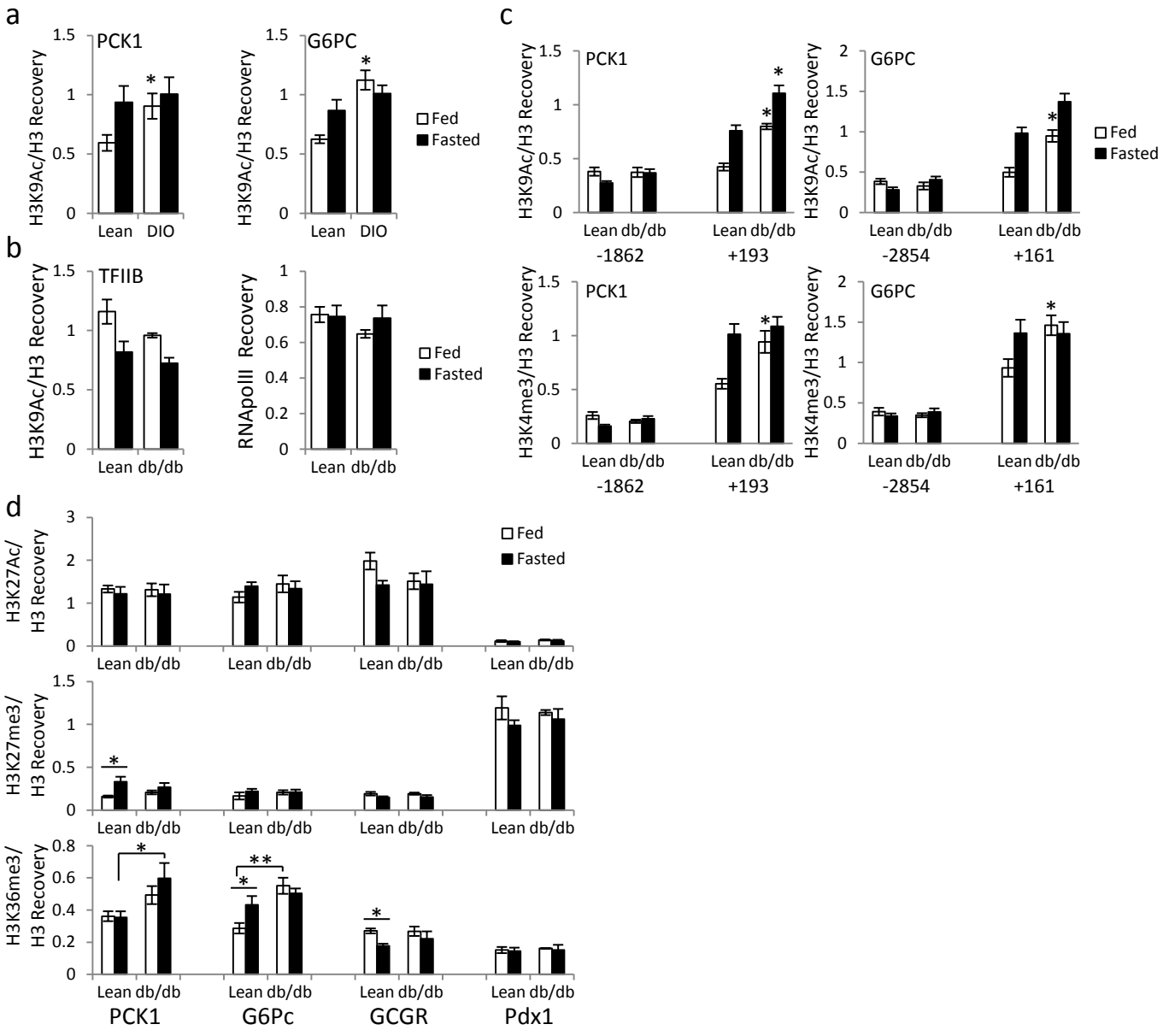
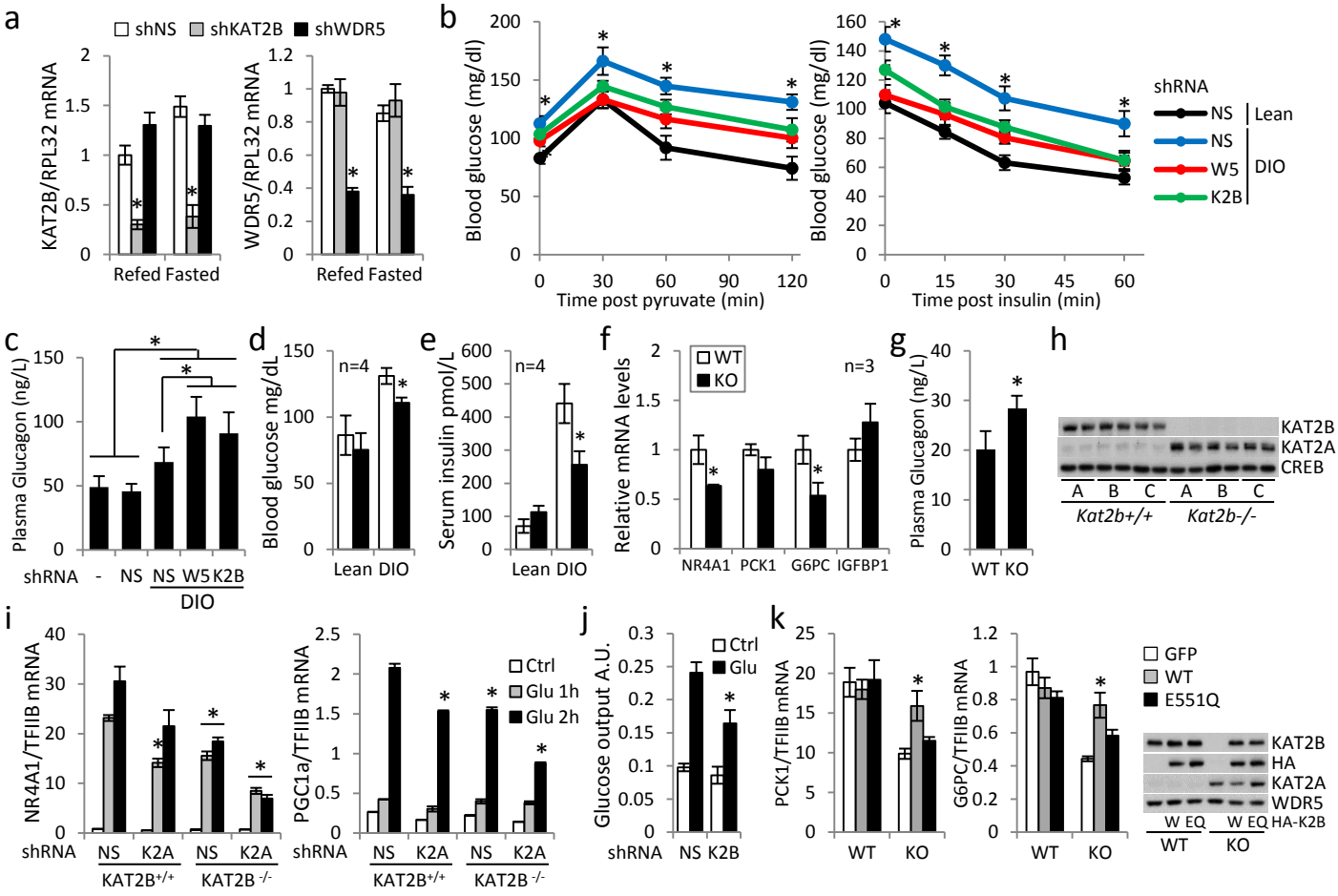
Supplementary Figure 1



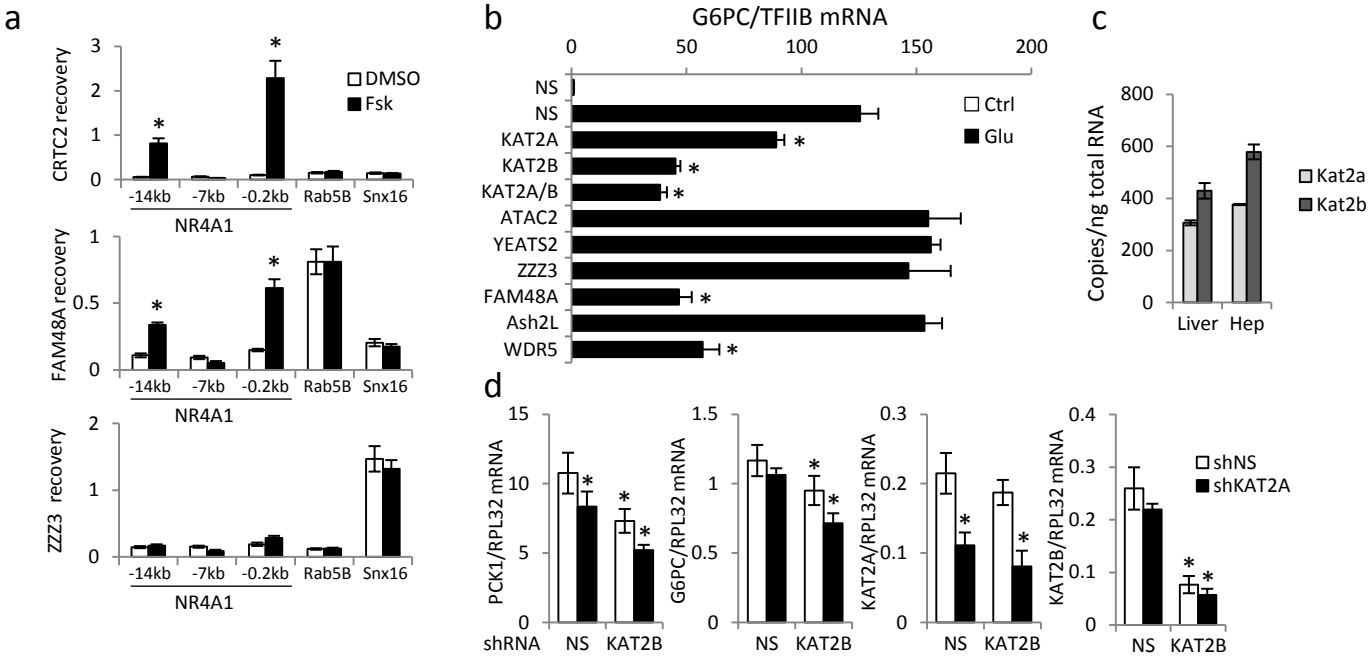
Supplementary figure 1. a, Chromatin Immunoprecipitation (ChIP) assay of H3K9Ac over *Pck1* and *G6pc* genes in livers of lean and DIO mice (*; *P<0.05* relative to lean mice; n=3). **b**, ChIP assay of H3K9Ac and RNA pol II levels over the *Tfiib* gene in livers from fasted or fed mice. **c**, ChIP 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 2



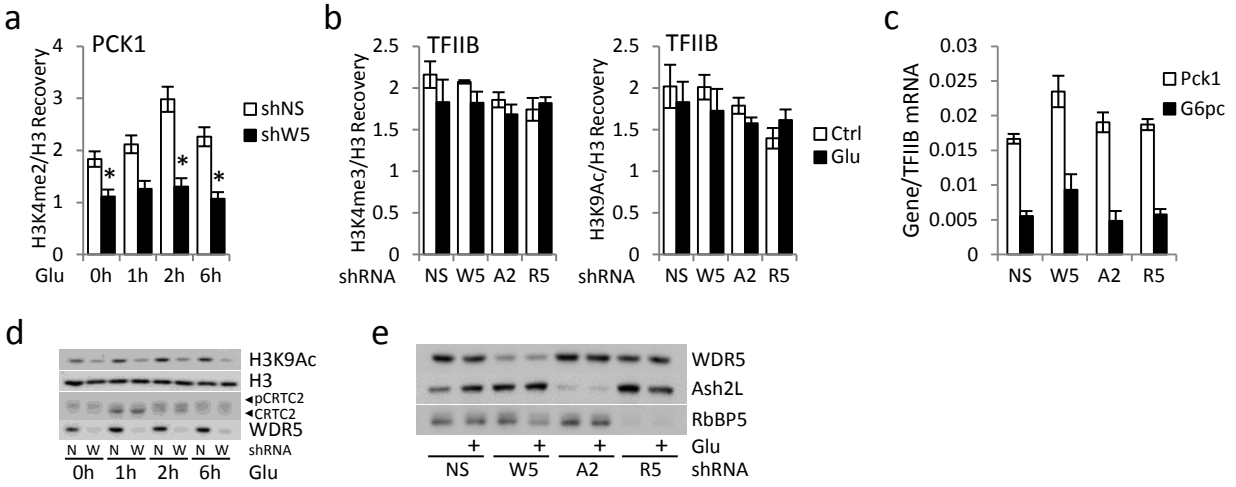
Supplementary figure 2. a, Effect of *Kat2b* or *Wdr5* RNAis on hepatic mRNA amounts for *Kat2b* and *Wdr5* from fasted or fed mice. **b**, Pyruvate tolerance test and insulin tolerance tests on lean and DIO mice depleted for either *Wdr5* (W5) or *Kat2b* (K2B) (*; $P<0.05$; n=5). **c**, Plasma glucagon 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 (*; $P<0.05$ relative to wt, shNS control mice; n=4). **k**, Effect of adenoviral wild-type or catalytically inactive (E551Q) KAT2B expression on *Pck1* and *G6pc* mRNA amounts in *Kat2b-/-* hepatocytes exposed to glucagon (*; $P<0.05$; n=3). Right, immunoblot showing levels of endogenous and HA-tagged WT or E551Q mutant KAT2B.

Supplementary Figure 3



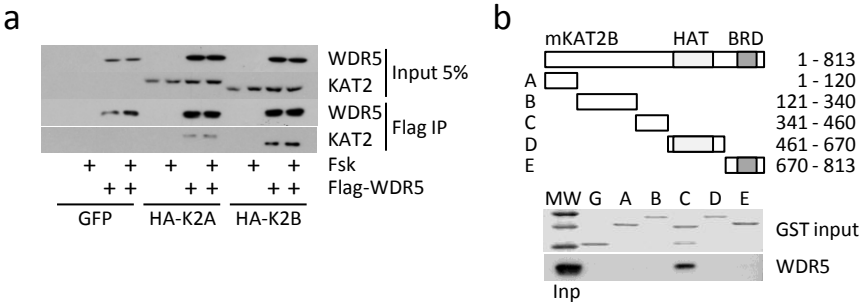
Supplementary figure 3. a, ChIP assay of HEK293T cells showing relative effects of FSK on recruitment of components in SAGA (FAM48A) and ATAC2 (ZZZ3) complexes to CREB binding sites (-14kb, -0.2kb) or CREB-negative region (-7kb) over the *Nr4a1* gene. FAM48A and ZZZ3 occupancy over known SAGA (*Rab5b*) 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



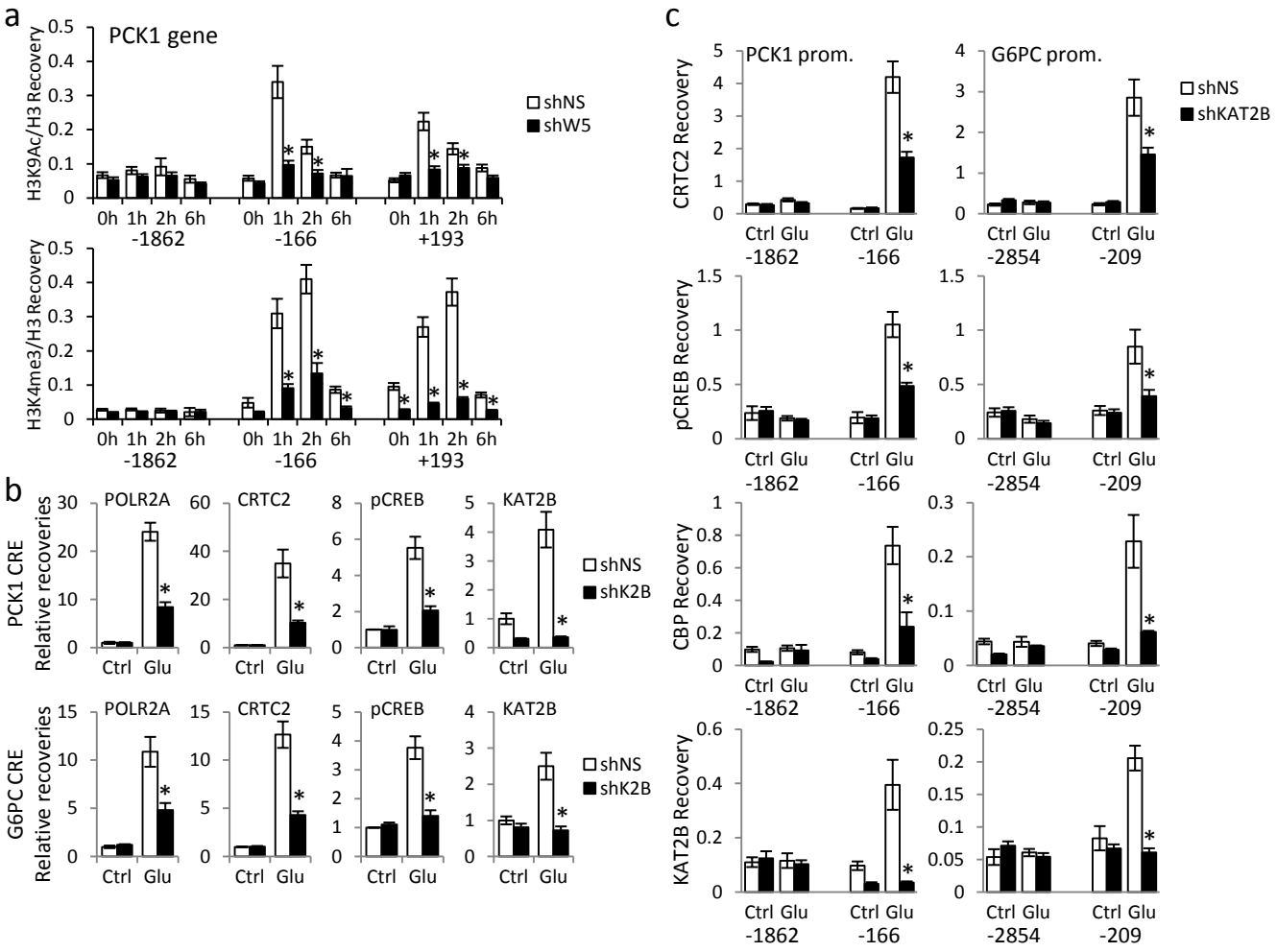
Supplementary figure 4. a, Effect of *Wdr5* RNAi on H3K4me2 over the *G6pc* promoter in hepatocytes exposed to glucagon. **b**, Effects of *Wdr5*, *Ash2l*, and *Rbbp5* depletion on H3K4me3 and H3K9Ac over the *TfIIb* promoter in hepatocytes exposed to glucagon. **c**, Basal *Pck1* and *G6pc* mRNA levels 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



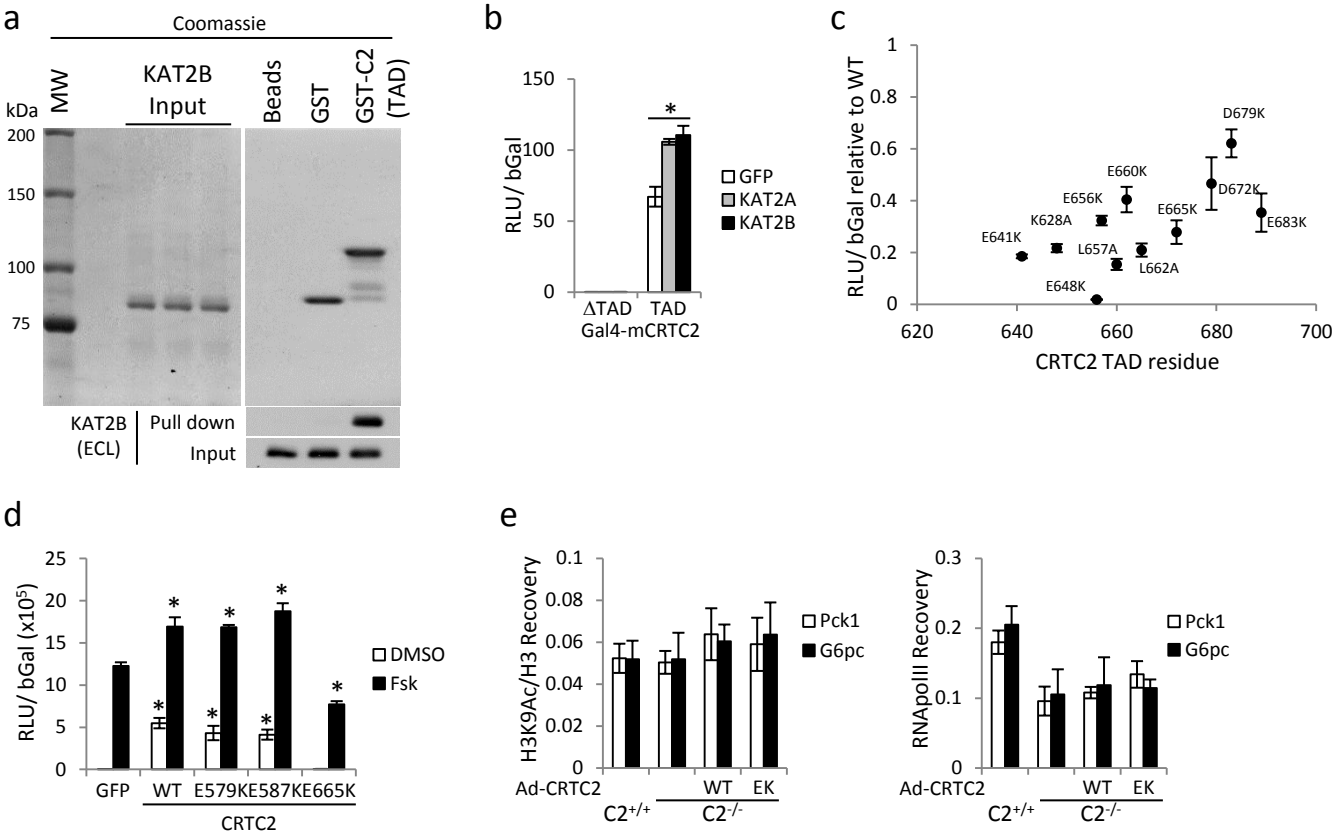
Supplementary figure 5. a, Immunoblot showing recovery of HA-tagged KAT2A and KAT2B from immunoprecipitates of Flag-tagged WDR5 prepared from HEK293T cells exposed to FSK. **b**, GST-pull down showing direct association between WDR5 and residues 341-460 of KAT2B.

Supplementary Figure 6



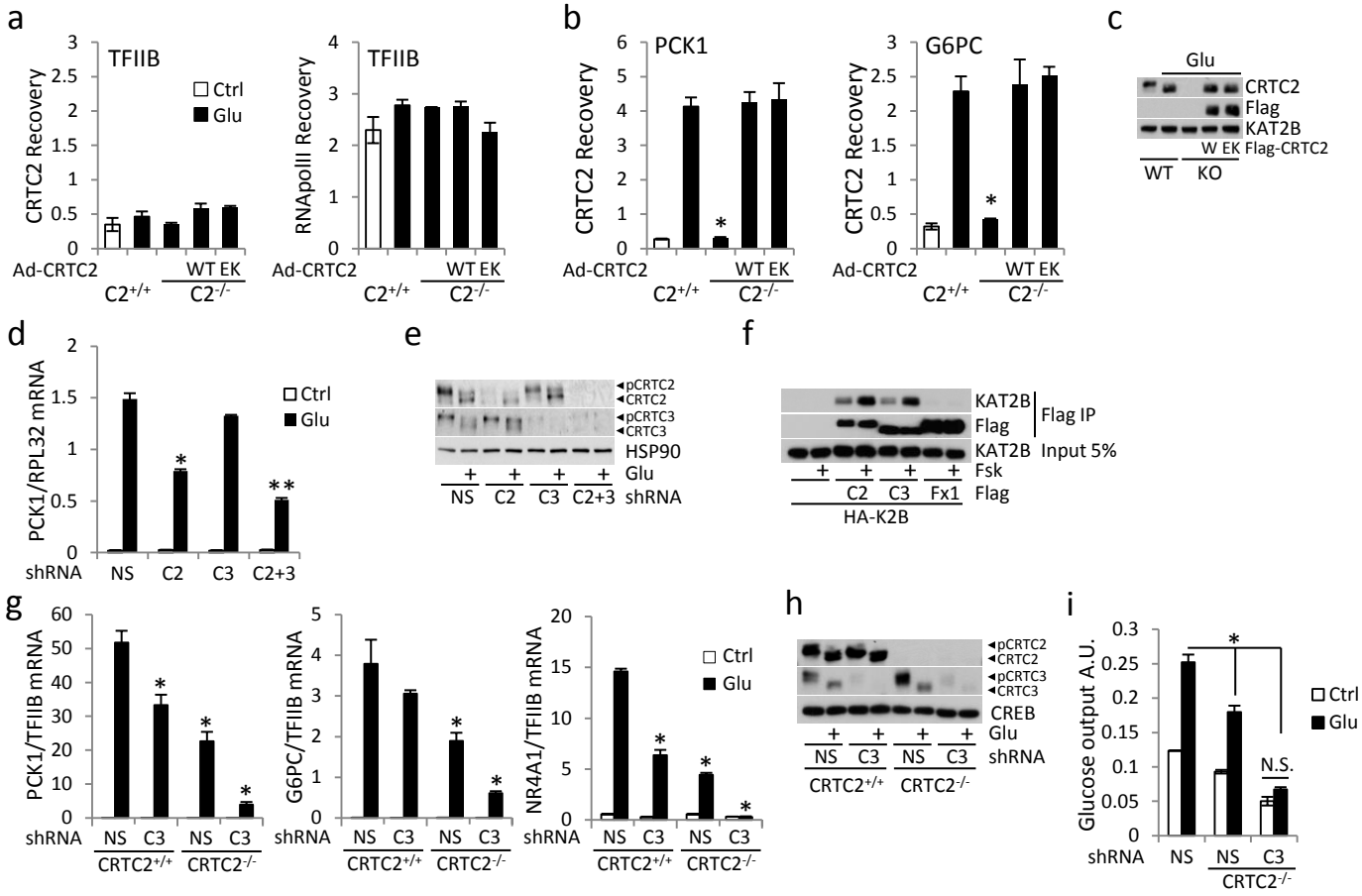
Supplementary figure 6. a, Effect of *Wdr5* depletion of on glucagon-induced H3K9Ac and H3K4me3 amounts over the *Pck1* gene in primary hepatocytes. **b**, **c**, ChIP assays showing effect of *Kat2b* depletion on recruitment of P-CREB, CRTC2, RNA polymerase II, CBP, KAT2B, and WDR5 to CREB binding sites 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



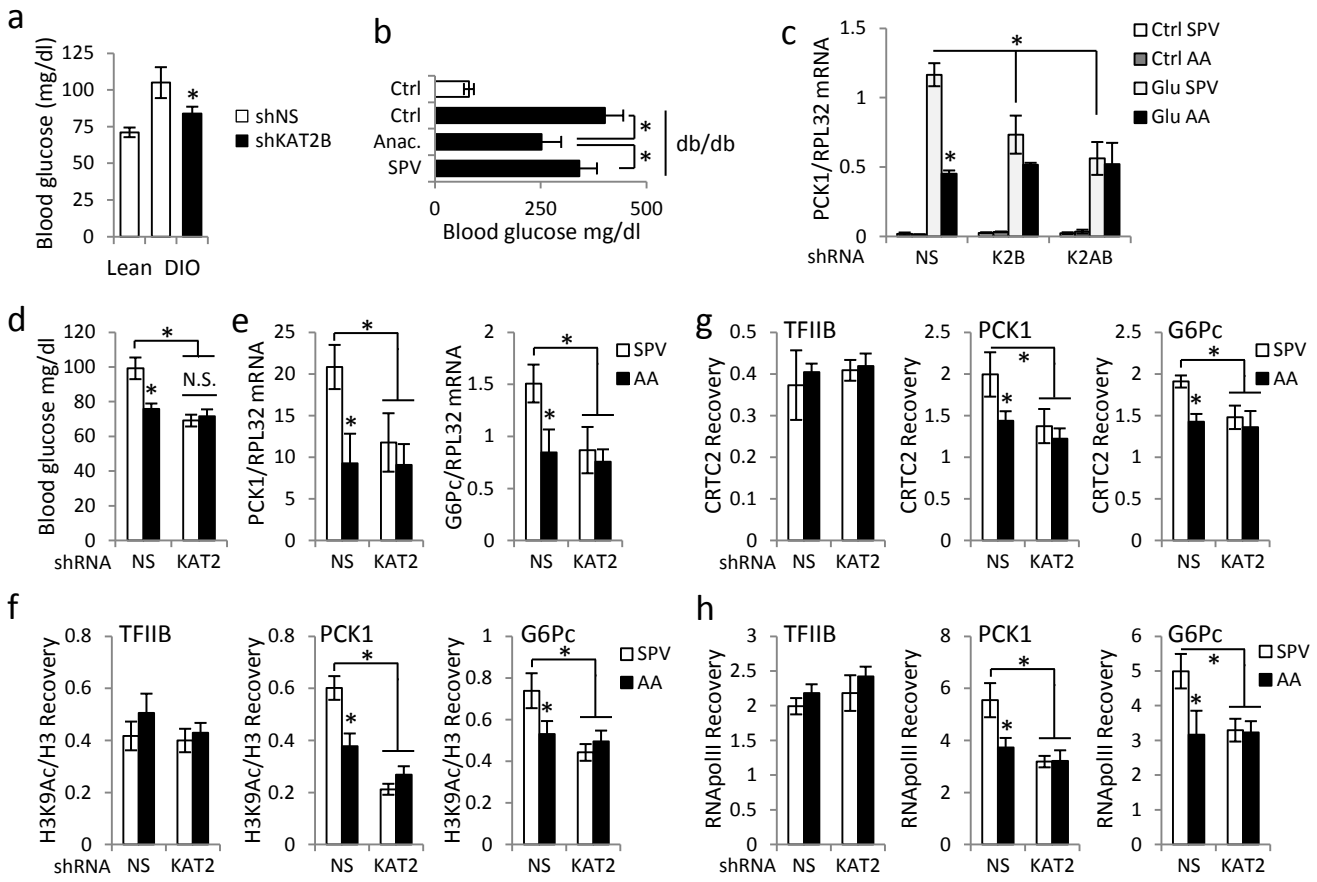
Supplementary figure 7. a, GST pull-down assay of purified KAT2B protein with purified GST-CRTC2 (TAD, aa. 601-692) or GST alone. **b**, Transient assay of chromosomal GAL4-luc reporter activity in HEK293T cells expressing GAL4-CRTC2 constructs containing the GAL4 DNA binding domain fused to CRTC2 lacking the trans-activation domain (ΔTAD, 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 β-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 β-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 RNApolII 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



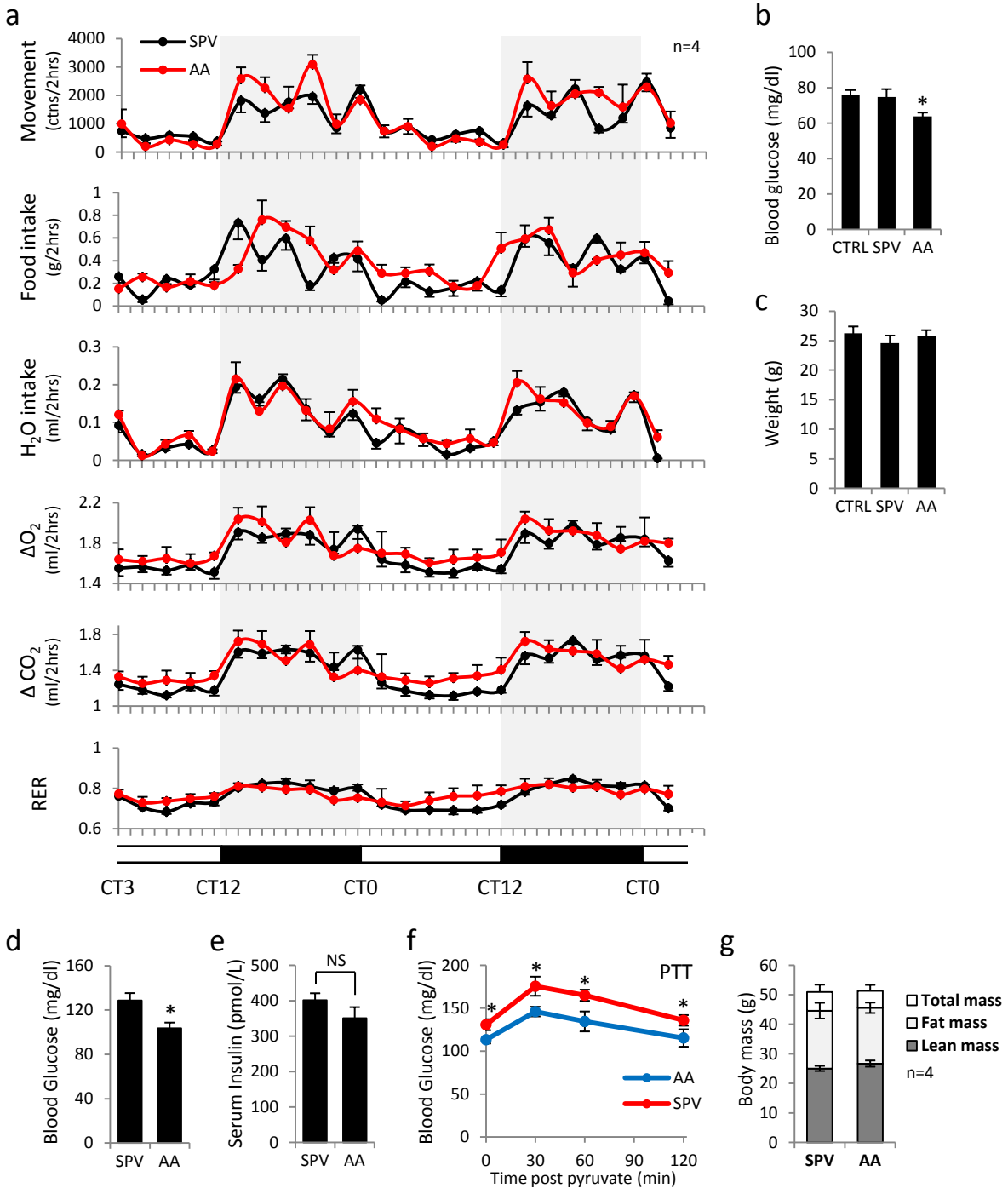
Supplementary figure 8. a, b, Chromatin Immunoprecipitation assay of CRTC2 and RNA Pol II occupancy over control (*TfIIb*) (**a**) and gluconeogenic (**b**) genes in wild-type or *Crtc2-/-* hepatocytes following reconstitution with wild-type or KAT2B-defective (E665K) mutant CRTC2 (*; *P<0.05*; n=3). **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 (g), protein levels (h) 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

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

Primers for ChIP analysis

mG6Pase (-2854)	Fwd	GTCTACTTTGCCCTCAACTC
	Rev	AGCTGTGGTGATTCTAGGAC
mG6Pase CRE	Fwd	ATCAGGCTGTTTTTGTGTG
	Rev	CATCATCAGTAGGTTGATGC
mG6Pase	Fwd	CTTGAATTGCTCAACTTCTG
	Rev	TAAACTACACGTGGGAACAC
mGCGR	Fwd	CAGCTTCCAGCTTCTCACAC
	Rev	GGAAGCGAATCCATCTGAAG
mGcK	Fwd	TACAGACATCTGGTGACAGC
	Rev	CCTCCTAGTGTGTCTCTTCC
mIGFBP1 prom.	Fwd	GTTTGTGTAGAGCTCACAAGC
	Rev	CACAGGTTAATGATTGTCAGG
mIGFBP1	Fwd	AAGAAAGTTTGCAGGTTAGG
	Rev	TCCACTGAAAGACCGAGTA
hNR4A1 Enh. CRE	Fwd	ATTTTTAGCCCCATTGATGAGG
	Rev	ATTGACGTCTCCGGAATCC
hNR4A1 prom.	Fwd	CAGGGTCACGCTCATGCT
	Rev	CAAGAGCCCAAAATAGTCAGCT
mhNR4A1 CRE	Fwd	GATCAAACAATCCGCGCTC
	Rev	ATGTCTGCGCGCGTGA
mNR4A1	Fwd	GCTTGTTTAGGAGGTTTCC
	Rev	CAGAGTACAGAGTGCCTCAC
mPCK1 (-1862)	Fwd	TCTCCTAGAGGATCATGGAC
	Rev	ATAGTAGCCCAATGATGGTG
mPCK1 CRE	Fwd	TCTCCCTGGAGTTTATTGTG
	Rev	TACTATATAGAAGGGAGGACAGC
mPCK1	Fwd	GTCATTTCATTCACCTCTCC
	Rev	AGGGTAAAGAACATGAGTGG
mPdx1	Fwd	CACCATGAACAGTGAGGAG
	Rev	TCCTTGTAGAGCTGTGTGG
hRab5b prom.	Fwd	CTCGTACTTGTTGGTGACAG
	Rev	ACCAATCCTCTGGAGAAAG
hSnx16 prom.	Fwd	TCAGGTAGCGAAGATAAATG
	Rev	AGATAGTGCAGAGAATGTCG
mTFIIB prom.	Fwd	GAAGATTTTGCCAATCAAC
	Rev	CTGTGTACTTCCTGGTTGTC
mTFIIB	Fwd	CTTCAACCGTCTTTGTGTC
	Rev	CGTAAGGGAGAAAATACACAG

Supplementary Table 2a: Recorded body weights for selected mice

Figure		Average BW
1a-e	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
1a-e	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

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

Supplementary Table 2b: 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