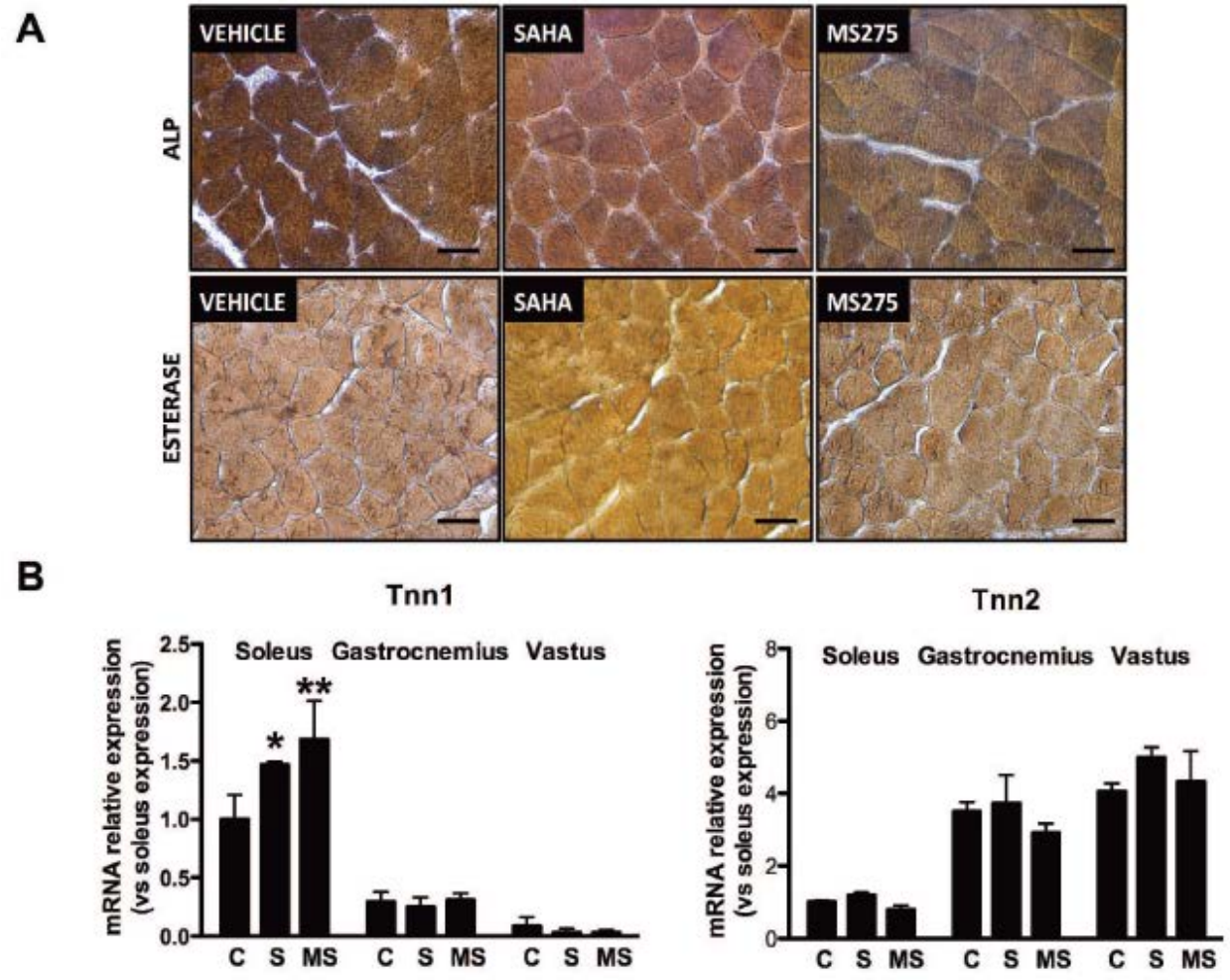
SUPPLEMENTARY DATA

Supplementary Figure 3. Effect of HDAC inhibitors in soleus and vastus lateralis of *db/db* mice. (A) RT-qPCR analysis of mitochondria-related and selected genes from metabolic pathways in vastus lateralis. (B) Triglyceride content in vastus lateralis of mice treated with HDACi. (C) Western blots analysis of mitochondrial complexes I to V of the electron transfer chain in vastus lateralis treated with HDAC inhibitors or vehicle for 23 days. (D) RT-qPCR analysis of mitochondria-related and selected genes from metabolic pathways in soleus. C= control, S= SAHA, MS= MS275. Data are presented as mean ± SD. *p<0.05, **p<0.01, ***p<0.001 versus control.



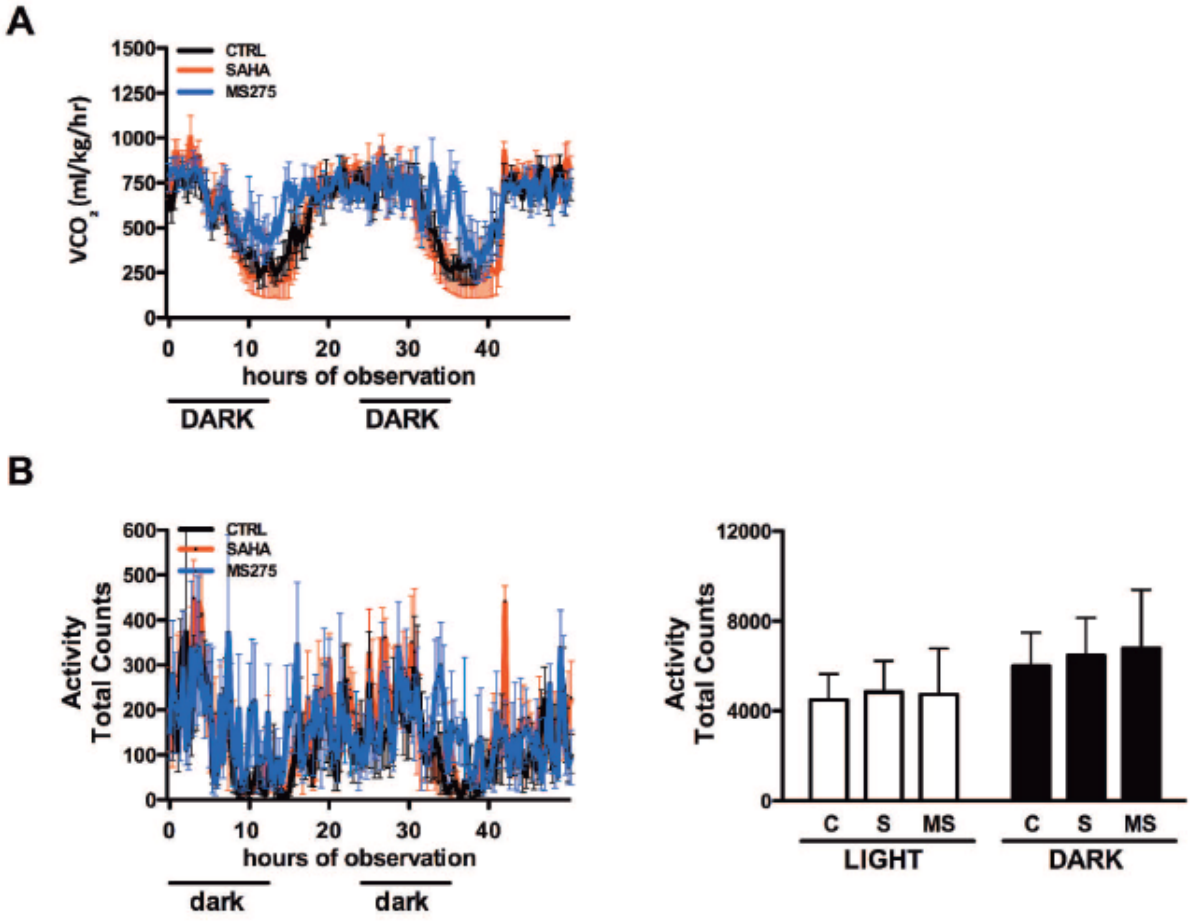
SUPPLEMENTARY DATA

Supplementary Figure 4. Analysis of muscle from SAHA and MS275-treated *db/db* mice.
(A) Alkaline phosphatase (ALP) and esterase staining of gastrocnemius muscle. (B) RT-qPCR analysis of *Tnn1* and *Tnn2* in soleus, gastrocnemius, and vastus lateralis of *db/db* mice treated with HDAC inhibitors. Data are presented as mean ± SD. C= control, S= SAHA, MS= MS275. *p<0.05, **p,0.01 versus control.



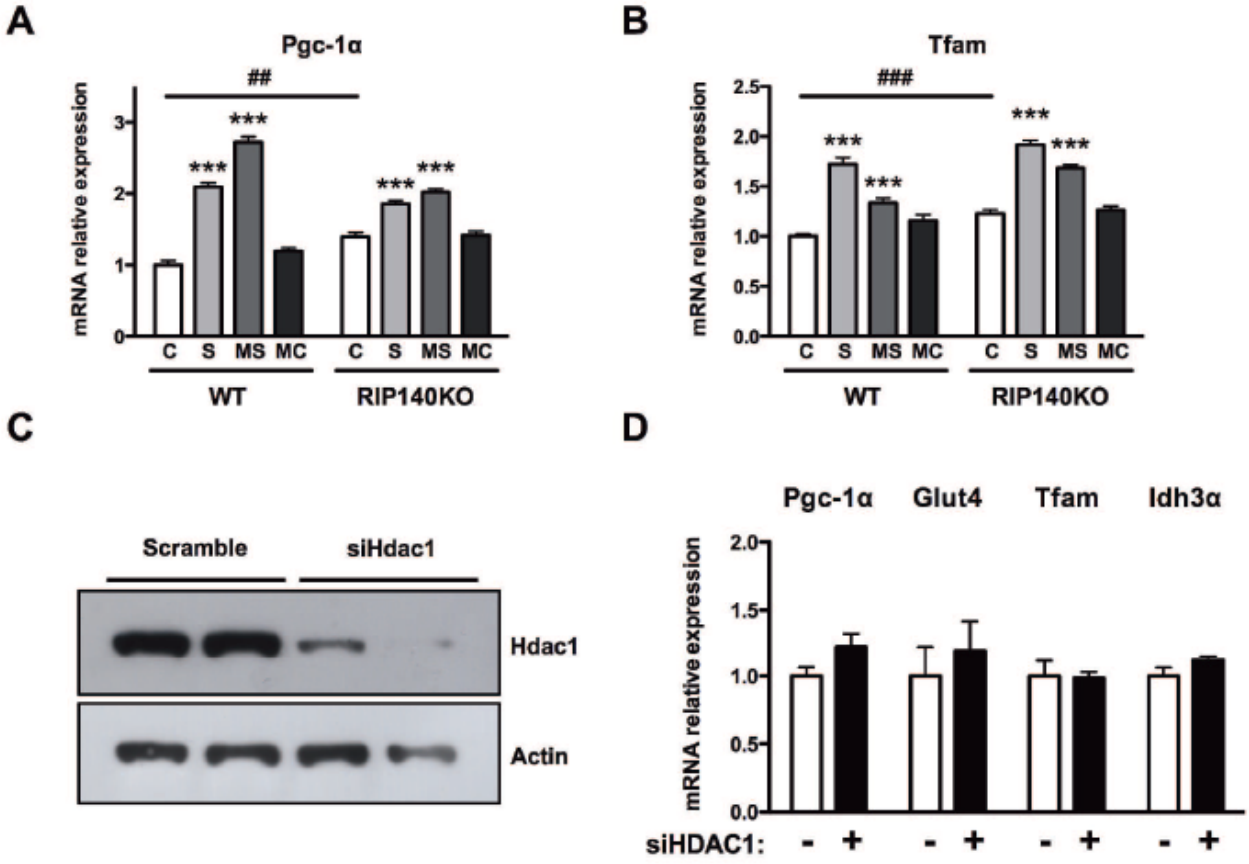
SUPPLEMENTARY DATA

Supplementary Figure 5. Effect of HDAC inhibitors on energy balance in *db/db* mice.
(A) Carbon dioxide consumption in *db/db* mice treated with HDAC inhibitors. (B) Locomotor activity. Measurements represent 2 days of analysis. Data are presented as mean ± SEM. C= control, S= SAHA, MS= MS275. *p<0.05 versus control.



SUPPLEMENTARY DATA

Supplementary Figure 6. Effect of HDAC inhibitors on RIP140 null myotubes.
(A, B) RT-qPCR analysis of *PGC-1α* and *Tfam* expression in RIP140 null myotubes treated with vehicle, 5 μM SAHA, 5 μM MS275, or 5 μM MC1568. (C, D) Hdac1 protein levels in C2C12 myoblasts transfected with scramble or Hdac1 siRNA and RT-qPCR analysis of *PGC-1α*, *Glut4*, *Tfam*, and *Idh3α* expression. Data are presented as mean ± SD. C= control, S= SAHA, MS= MS275, MC = MC1568. ***p<0.001 versus control; ## p< 0.01, ###p<0.001 versus WT cells.



SUPPLEMENTARY DATA

Supplementary Figure 7. Effect of HDAC inhibitors on white adipose tissue of *db/db* mice.
(A) Cell size quantification in WAT of animals treated with vehicle, SAHA, or MS275. (B) Magnetic resonance analysis of visceral white fat in *db/db* mice treated for 15 days with HDAC inhibitors. (C) MitoTracker Green FM images and fluorescence quantification of mitochondrial density in sections of white adipose tissue after 23 days of treatment with vehicle or HDAC inhibitors (bar = 100 μm). (D) Expression of pro-inflammatory genes in WAT of treated *db/db* mice. (E) Quantification of crown-like structures indicating macrophage infiltration in white adipose tissue. C= control, S= SAHA, MS= MS275. Data are presented as mean ± SD. *p<0.05, **p<0.01, ***p<0.001 versus control.