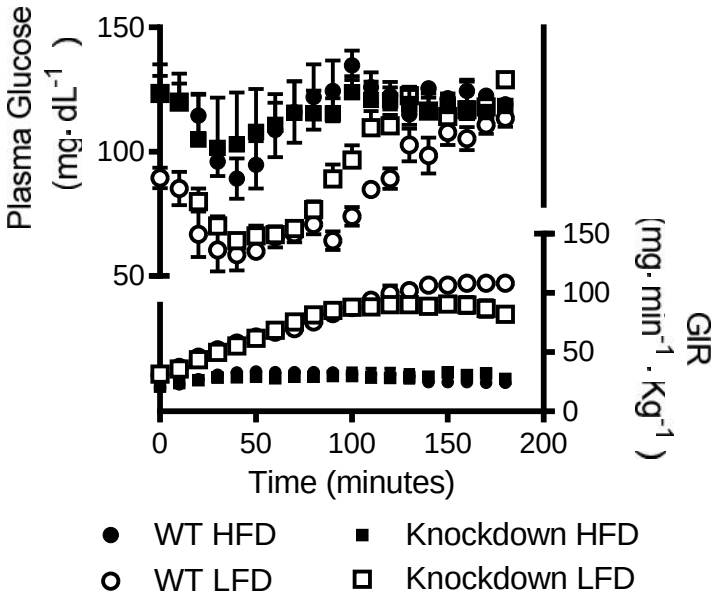
Mitochondrial metabolism mediates oxidative stress and inflammation in fatty liver

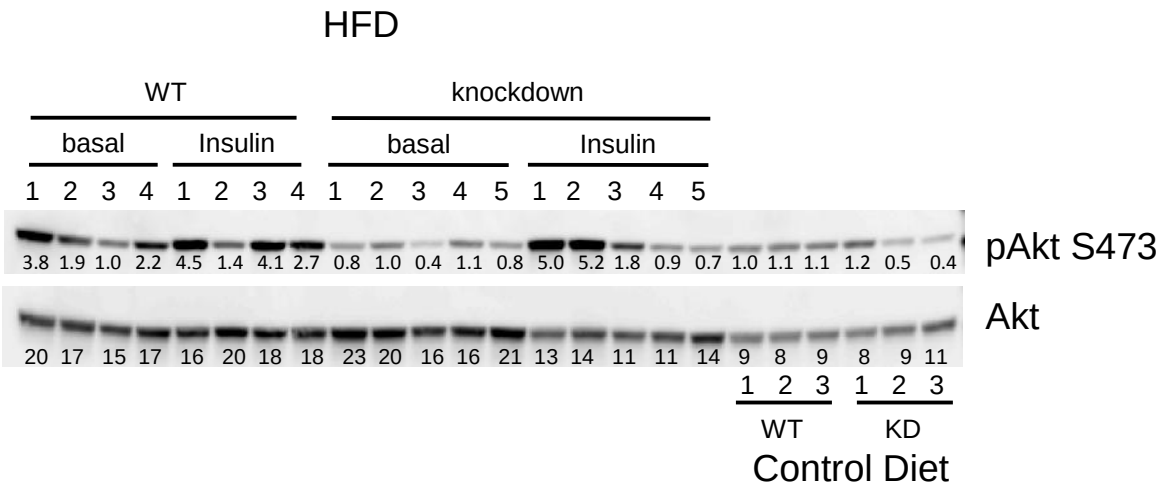
Santhosh Satapati1, Blanka Kucejova1, Joao A. G. Duarte1, Justin A. Fletcher1, Lacy Reynolds1, Nishanth E. Sunny1, Tianteng He1, Arya Nair1, Kenneth Livingston1, Xiaorong Fu1 , Matthew E. Merritt1, A. Dean Sherry1, Craig R. Malloy12, John M. Shelton3, Jennifer Lambert2 Elizabeth J. Parks5, Ian Corbin1, Mark A. Magnuson6, Jeffrey D. Browning12, and Shawn C. Burgess14

1AIRC Division of Metabolic Mechanisms of Disease, 2 Department of Internal Medicine, 3Department of Pathology and 4Department of Pharmacology, The University of Texas Southwestern Medical Center, Dallas, Tx, USA, 5 Department of Nutrition, University of Missouri, Columbia, Mo, 6Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN

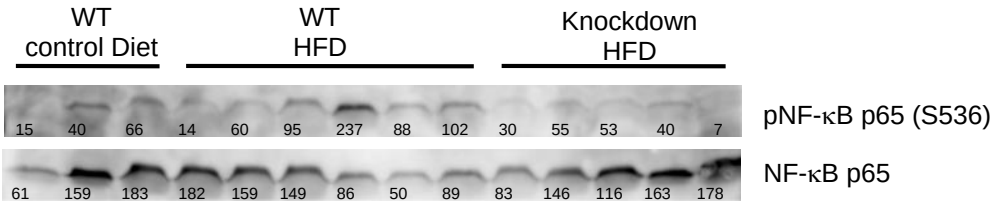
Supplemental Data



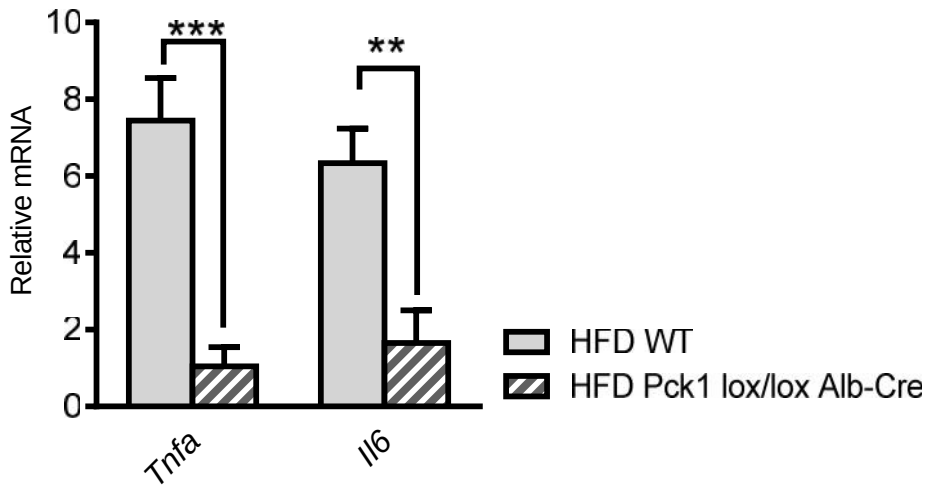
Supplemental Figure 1. Plasma glucose levels and rates of glucose infusion during hyperinsulinemic euglycemic clamps.



Supplemental Figure 2. Insulin signaling in HFD mice before and 3 minutes after portal vein insulin injection. Akt and pAkt Western blots shown with quantification below individual bands were used to calculate Akt signaling shown in Figure 4.



Supplemental Figure 3. Western blot of NF-κB phosphorylation. Quantification below individual bands were used to calculate pNF-κB/ NF-κB signaling shown in Figure 6.



Supplemental Figure 4. Inflammatory gene expression was decreased in liver specific knockout mice on a HFD.

Supplemental Table 1. Organic acid concentration (nmol•g^{-1} liver) of snap frozen liver determined by GC-MS (n=3-4 control diet or n=6-9 HFD, mean ± SEM).

	Citrate		aKG		Succinate		Fumarate		Malate		Oxaloacetate		Pyr		Lac	
WT	404	±30	30.2	±3.0	437	±52	70.6	±8.4	123	±21	1.4	±0.2	104	±18.5	532	±42
Knockdown	724*	±46	70.1*	±25.7	377*	±61	378*	±61.8	667*	±93	4.7*	±0.5	85.3	±15.4	623	±140
WT HFD	543	±58	54.1	±8.7	186	±15	148	±10.7	742	±74	7.7	±1.0	141	±15.6	1134	±178
Knockdown HFD	1150*	±348	44.4	±5.3	278*	±29	691*	±52.7	2676*	±177	42.8*	±2.5	63.4*	±4.3	798.0*	±72

*Different from WT by t-test ($p<0.05$)

Supplemental Table 2. Data used to calculate oxygen consumption in human studies from Sunny et al. Cell Metab. 2011;14(6):804-10, according to equations given in the methods section.

Subject	TCA Cycle Flux	Ketogenesis (BHB turnover)	GNG From TCA Cycle	GNG From Glycerol	Calculated O_2 Consumption	NAS	Ishak
	5.75 NADH	2.5 NADH	-0.1 NADH	1 NADH	½ total NADH		
1	0.40	0.03	0.53	0.19	1.26	0	0
2	0.61	0.14	0.63	0.16	1.99	3	2
3	0.54	0.16	0.63	0.15	1.80	2	3
4	0.64	0.17	0.62	0.20	2.12	4	4
5	1.28	0.07	0.54	0.29	3.89	4	3
6	1.04	0.08	0.67	0.15	3.12	6	10
7	0.62	0.08	0.63	0.19	1.94	1	1
8	1.16	0.09	0.92	0.09	3.44	6	7

Flux reported in mmol•min^{-1} . The highlighted area is the data used in the manuscript