

**Supplementary figure 1. a**, Chromatin Immunoprecipitation (ChIP) assay of H3K9Ac over *Pck1* and *G6pc* genes in livers of lean and DIO mice (\*; *P*<0.05 relative to lean mice; n=3). **b**, ChIP assay of H3K9Ac and RNA pol II levels over the *Tfiib* gene in livers from fasted or fed mice. **c**, ChIP assay of H3K9Ac and H3K4me3 levels over proximal and distal regions of the *Pck1* and *G6pc* genes in livers from fasted or fed mice (\*; *P*<0.05 relative to lean mice; n=3). **d**, ChIP assay of H3K27Ac, H3K27me3 and H3K36me3 over gluconeogenic genes *Pck1* and *G6pc* and control genes *Gcgr* and *Pdx1* in livers from fasted or fed lean db/+ and diabetic db/db mice (\*; *P*<0.05; n=3).

## Supplementary Figure 1

### Supplementary Figure 2



**Supplementary figure 2. a**, Effect of *Kat2b* or *Wdr5* RNAis on hepatic mRNA amounts for *Kat2b* and *Wdr5* from fasted or fed mice. **b**, Pyruvate tolerance test and insulin tolerance tests on lean and DIO mice depleted for either *Wdr5* (W5) or *Kat2b* (K2B) (\*; P < 0.05; n=5). **c**, Plasma glucagon levels from 12 hour fasted, lean or DIO mice depleted of *Wdr5* or *Kat2b* (\*; P < 0.05; n=4). **d-h**, Fasting blood glucose (**d**), circulating insulin (**e**), hepatic gene expression (**f**), circulating glucagon (**g**) and protein levels (**h**) in wild-type and *Kat2b-/-* mice under lean and high fat diet (DIO) conditions. mRNA levels in panel **f** measured in livers from DIO mice (\*; P < 0.05; n=3) and circulating glucagon (**g**) from lean mice (\*; P < 0.05; n=4). Hepatic levels of KAT2A, KAT2B and CREB protein (**h**) from wild-type and *Kat2b-/-* DIO mice run in duplicates (n=3). **i**, Effect of *Kat2a* depletion on mRNA amounts for *Nr4a1* and *Ppargc1a* in cultured hepatocytes from wild-type or *Kat2b-/-* mice exposed to glucagon for 1 or 2 hours (\*; P < 0.05; n=3). **j**, *In vitro* glucose output from hepatocytes depleted for *Kat2b* normalized to whole cell protein (\*; P < 0.05; n=3). Right, immunoblot showing levels of endogenous and HA-tagged WT or E551Q mutant KAT2B.

Supplementary Figure 3



**Supplementary figure 3. a**, ChIP assay of HEK293T cells showing relative effects of FSK on recruitment of components in SAGA (FAM48A) and ATAC2 (ZZZ3) complexes to CREB binding sites (-14kb, -0.2kb) or CREB-negative region (-7kb) over the *Nr4a1* gene. FAM48A and ZZZ3 occupancy over known SAGA (*Rab5b*) and ATAC2 (*Snx16*) target genes shown for comparison. **b**, mRNA levels for *G6pc* in cultured hepatocytes following RNAi mediated knockdown of components in ATAC (*Kat2a, Kat2b, Atac2, Yeats2, Zzz3*), SAGA (*Kat2a, Kat2b, Fam48*), and KMT (*Wdr5, Ash2l*) complexes. Exposure to glucagon indicated (\*; *P*<0.05; n=3). **c**, Absolute quantification of *Kat2a* and *Kat2b* mRNA levels in primary hepatocytes and livers from lean, fasted mice. **d**, Fasting mRNA levels from livers depleted for *Kat2a, Kat2b* or *Kat2a* and *b* in combination (\*; *P*<0.05; n=4).



**Supplementary figure 4. a**, Effect of *Wdr5* RNAi on H3K4me2 over the *G6pc* promoter in hepatocytes exposed to glucagon. **b**, Effects of *Wdr5*, *Ash2l*, and *Rbbp5* depletion on H3K4me3 and H3K9Ac over the *TfIIb* promoter in hepatocytes exposed to glucagon. **c**, Basal *Pck1* and *G6pc* mRNA levels in primary hepatocytes depleted for *Wdr5*, *Ash2L* or *Rbbp5*. **d**, Immunoblots showing cellular levels of H3K9 acetylation and CRTC2 protein in *Wdr5*-depleted hepatocytes stimulated with glucagon. **e**, Immunoblot showing effect of adenovirally encoded RNAi for *Wdr5*, *Ash2l*, and *Rbbp5* on protein amounts for each gene in hepatocytes exposed to glucagon (\*; P < 0.05; n=3).

#### Supplementary Figure 5



**Supplementary figure 5. a**, Immunoblot showing recovery of HA-tagged KAT2A and KAT2B from immunoprecipitates of Flag-tagged WDR5 prepared from HEK293T cells exposed to FSK. **b**, GST-pull down showing direct association between WDR5 and residues 341-460 of KAT2B.



**Supplementary figure 6. a,** Effect of *Wdr5* depletion of on glucagon-induced H3K9Ac and H3K4me3 amounts over the *Pck1* gene in primary hepatocytes. **b, c,** ChIP assays showing effect of *Kat2b* depletion on recruitment of P-CREB, CRTC2, RNA polymerase II, CBP, KAT2B, and WDR5 to CREB binding sites and upstream regions of the *Pck1* and *G6pc* promoters in hepatocytes exposed to glucagon for 1 hour (\*; P < 0.05; n=3).



**Supplementary figure 7. a**, GST pull-down assay of purified KAT2B protein with purified GST-CRTC2 (TAD, aa. 601-692) or GST alone. **b**, Transient assay of chromosomal GAL4-luc reporter activity in HEK293T cells expressing GAL4-CRTC2 constructs containing the GAL4 DNA binding domain fused to CRTC2 lacking the trans-activation domain ( $\Delta$ TAD, aa. 1-632) or to the TAD alone (aa. 624-692). Effects of GFP, KAT2A, or KAT2B over-expression on GAL4-CRTC2 activity shown. Luciferase activity normalized to  $\beta$ -gal activity (\*; *P*<0.05; n=3). **c**, Effect of mutations in the CRTC2 trans-activation domain (TAD) on its activity in the context of GAL4 DNA binding domain-TAD (GAL4-TAD) fusion proteins. Activity from a chromosomal GAL4-luc reporter in HEK293T cells normalized to  $\beta$ -galactosidase activity. **d**, Transient assay of wild-type and mutant CRTC2 (E579K, E587K or E665K) in HEK293T cells co-transfected with CRE-luc reporter plasmid. Exposure to FSK indicated. Luciferase activity normalized to beta-galactosidase activity (\*; *P*<0.05; n=3). **e**, Basal H3K9Ac and RNApoIII association with Pck1 and G6pc genes in wild-type or *Crtc2-/-* hepatocytes following reconstitution with wild-type or KAT2B-defective (E665K) mutant CRTC2.



**Supplementary figure 8. a**, **b**, Chromatin Immunoprecipitation assay of CRTC2 and RNA Pol II occupancy over control (*TfIIb*) (**a**) and gluconeogenic (**b**) genes in wild-type or *Crtc2-/-* hepatocytes following reconstitution with wild-type or KAT2B-defective (E665K) mutant CRTC2 (\*; P < 0.05; n=3). **c**, Immunoblot showing levels of endogenous and ectopically expressed Flag-tagged wild type (W) and E665K (EK) CRTC2 proteins. **d-e**, Pck1 mRNA levels (d) and western blots (e) from primary hepatocytes depleted for CRTC2 and 3 alone or in combination (\*; P < 0.05, \*\*; P < 0.01). **f**, Co-immunoprecipitation of HA-KAT2B with Flag-CRTC2 (C2) and Flag-CRTC3 (C3) from HEK293T cell lysates. Flag-FoxO1 (Fx1) is used as negative control. Treatment with FSK (1 hour) indicated. **g-i**, Wild type and Crtc2 deficient hepatocytes depleted for CRTC3 (C3); mRNA levels (b) and glucose output (i) (\*; P < 0.05; n=4).

**Supplementary Figure 9** 



**Supplementary figure 9. a**, Effects of *Kat2b* depletion on fasting blood glucose in DIO mice (\*; P < 0.05; n=3). **b**, Fasting blood glucose in lean and obese db/db mice injected IP for 5 consecutive days with anacardic acid (15mg/kg), SPV-106, or vehicle (\*; P < 0.05; n=4). **c**, Effect of glucagon on *Pck1* mRNA levels in primary hepatocytes depleted for KAT2B alone or KAT2A and B in the presence of SPV-106 or anacardic acid (20uM). **d-h**, fasting blood glucose (d), mRNA levels (e), H3K9Ac levels (f), RNApolII (g) and CRTC2 recruitment (h) to *Pck1*, *G6pc* and *Tfiib* promoters in control or KAT2A/B depleted livers from mice treated with SPV-106 or anacardic acid (15mg/kg). (\*; P < 0.05 relative to SPV-106; n=3).

Supplementary Figure 10



**Supplementary figure 10. a**, Metabolic data for adlib fed, lean mice after a 5-day treatment with SPV-106 or anacardic acid (15mg/kg). **b-c**, Fasting blood glucose (b) and body weight (c) in lean mice injected IP for 5 consecutive days with anacardic acid (15mg/kg), SPV-106, or vehicle (\*; P < 0.05; n=4). **d-g**, Effects of SPV-106 and anacardic acid treatment (15mg/kg) on blood glucose levels (d), serum insulin (e), pyruvate tolerance (f) and body composition (g) in DIO mice (\*; P < 0.05; n=4).

# Supplementary Table 1

# Primers for gene expression analysis

# Primers for ChIP analysis

	_	
mG6Pase	Fwd	CTGCTACTAAAAGGGCTAGG
	Rev	CTTAGCTTTCTCCAAAGTCC
mGcK	Fwd	CAGAACTGTAAGCCACTCAG
	Rev	CACAAACATTCCAGAGACAG
mIGFBP1	Fwd	AGCAAACAGTGTGAGACATC
	Rev	GTAGACACACCAGCAGAGTC
mKAT2A	Fwd	GCTCTTGGGAATGGTAGTAG
	Rev	CCTTGTGAACAGACATGAAC
mKAT2B	Fwd	ATGTGGAGTACCTCTTCACC
	Rev	TGTTTGGTATCTGCATCTTC
mNR4A1	Fwd	TCCTCCACGTCTTCTTCCTC
	Rev	CCGTACACCTGGAAGTCCTC
mPCK1	Fwd	TGAGTAGCACAGAGAACAGG
	Rev	GTGTCAAATGCAAACTTCAG
mPGC1a	Fwd	GCAGCGGTCTTAGCACTCA
	Rev	TGATCCTGTGGGTGTGGTTT
mRPL32	Fwd	GAGATTGCTCACAATGTGTC
	Rev	GCTGCTCTTTCTACAATGG
mTFIIB	Fwd	TCAGCTGAGAAGCGAACACA
	Rev	AGCAACACCAGCAATATCCC
mWDR5	Fwd	GTCCTTCGTGAAGTTCTCTC
	Rev	CTTCAGTGTGTTGTCCAAAG

RevAGCTGTGGTGATTCTAGGACmG6Pase CREFwdATCAGGCTGTTTTTGTGTGRevCATCATCAGTAGGTTGATGCmG6PaseFwdCTTGAATTGCTCAACTTCTGmGCGRFwdCAGCTTCCAGCTTCTCACACRevGGAAGCGAATCCATCTGGAAGCRevGGAAGCGAATCCATCTGAAGCmGCKFwdTACAGACATCTGGTGACAGCRevCCTCCTAGTGTGTCTCTCCmIGFBP1 prom.FwdGTTTGTGTAGAGCTCACAAGCRevCACAGGTTAATGATTGCAGGmIGFBP1FwdAAGAAAGTTTGCAGGTAAGGRevTCCACTGAAAGACCGAGTAhNR4A1 Enh. CREFwdATTTTAGCCCCATGGATChNR4A1 prom.FwdGATCAAACAATCCGCGCTCRevATGACGTCTGCGCGCGTGAmNR4A1FwdGCTTGTTAGGAGGTTCCRevATGATCACGAGGTGCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGACmPCK1FwdGTCATTCATTCATCACCTCTCCRevAGGTAAAGAACATGAGGGAGAGACAGCmPCK1FwdGTCATTTGTGTGGGGAGAGACAGCmPCK1FwdGTCATTCATTCATCACCTCTCCRevAGGGTAAAGAACATGAGGGAGAGAGAmPCK16 prom.FwdCTCGTACTGTTGGTGAGAAGhSnx16 prom.FwdCTCGTACTTGTTGGTGACAGRevAGATAGTGCAAGAAAAGAAATGRevRevAGATAGTGCAAGAAAAATGCAAGGmTFIIB prom.FwdCTCAACCGTCTTGTGTCmTFIIBFwdCTTCAACCGTCTTGTGTCmTFIIBFwdCTTCAACCGTCTTGTGTCRevCAGATAGTGCAAAAAAACAACAG	mG6Pase (-2854)	Fwd	GTCTACTTTGCCCTCAACTC
mG6Pase CREFwdATCAGGCTGTTTTTGTGTG RevmG6PaseFwdCTTGAATTGCTCAACTTCTG RevmGCGRFwdCAGCTTCCAGCTTCTCACAC RevmGCKFwdTACAGACATCTGGTGACAGC RevmGFBP1 prom.FwdGTTTGTGTAGAGCTCACAAGG RevmIGFBP1FwdAAGAAAGTTTGCAGGTAAGG RevnNR4A1 Enh. CREFwdATCAGACCAAACCGGCTC RevmNR4A1 prom.FwdGATCAAACAATCCGCGCTC RevmNR4A1FwdGATCAAACAATCCGCGCTC RevmNR4A1FwdGCTTGTTTAGGAGGTTCC RevmNR4A1FwdGCTTGTTTAGGAGGTTCC RevmNR4A1FwdGCTTGTTTAGGAGGTTCC RevmNR4A1FwdGCTTGTTAGGAGGTTCC RevmNR4A1FwdGCTTGTTAGGAGGTTCC RevmNR4A1FwdGCTTGTTAGGAGGTCCCAC RevmPCK1 (-1862)FwdTCTCCTGGAGGTCATGGG RevmPCK1 RevFwdGTCATTCATTCATCACCTCCC RevAGGTAAAGAACAATGAGGGAGAGAGC RevFwdCCCACATGAACAGTGAGGG GGGTAAAGAACATGAGGGAGAGAGCmPCK1FwdGCCACTGTATGTGGGGAGAGGG RevmPCK1FwdCCCCATGAACAGTGAGGAG RevhNR4A1FwdGCCATGTCTGTGGGAAAAG hSnx16 prom.FwdGAAGATTTGCCAAACAAGGAAAAAG RevhNR4A1FwdGCCTTGTAGCGAAGAATAAAGG RevmTFIIB prom.FwdGAAGATTTGCCAATCAAC RevGGGTAACGAGAAATAACACAG RevGGGTAACGGAAAATACACAG RevGGGTAACGGAAAATACACAGCGTCTTGTGTCmTFIIBFwdGAAGGGAAAATAC		Rev	AGCTGTGGTGATTCTAGGAC
RevCATCATCAGTAGGTTGATGCmG6PaseFwdCTTGAATTGCTCAACTTCTGRevTAAACTACACGTGGGAACACmGCGRFwdCAGCTTCCAGCTTCTCACACRevGGAAGCGAATCCATCTGAAGmGcKFwdTACAGACATCTGGTGACAGCRevCCTCCTAGTGTGTCTTTCCmIGFBP1 prom.FwdGTTTGTGTAGAGCTCACAGGRevCACAGGTTAATGATTGCAGGTAGGRevCACAGGTTAATGATTGTCAGGmIGFBP1FwdAAGAAGTTTGCAGGTAGGRevTCCACTGAAAGACCGAGTAhNR4A1 Enh. CREFwdATTTTAGCCCCATGGTRevAAGGGTCACGCTCATGCThNR4A1 prom.FwdCAGGGTCACGCTCATGCTmhNR4A1 CREFwdGATCAAACAATCCGCGCTCRevATGTCTGCGCGCGTGAmNR4A1FwdGCTTGTTAGGAGGTTTCCRevATGTCTGTGGCGCGTGAmPCK1 (-1862)FwdTCTCCTGAGAGATCATGGACmPCK1FwdGTCATTTATTAGAAGGAGAGACAGCmPCK1FwdGTCATTTCATTCACCTCTCCRevAGGGTAAAGAACATGAGGGAGACAGCmPCK1FwdCTCGTACTGTGGGAGAGARevACCAATCCTCTGGAGAAAGAhRab5b prom.FwdCTCGTACTGTGGGAAAAGAhSnx16 prom.FwdGAAGATTTGCCAATCAACRevCTGGTACTTCCTGGTGTCmTFIIB prom.FwdCTCGAGGAGAAAATGCAACRevCTGTGTACTTCCTGGTGTCmTFIIBFwdCTCCAGGTACTGTGTCmTFIIBFwdCTCAACCGTCTTGTGTC	mG6Pase CRE	Fwd	ATCAGGCTGTTTTTGTGTG
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mGcKFwdTACAGACATCTGGTGACAGCRevCCTCCTAGTGTGTCTCTTCCmIGFBP1 prom.FwdGTTTGTGTAGAGCTCACAAGCRevCACAGGTTAATGATTGTCAGGmIGFBP1FwdAAGAAAGTTGCAGGTAAGGRevTCCACTGAAAGACCGAGTAhNR4A1 Enh. CREFwdATTTTTAGCCCCATTGATGAGGRevATGACGTCTCCGGAATCChNR4A1 prom.FwdGATCAAACAATCCGCGCTCmNR4A1 CREFwdGATCAAACAATCCGCGCTCRevATGTCTGCGCGCGTGAmNR4A1FwdGCTTGTTAGGAGGTTCCRevATGTCTGCGCGCGTGAmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGACmPCK1 (-1862)FwdTCTCCTGGAGTTATTGTGmPCK1 CREFwdGTCATTTCATTCACCTCTCCRevAGGTAAAGAACATGAGGAGGACAGCmPCK1FwdGTCATTTCATTCACCTCTCCRevAGGGTAAAGAACATGAGGAGmPCK1FwdCACCATGAACAGTGAGGAGmPCK1FwdCACCATGAACAGTGAGGAGmPCK1FwdCACCATGAACAGTGAGAGAmPCK1FwdCACCATGAACAGTGAGAGAmPCK1FwdCACCATGAACAGTGAGAGAmPCK1FwdCTCGTACTTGTGGTGACAGmPCK1FwdCACGATCCTCTGGAGAAAGhSnx16 prom.FwdCAGGTAAGGAGAATGTCGmTFIIB prom.FwdGAGATTTGCCAATCAACRevCTGTGTACTTCCTGGTGTGTCmTFIIBFwdCTTCAACCGTCTTTGTGTCRevCGTAAGGGAGAAAATACACAG		Rev	GGAAGCGAATCCATCTGAAG
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mIGFBP1 prom.FwdGTTTGTGTAGAGCTCACAAGC RevmIGFBP1FwdAAGAAAGTTTGCAGGTTAGG RevhNR4A1 Enh. CREFwdATTTTTAGCCCCATTGATGAGG RevhNR4A1 prom.FwdCAGGGTCACGCTCATGCT CAGAGCCCAAAATAGTCAGCThNR4A1 prom.FwdGATCAAACAATCCGCGCTC RevmhNR4A1 CREFwdGATCAAACAATCCGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTTTCC RevATGTCTGCGCGCGTGARevATGTCTGCGGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTTCC RevmPCK1 (-1862)FwdTCTCCCTAGAGGATCATGGAC RevmPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGGAGGACAGCRevmPCK1FwdGTCATTGTAGAGCTGTGGGhRab5b prom.FwdKevACCAATCCTCTGGAGAAAG AGATAGTGCGAGAGATAAAGhSnx16 prom.FwdGAAGATTTGCCAATGAACGG RevmTFIIB prom.FwdGAAGATTTGCCAATCAAC RevRevCTGTGTACTTCCTGGTGTGTC RevmTFIIB prom.FwdCTTCAACCGTCTTTGTGTC RevCGTAAGGGAGAAAATACACAGRevCTTCAACCGTCTTTGTGTC RevCGTAAGGGAGAAAATACACAG		Rev	CCTCCTAGTGTGTCTCTTCC
RevCACAGGTTAATGATTGTCAGGmIGFBP1FwdAAGAAAGTTTGCAGGTTAGG RevhNR4A1 Enh. CREFwdATTTTTAGCCCCATTGATGAGG RevhNR4A1 prom.FwdCAGGGTCACGCTCATGCT CAGAGCCCAAAATAGTCAGCTmhNR4A1 CREFwdGATCAAACAATCCGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTTTCC RevATGTCTGCGCGCGTGAFwdGCTTGTTATAGGAGGTTCC RevmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGAC RevmPCK1 CREFwdTCTCCTGGAGTTATTGTG RevmPCK1FwdGCTATTTCATTCATCACCTCTCC RevmPCK1FwdGCCATTTCATTCATCACCTCTCC RevmPCK1FwdGCCATTGTAGAGGAGACAGCmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGTAAAGAACATGAGTGG RevTCCTTGTAGAGCTGTGGGhRab5b prom.FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdTCAGGTAGCGAAGAAAAG AGATAGTGCAAGAAAATGC RevAGATAGTGCAAGAAAATGC RevAGATAGTGCAAAAAATG AGATAGTGCAAAAATGCAAC RevmTFIIB prom.FwdCATCAACCGTCTTTGTGTC RevmTFIIBFwdCTTCAACCGTCTTTGTGTC RevmTFIIBFwdCTTCAACCGTCTTTGTGTC Rev	mIGFBP1 prom.	Fwd	GTTTGTGTAGAGCTCACAAGC
mIGFBP1FwdAAGAAAGTTTGCAGGTTAGG RevhNR4A1 Enh. CREFwdATTTTAGCCCCATTGATGAGG ATTGACGTCTCCGGAATCChNR4A1 prom.FwdCAGGGTCACGCTCATGCT CAGAGCCCAAAATAGTCAGCTmhNR4A1 CREFwdGATCAAACAATCCGCGCGCG CRevmNR4A1FwdGCTTGTTTAGGAGGTTTCC RevmNR4A1FwdGCTTGTTAGGAGGTTCCC RevmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGAC RevmPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevmPCK1 CREFwdGTCATTTCATTCACCTCTCC RevmPCK1FwdGTCATTTCATTCACCTCTCC RevmPCK1FwdGTCATTTCATTCACGGAGAGACAGCmPCK1FwdGTCATTTCATTGAGGGAGACAGCmPCK1FwdGTCATTTCATTGAGGGAGAAGACAGGmPCK1FwdCACCATGAACAGTGAGGAGmPCK1FwdCACCATGAACAGTGAGGAGAmPCK1FwdCACCATGAACAGTGAGAGAGAmPCK1FwdCACCATGAACAGTGAGAGAGAmPCK1FwdCACCATGAACAGTGAGAGAGAmPCK1FwdCACCATGAACAGTGAGAGAGAmPCK1FwdCACCATGAACAGTGAGAGAAAGhSnx16 prom.FwdTCAGGTAGCGAAGAATAAATG RevAGATAGTGCAAGAAAGGCAGAAAATGC RevCTGTGTACTTCCTGGTTGTCmTFIIB prom.FwdCTTCAACCGTCTTTGTGTC RevmTFIIBFwdCTTCAACCGTCTTTGTGTC RevmTFIIBFwdCTTCAACCGTCTTTGTGTC RevmTFIIBFwdCTTCAACCGTCTTTGTGTCmTFIIBFwdCTTCAACCGTCTTTGTGTCmTFIIBFwdCTTCAACCGTCTTTGTGTCM		Rev	CACAGGTTAATGATTGTCAGG
RevTCCACTGAAAGACCGAGTAhNR4A1 Enh. CREFwdATTTTTAGCCCCATTGATGAGG RevhNR4A1 prom.FwdCAGGGTCACGCTCATGCT RevnhNR4A1 prom.FwdGATCAAACAATCGCGCGCTG RevmhNR4A1 CREFwdGATCAAACAATCGGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTTTCC RevCAGAGTACAGAGTGCCTCACRevATGTCTGCGCGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTCCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGAG RevmPCK1 CREFwdTCTCCCTGGAGTTTATTGTGmPCK1FwdGTCATTTCATTCACCTCTCCRevAGGGTAAAGAACATGAGTGGGmPdx1FwdCACCATGAACAGTGAGGAGAGAGRevTCCTTGTAGAGCTGTGTGGGhRab5b prom.FwdCTCGTACTTCTTGGGACAAGhRab5b prom.FwdGAAGATTTTGCCAATGAAGGRevAGATAGTGCAGAGAAAATGRevAGATAGTGCCAAGAAAATGRevAGATAGTGCAGAGAAAATGCRevCTGTGTACTTCCTGGTTGTCmTFIIB prom.FwdCTTCAACCGTCTTTGTGTCmTFIIBFwdCTTCAACCGTCTTGTGTGTCmTFIIBFwdCTTCAACCGTCTTGTGTC	mIGFBP1	Fwd	AAGAAAGTTTGCAGGTTAGG
NNR4A1 Enh. CREFwdATTTTTAGCCCCATTGATGAGGRevATTGACGTCTCCGGAATCChNR4A1 prom.FwdCAGGGTCACGCTCATGCTRevCAAGAGCCCAAAATAGTCAGCTmhNR4A1 CREFwdGATCAAACAATCCGCGCTCRevATGTCTGCGCGCGTGAmNR4A1FwdGCTTGTTAGGAGGTTCCRevCAGAGTACAGAGTGCCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGACRevATAGTAGCCCAATGATGGTGmPCK1 CREFwdTCTCCTGGAGTTTATTGTGRevATAGTAGCCCAATGATGGAGACAGCmPCK1FwdGTCATTTCATTCACCTCTCCRevAGGGTAAAGAACATGAGTGGGmPCK1FwdCACCATGAACAGTGAGGAGARevACCAATCCTCTGGAGAAGAhRab5b prom.FwdCTCGTACTTGTTGGTGACAGRevACCAATCCTCTGGAGAAAGAhSnx16 prom.FwdGAAGATTTTGCCAATCAACRevAGATAGTGCAGAGAATGTCGmTFIIB prom.FwdCTTCAACCGTCTTGGTGTCmTFIIBFwdCTTCAACCGTCTTGGTGTC		Rev	TCCACTGAAAGACCGAGTA
RevATTGACGTCTCCGGAATCChNR4A1 prom.FwdCAGGGTCACGCTCATGCTRevCAAGAGCCCAAAATAGTCAGCTmhNR4A1 CREFwdGATCAAACAATCCGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTTTCCRevATGTCTGCGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTCCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGACRevATAGTAGCCCAATGATGGTGmPCK1 CREFwdTCTCCCTGGAGTTTATTGTGRevTACTATATAGAAGGGAGGACAGCmPCK1FwdGTCATTTCATTCACCTCTCCRevAGGGTAAAGAACATGAGTGGmPdx1FwdCACCATGAACAGTGAGGAGRevACCAATCCTCTGGAGAAAGhSnx16 prom.FwdTCAGGTAGCGAAGAATAATGRevAGATAGTGCAAGAAATGACGRevCTGTGTACTTGTGGTGTCmTFIIBFwdCTTCAACCGTCTTGTGTCRevCTGTGTACTTCCTGGTGTCRevCTGTAAGGGAGAAAATACACAGRevCTGTGTACTTCCTGGTTGTCRevCTGTGTACTTCCTGGTGTC	hNR4A1 Enh. CRE	Fwd	ATTTTTAGCCCCATTGATGAGG
hNR4A1 prom.FwdCAGGGTCACGCTCATGCT RevRevCAAGAGCCCAAAATAGTCAGCTmhNR4A1 CREFwdGATCAAACAATCCGCGCTC RevMNR4A1FwdGCTTGTTTAGGAGGTTTCC RevRevCAGAGTACAGAGTGCCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGAC RevMPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevmPCK1FwdTCTCCTGGAGTTTATTGTG RevMPCK1FwdGCTATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGGGGRevMPdx1FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdCTCGTGTACTGTGGGAAAG RevhSnx16 prom.FwdGAAGATTTTGCCAATCAAC RevMTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevRevCTGTGTACTTCCTGGTGTC CTGTGTACTCCTGGTGTGTGmTFIIBFwdCTTCAACCGTCTTGTGTC RevRevCTGTGTACTTCCTGGTGTC RevRevCTGTGTACTTCCTGGTGTC RevRevCTGTGTACTTCCTGGTGTC Rev		Rev	ATTGACGTCTCCGGAATCC
RevCAAGAGCCCAAAATAGTCAGCTmhNR4A1 CREFwdGATCAAACAATCCGCGCTC RevMNR4A1FwdGCTTGTTTAGGAGGTTTCC RevCAGAGTACAGAGTGCCTCACRevCAGAGTACAGAGTGCCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGAC RevMPCK1 CREFwdTCTCCTGGAGTTTATTGTG RevmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGGGGRevMPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGTGGmPCK1FwdCACCATGAACAGTGAGGAG RevMPdx1FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdCTCGTACTTGTTGGTGACAG RevhSnx16 prom.FwdTCAGGTAGCGAAGAATGTCGmTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevCTGTGTACTTCCTGGTGTCRevCTGTGTACTTCTGGTGTCmTFIIBFwdCTTCAACCGTCTTTGTGTC RevRevCGTAAGGGAGAAAATACACAG	hNR4A1 prom.	Fwd	CAGGGTCACGCTCATGCT
mhNR4A1 CREFwdGATCAAACAATCCGCGCTC RevRevATGTCTGCGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTTTCC RevCAGAGTACAGAGTGCCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGAC RevMPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevmPCK1FwdTCTCCCTGGAGTTTATTGTG RevmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGGGAG RevTCCTTGTAGAGCTGTGTGGmPdx1FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdCTCGTACTTGTTGGTGACAG RevhSnx16 prom.FwdTCAGGTAGCGAAGAATAATG RevMTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevMTFIIBFwdCTTCAACCGTCTTGTGTC RevMTFIIBFwdCTTCAACCGTCTTGTGTC Rev		Rev	CAAGAGCCCAAAATAGTCAGCT
RevATGTCTGCGCGCGTGAmNR4A1FwdGCTTGTTTAGGAGGTTTCC RevRevCAGAGTACAGAGTGCCTCACmPCK1 (-1862)FwdTCTCCCTAGAGGATCATGGAC RevmPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGGGGRevmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGTGGFwdMPdx1FwdCACCATGAACAGTGAGAGA RevTCCTTGTAGAGCTGTGTGGhRab5b prom.FwdCTCGTACTTGTTGGTGACAG RevAGATAGTGCCAAGAAAAGAFwdMTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevMTFIIBFwdCTTCAACCGTCTTGTGTG CTTCAACCGTCTTGTGTG	mhNR4A1 CRE	Fwd	GATCAAACAATCCGCGCTC
mNR4A1FwdGCTTGTTTAGGAGGTTTCC RevRevCAGAGTACAGAGTGCCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGAC RevmPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevmPCK1FwdGTCATTTCATTCACCTCTCC RevmPCK1FwdGTCATTTCATTCACCTCTCC RevmPdx1FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdCTCGTACTTGTTGGTGACAG RevhRab5b prom.FwdCTCGTACTTGTGGGAAAAGhSnx16 prom.FwdGAAGATTTTGCCAATCAAC RevmTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevmTFIIBFwdCTTCAACCGTCTTGGTGTCmTFIIBFwdCTTCAACCGTCTTGGTGTC		Rev	ATGTCTGCGCGCGTGA
RevCAGAGTACAGAGTGCCTCACmPCK1 (-1862)FwdTCTCCTAGAGGATCATGGACRevATAGTAGCCCAATGATGGTGmPCK1 CREFwdTCTCCCTGGAGTTTATTGTGRevTACTATATAGAAGGGAGGACAGCmPCK1FwdGTCATTTCATTCACCTCTCCRevAGGGTAAAGAACATGAGTGGmPdx1FwdCACCATGAACAGTGAGGAGRevTCCTTGTAGAGCTGTGTGGhRab5b prom.FwdCTCGTACTTGTTGGTGACAGRevACCAATCCTCTGGAGAAAGhSnx16 prom.FwdTCAGGTAGCGAAGAATGTCGmTFIIB prom.FwdGAAGATTTTGCCAATCAACRevCTGTGTACTTCCTGGTTGTCmTFIIBFwdCTTCAACCGTCTTTGTGTCRevCGTAAGGGAGAAAATACACAG	mNR4A1	Fwd	GCTTGTTTAGGAGGTTTCC
mPCK1 (-1862)FwdTCTCCTAGAGGATCATGGAC RevATAGTAGCCCAATGATGGTGmPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGTGGMPdx1FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdCTCGTACTTGTTGGTGACAG RevACCAATCCTCTGGAGAAAGhSnx16 prom.FwdGAAGATTTTGCCAATGAC RevMTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevMTFIIBFwdCTTCAACCGTCTTGTGTGTCMTFIIBFwdCTTCAACCGTCTTGTGTGTCMTFIIBFwdCTTCAACCGTCTTGTGTCMTFIIBFwdCTTCAACCGTCTTGTGTC		Rev	CAGAGTACAGAGTGCCTCAC
RevATAGTAGCCCAATGATGGTGmPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevRevTACTATATAGAAGGGAGGACAGCmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGTGGRevmPdx1FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdCTCGTACTTGTTGGTGACAG RevhSnx16 prom.FwdTCAGGTAGCGAGAAAATG RevMTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevmTFIIBFwdCTTCAACCGTCTTGTGTG CTTCAACCGTCTTGTGTC	mPCK1 (-1862)	Fwd	TCTCCTAGAGGATCATGGAC
mPCK1 CREFwdTCTCCCTGGAGTTTATTGTG RevRevTACTATATAGAAGGGAGGACAGCmPCK1FwdGTCATTTCATTCACCTCTCC RevAGGGTAAAGAACATGAGTGGFwdCACCATGAACAGTGAGGAGmPdx1FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdCTCGTACTTGTTGGTGACAG RevhSnx16 prom.FwdTCAGGTAGCGAAGAATGTCGmTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevCTTGTGTACTTCCTGGTGTGTCFwdCTTCAACCGTCTTGTGTGmTFIIBFwdCTTCAACCGTCTTGTGTCRevCGTAAGGGAGAAAATACACAG		Rev	ATAGTAGCCCAATGATGGTG
RevTACTATATAGAAGGGAGGACAGCmPCK1FwdGTCATTTCATTCACCTCTCCRevAGGGTAAAGAACATGAGTGGmPdx1FwdCACCATGAACAGTGAGGAGRevTCCTTGTAGAGCTGTGTGGhRab5b prom.FwdCTCGTACTTGTTGGTGACAGRevACCAATCCTCTGGAGAAAGhSnx16 prom.FwdTCAGGTAGCGAGAAATGTCGmTFIIB prom.FwdGAAGATTTTGCCAATCAACRevCTGTGTACTTCCTGGTTGTCmTFIIBFwdCTTCAACCGTCTTGTGTCAGG	mPCK1 CRE	Fwd	TCTCCCTGGAGTTTATTGTG
mPCK1FwdGTCATTTCATTCACCTCTCC RevRevAGGGTAAAGAACATGAGTGGmPdx1FwdCACCATGAACAGTGAGGAG RevhRab5b prom.FwdCTCGTACTTGTTGGTGACAG RevhSnx16 prom.FwdTCAGGTAGCGAAGAAAGGhSnx16 prom.FwdGAAGATTTTGCCAATCAAC RevMTFIIB prom.FwdGAAGATTTTGCCAATCAAC RevRevCTTCTGTGTGTGTGTCMTFIIBFwdCTTCAACCGTCTTTGTGTC RevRevCGTAAGGGAGAAAATACACAG		Rev	TACTATATAGAAGGGAGGACAGC
Rev   AGGGTAAAGAACATGAGTGG     mPdx1   Fwd   CACCATGAACAGTGAGGAG     Rev   TCCTTGTAGAGCTGTGTGG     hRab5b prom.   Fwd   CTCGTACTTGTTGGTGACAG     Rev   ACCAATCCTCTGGAGAAAG     hSnx16 prom.   Fwd   TCAGGTAGCGAGAAAGGAAAGG     mTFIIB prom.   Fwd   GAAGATTTTGCCAATCAAC     Rev   AGATAGTGCAGAGAATGTCG     mTFIIB   Fwd   CTTCAACCGTCTTTGTGTC     Rev   CGTAAGGGAGAAAATACACAG	mPCK1	Fwd	GTCATTTCATTCACCTCTCC
mPdx1 Fwd CACCATGAACAGTGAGGAG   Rev TCCTTGTAGAGCTGTGTGG   hRab5b prom. Fwd CTCGTACTTGTTGGTGACAG   Rev ACCAATCCTCTGGAGAAAG   hSnx16 prom. Fwd TCAGGTAGCGAAGAATGTCG   MTFIIB prom. Fwd GAAGATTTTGCCAATCAAC   Rev CTGTGTACTTCCTGGTTGTC   MTFIIB Fwd CTTCAACCGTCTTTGTGTC   Rev CGTAAGGGAGAAAATACACAG		Rev	AGGGTAAAGAACATGAGTGG
Rev   TCCTTGTAGAGCTGTGTGG     hRab5b prom.   Fwd   CTCGTACTTGTTGGTGACAG     Rev   ACCAATCCTCTGGAGAAAG     hSnx16 prom.   Fwd   TCAGGTAGCGAAGAAATG     Rev   AGATAGTGCAGAGAATGTCG     mTFIIB prom.   Fwd   GAAGATTTTGCCAATCAAC     Rev   CTGTGTACTTCCTGGTTGTC     mTFIIB   Fwd   CTTCAACCGTCTTTGTGTCAGC     Rev   CGTAAGGGAGAAAATACACAG	mPdx1	Fwd	CACCATGAACAGTGAGGAG
hRab5b prom.   Fwd   CTCGTACTTGTTGGTGACAG     Rev   ACCAATCCTCTGGAGAAAG     hSnx16 prom.   Fwd   TCAGGTAGCGAAGATAAATG     Rev   AGATAGTGCAGAGAATGTCG     mTFIIB prom.   Fwd   GAAGATTTTGCCAATCAAC     Rev   CTGTGTACTTCCTGGTTGTC     mTFIIB   Fwd   CTTCAACCGTCTTTGTGTCAGTGTC     Rev   CGTAAGGGAGAAAATACACAG		Rev	TCCTTGTAGAGCTGTGTGG
Rev   ACCAATCCTCTGGAGAAAG     hSnx16 prom.   Fwd   TCAGGTAGCGAAGAATATG     Rev   AGATAGTGCAGAGAATGTCG     mTFIIB prom.   Fwd   GAAGATTTTGCCAATCAAC     Rev   CTGTGTACTTCCTGGTTGTC     mTFIIB   Fwd   CTTCAACCGTCTTTGTGTC     Rev   CGTAAGGGAGAAAATACACG     Rev   CGTAAGGGAGAAAATACACG	hRab5b prom.	Fwd	CTCGTACTTGTTGGTGACAG
hSnx16 prom. Fwd TCAGGTAGCGAAGATAAATG Rev AGATAGTGCAGAGAATGTCG mTFIIB prom. Fwd GAAGATTTTGCCAATCAAC Rev CTGTGTACTTCCTGGTTGTC mTFIIB Fwd CTTCAACCGTCTTTGTGTC Rev CGTAAGGGAGAAAATACACAG		Rev	ACCAATCCTCTGGAGAAAG
Rev AGATAGTGCAGAGAATGTCG   mTFIIB prom. Fwd GAAGATTTTGCCAATCAAC   Rev CTGTGTACTTCCTGGTTGTC   mTFIIB Fwd CTTCAACCGTCTTTGTGTCC   Rev CGTAAGGGAGAAAATACACAG	hSnx16 prom.	Fwd	TCAGGTAGCGAAGATAAATG
mTFIIB prom.   Fwd   GAAGATTTTGCCAATCAAC     Rev   CTGTGTACTTCCTGGTTGTC     mTFIIB   Fwd   CTTCAACCGTCTTTGTGTCC     Rev   CGTAAGGGAGAAAATACACAG		Rev	AGATAGTGCAGAGAATGTCG
Rev     CTGTGTACTTCCTGGTTGTC       mTFIIB     Fwd     CTTCAACCGTCTTTGTGTC       Rev     CGTAAGGGAGAAAATACACAG	mTFIIB prom.	Fwd	GAAGATTTTGCCAATCAAC
mTFIIB Fwd cttcaaccgtctttgtgtc Rev cgtaagggagaaaatacacag		Rev	CTGTGTACTTCCTGGTTGTC
Rev CGTAAGGGAGAAAATACACAG	mTFIIB	Fwd	CTTCAACCGTCTTTGTGTC
		Rev	CGTAAGGGAGAAAATACACAG

Supplementary Table 2a:

Recorded body weights for selected mice

Figure		Average BW	
1а-е	Lean	31.2	
	db/db	50.8	
2a,b	shNS	33.2 (33.4)	
	shKAT2B	32.8 (32.5)	
	shWDR5	33.7 (32.9)	
2c	shNS	31.7	
	shKAT2A	30.9	
	shKAT2B	31.2	
	shKAT2AB	32.0	
2d	shNS	25.3	
	shKAT2B	24.7	
5a	Lean	34.6	
	db/db	49.3	
5b	Lean	30.5	
	DIO	44.7	
	Lean	36.1	
	db/db	55.3	
5d	Lean	32.0	
	DIO	44.6	
	DIO, Anac.	45.4	
	DIO, SPV	44.5	

Suppl. Figure		Average BW
1а-е	Lean	32.2
	DIO	40.8
2b	Lean	33.3
	Lean, shNS	32.9
	DIO, shNS	42.8
	DIO, shW5	43.8
	DIO, shK2B	43.5
2d-f	Lean, WT	30.4
	Lean, KO	28.9
	DIO, WT	46.1
	DIO, KO	44.9
9b	Lean	34.4
	db/db	52.6
	db, Anac.	51.4
	db, SPV	53.0
9d-h	shNS, SPV	31.0
	shNS, AA	31.4
	shK2B, SPV	30.7
	shK2B, AA	30.5

Supplementary Table 2b: GO an

( ) indicates BW before i.v. adenoviral infection.

GO analysis of biological process affected by both shK2B and shW5 in primary hepatocytes

GO Term	Description	P-value	Enrichment
GO:0030240	skeletal muscle thin filament assembly	1.09E-06	96.39
GO:0002526	acute inflammatory response	1.28E-05	16.07
GO:0006006	glucose metabolic process	2.17E-05	8.23
GO:0050878	regulation of body fluid levels	5.64E-05	7.1
GO:0051336	regulation of hydrolase activity	5.68E-05	3.08
GO:0015748	organophosphate ester transport	6.92E-05	11.48
GO:0070857	regulation of bile acid biosynthesis	3.18E-04	64.26
GO:0006082	organic acid metabolic process	3.67E-04	2.73
GO:0010035	response to inorganic substance	4.32E-04	4.46
GO:0006641	triglyceride metabolic process	6.84E-04	9.89
GO:0030162	regulation of proteolysis	9.40E-04	4.5