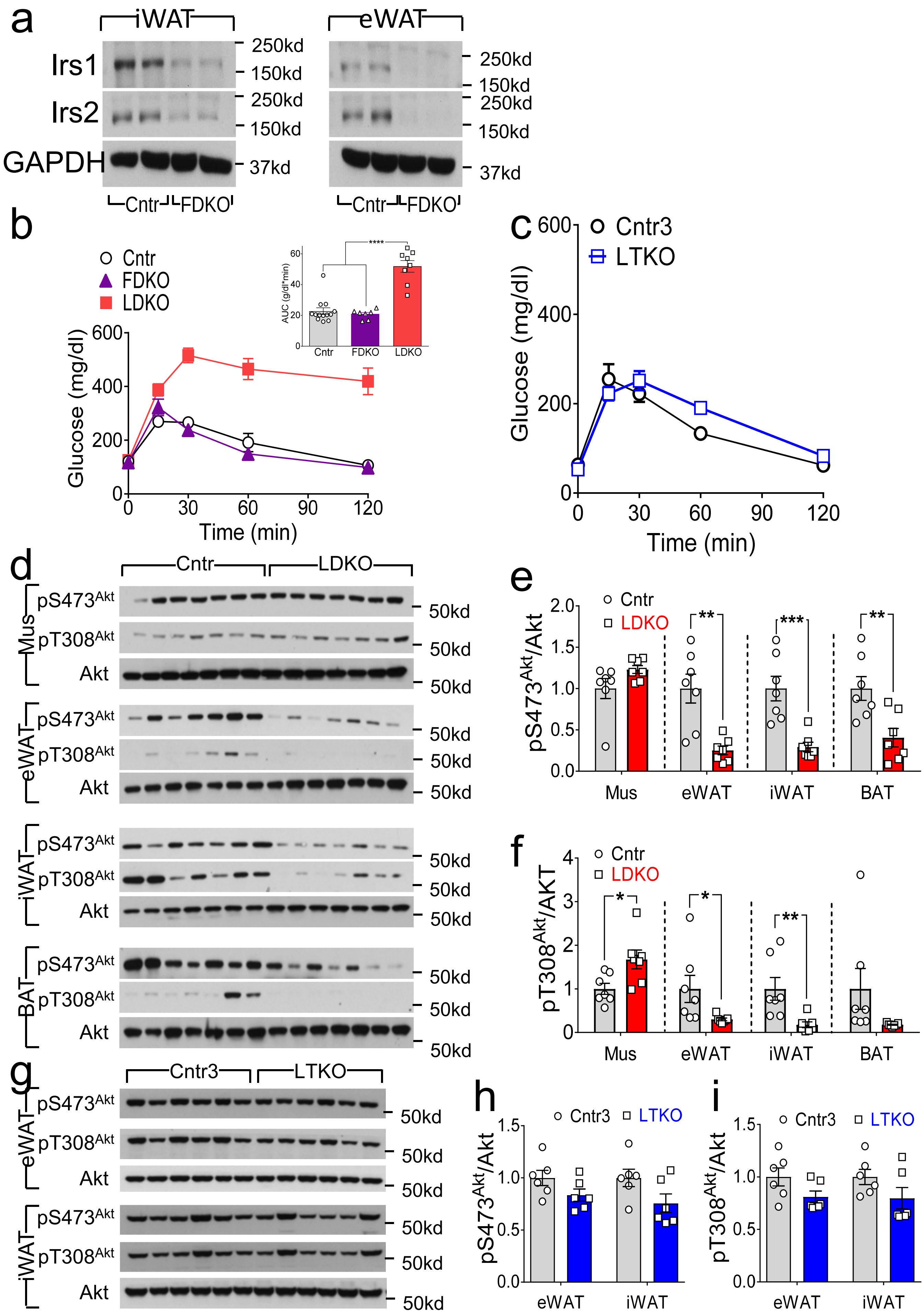
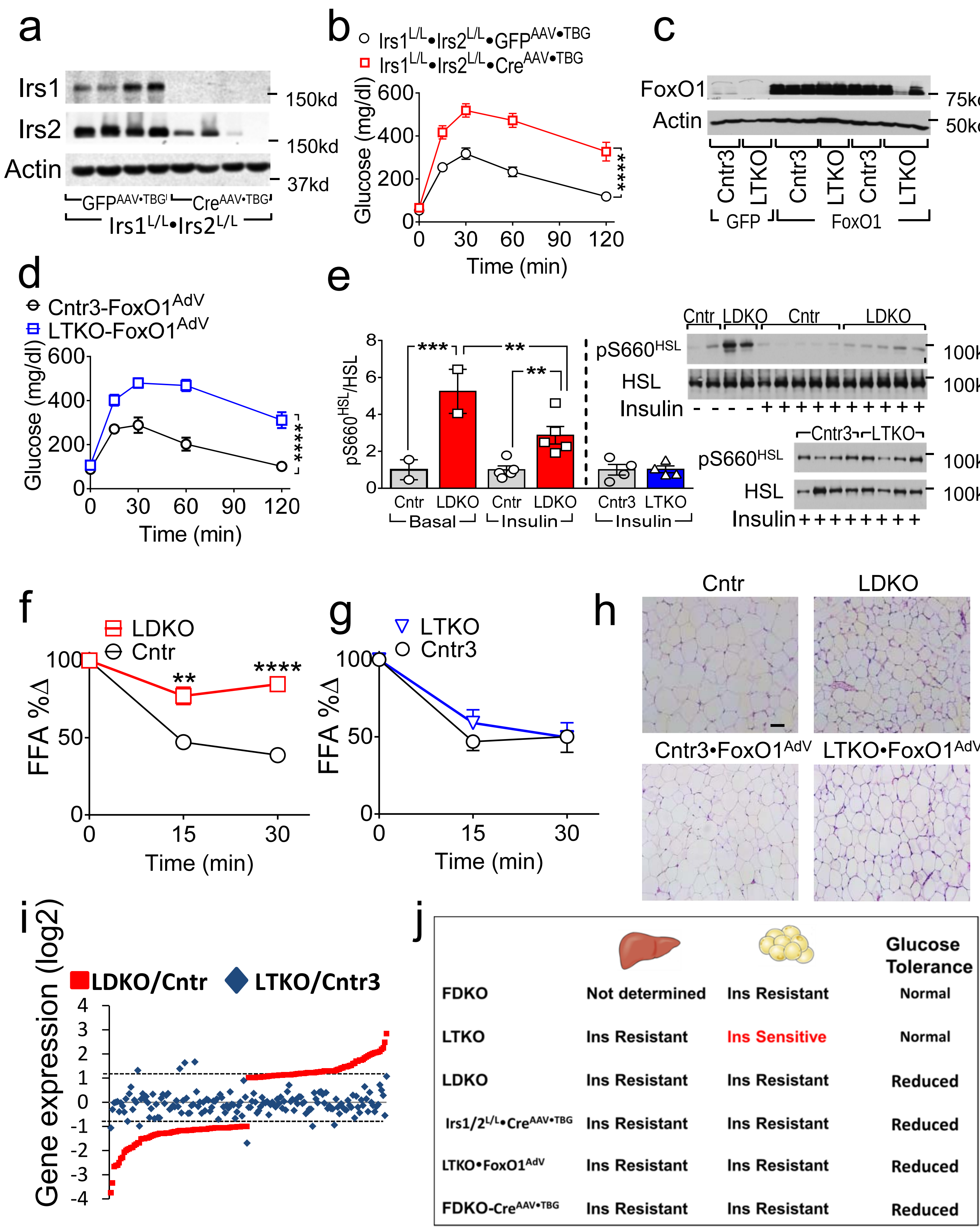
Supplemental Figure 1



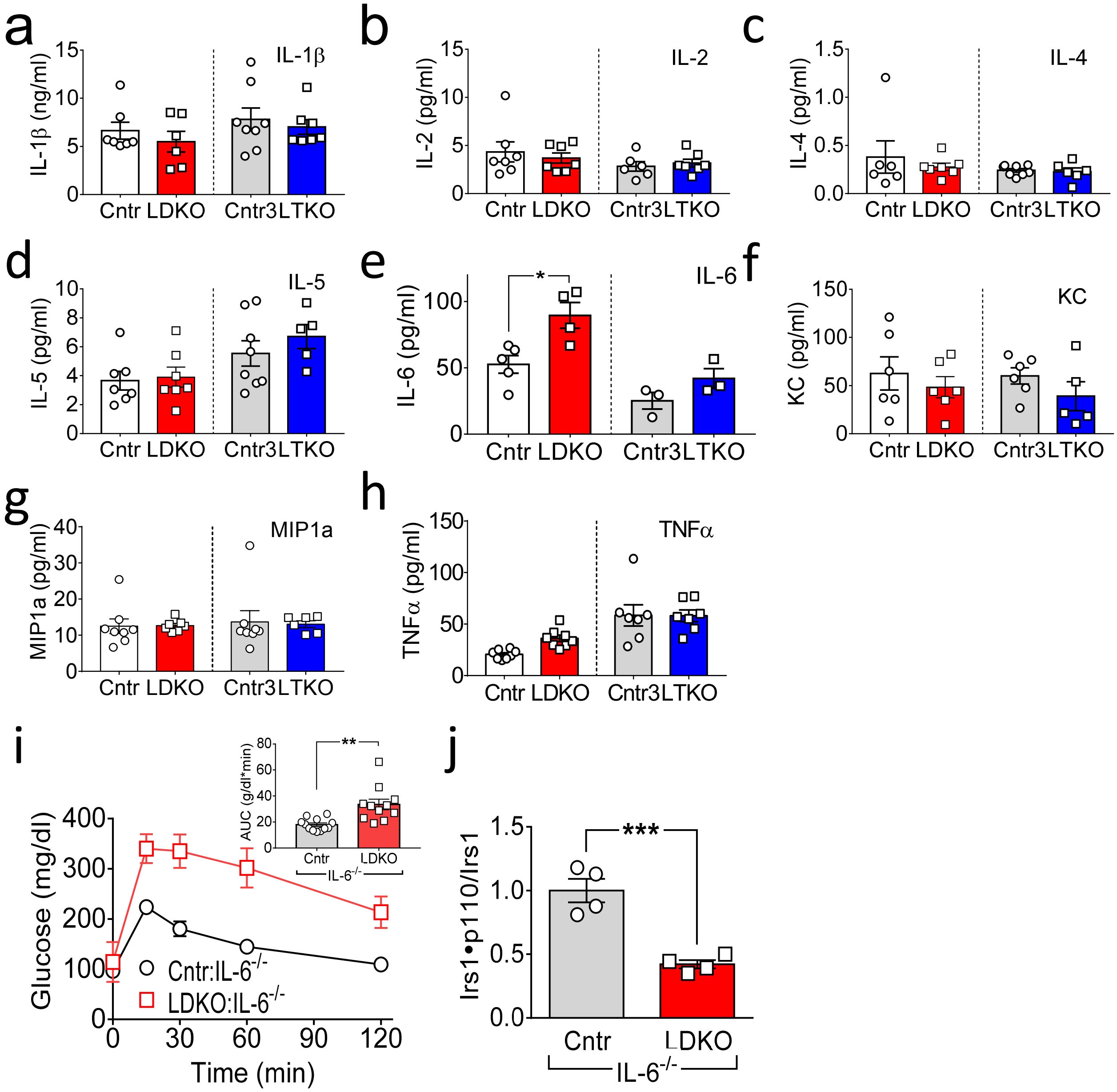
Supplemental Fig. 1. Hepatic FoxO1 dysregulates WAT insulin signaling. (**a**) Western blotting of Irs1 and Irs2 proteins in eWAT and iWAT depots of eight-week old FDKO and control (Cntr) mice. (**b**) Glucose tolerance test (GTT) performed on three-month old FDKO, LDKO and control mice (*n* = 7-13). (**c**) GTT performed on 18-week old LTKO and control (Cntr3) mice (*n* = 5-8). (**d**) Western blotting of phospho- and total Akt protein in hind-limb muscle, eWAT, iWAT and BAT upon completion of the hyperinsulinemic-euglycemic clamp in LDKO and Cntr mice. (**e**,**f**) Densitometric quantitation of (**e**) phospho-S473 and (**f**) phospho-T308, normalized by total Akt from Western blots of LDKO and control tissues. (**g**) Western blotting of phospho- and total Akt protein in eWAT and iWAT upon completion of the hyperinsulinemic-euglycemic clamp in LTKO and Cntr3 mice. (**h**,**i**) Densitometric quantitation of (**h**) phospho- S473 and (**i**) phospho-T308, normalized by total Akt from Western blots of LTKO and control tissues. Data were analyzed by two-way ANOVA (**b**, **c**) and unpaired Student's t-test (**e**, **f**, **h**, **i**). All data are presented as mean ± SEM. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

Supplemental Figure 2



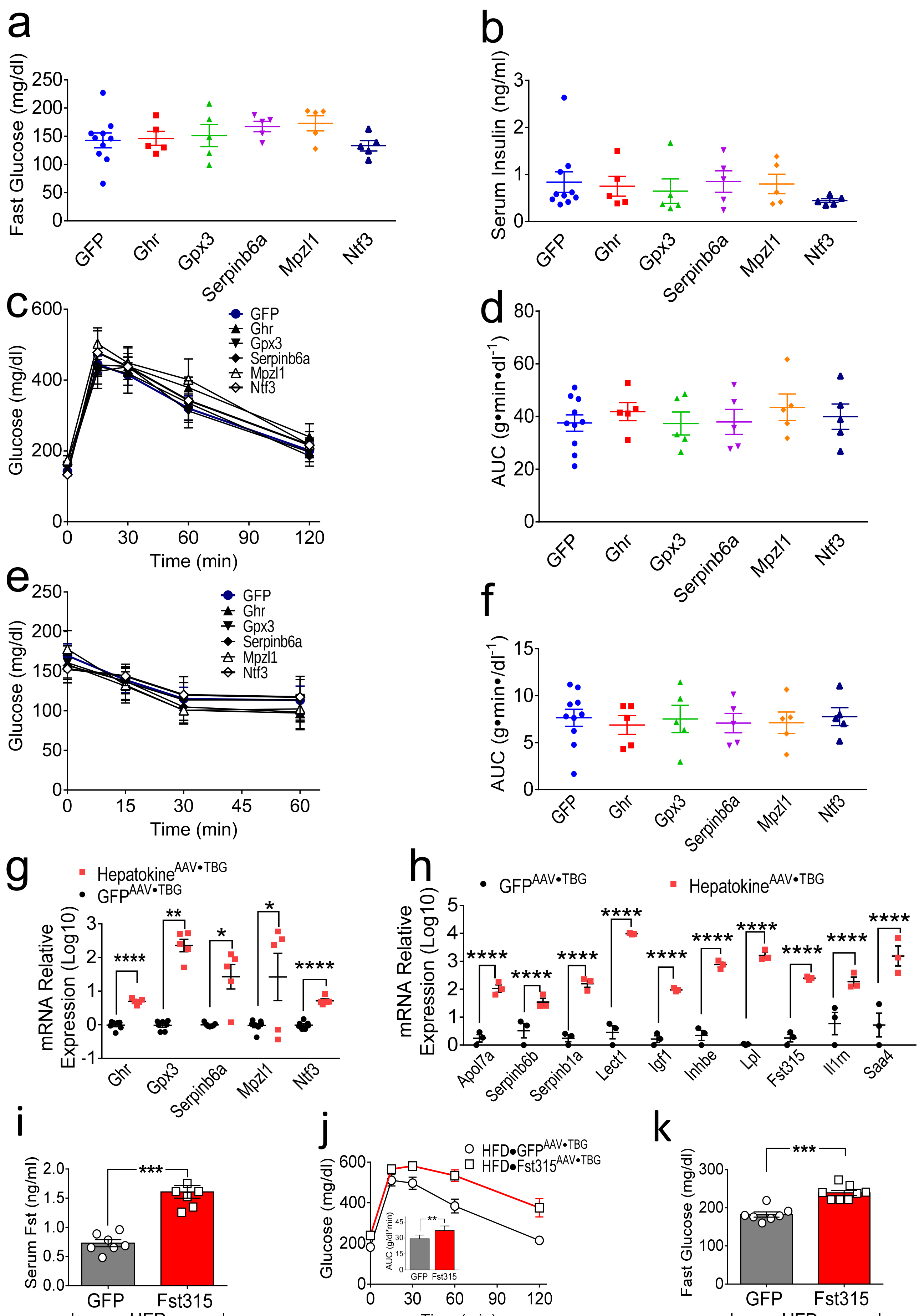
Supplemental Fig. 2. Related to Figure 1. (**a**) Western blot analysis of Irs1 and Irs2 proteins in liver of three-month old Irs1/2$^{L/L}$ mice three weeks after injection with Cre$^{AAV•TBG}$ or control GFP$^{AAV•TBG}$. (**b**) GTTs performed on mice in '**a**' two weeks after AAV infection (*n* = 5-6). (**c**) Western blot analysis of FoxO1 in the liver extracts from eighteen-week old LTKO and Cntr3 mice two weeks after injection with FoxO1^{AdV} or control GFP^{AdV}. (**d**) GTTs performed on mice in '**c**' one week after AAV infection (*n* = 5). (**e**) Western blot and densitometric quantitation of pS660^{HSL} in eWAT of four-month old LDKO and LTKO mice five minutes after injection with insulin (+) (1U/kg i.v.) or saline (−). (**f,g**) Change in serum free fatty acids (% of overnight-fasted baseline) following insulin treatment (1 U/kg, i.p.) of four-month old (**f**) LDKO and Cntr mice (*n* = 7) or (**g**) LTKO and Cntr3 mice (*n* = 5-9). (**h**) H&E staining of paraffin-sectioned eWAT from four-month old LDKO and Cntr mice and from eighteen-week old LTKO and Cntr3 mice two weeks after injection with FoxO1^{AdV}. Scale bar, 50 µm. (**i**) Differential/restored expression in eWAT of LTKO (versus Cntr3) mice of ~160 genes that were up- or down-regulated ≥2-fold in eWAT of LDKO (versus Cntr) mice. The results for each gene may be found in **Supplemental Table 1**. (**j**) Summary of hepatic and WAT insulin sensitivity and associated glucose tolerance of mice shown in **Figure 1** and **Supplemental Figure 1** and **2**. Data were analyzed by two-way ANOVA (**b**, **d**, **f**, **g**) and one-way ANOVA (**e**). All data are presented as mean ± SEM. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

Supplemental Figure.3



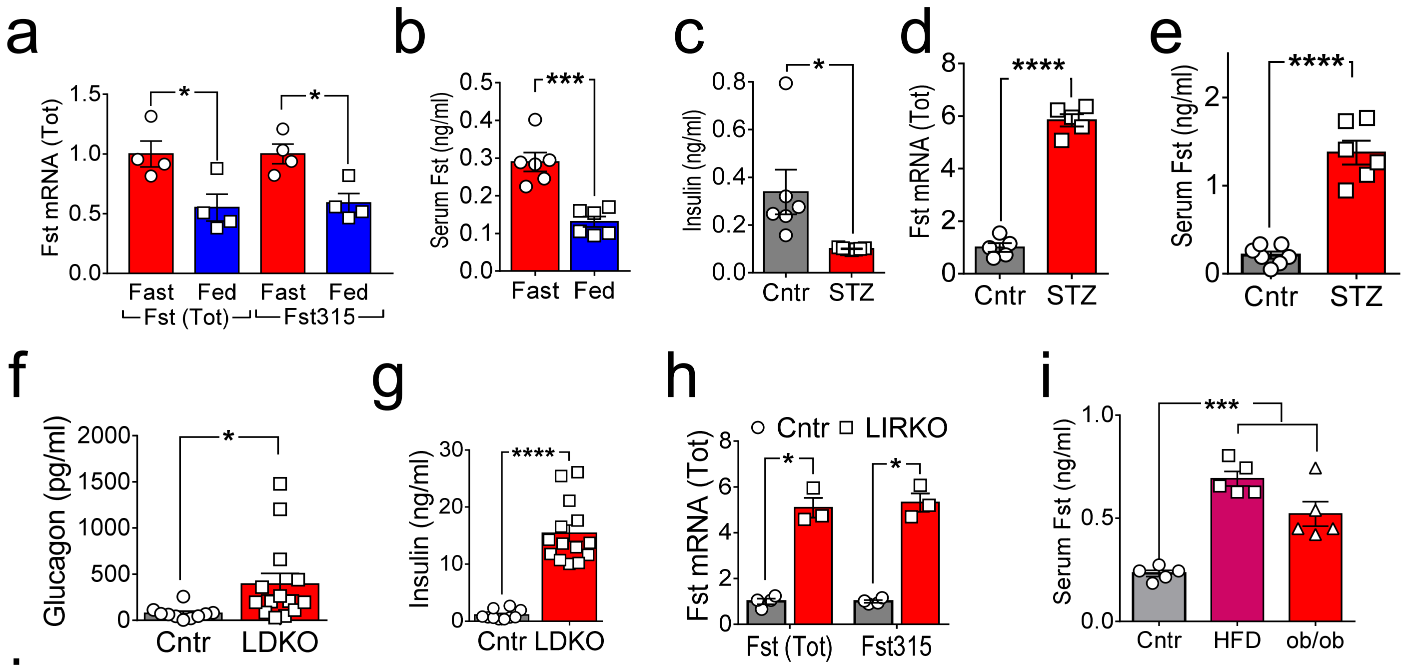
Supplemental Fig. 3. Related to Figure 2. Additional data concerning the role of IL6 in LDKO mice. (**a-h**) Measured concentrations of (**a**) IL1-β, (**b**) IL-2, (**c**) IL-4, (**d**) IL-5, (**e**) IL-6, (**f**) KC, (**g**) MIP1a and (**h**) TNFα in serum of four-month old male LDKO and LTKO mice. (**i**) GTTs were performed in seven-month old LDKO•IL-6$^{-/-}$ and Cntr•IL-6$^{-/-}$ mice, and summarized by the AUC (n = 11-12). (**j**) Insulin-stimulated Irs1•p110^{PI3K} complex formation in the eWAT of seven-month old LDKO•IL-6$^{-/-}$ and Cntr•IL-6$^{-/-}$ mice (n = 4). Data were analyzed by one-way ANOVA (**a-h**), two-way ANOVA (**i**) and unpaired Student's t-test (**j**). Data are reported as the mean±SEM. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

Supplemental Figure 4



Supplemental Fig. 4. Related to Figure 2. Additional data from functional screening of putative hepatokines. Five-week old C57BL6 mice were challenged with high fat diet (45% fat) for 3 months and then infected with $GFP^{AAV \cdot TBG}$ or $hepatokine^{AAV \cdot TBG}$ ($2x10^{11}$ GC/mouse) encoding the indicated genes (*n* = 5-10), four weeks after which (**a**) fasting blood glucose and (**b**) fasting serum insulin levels were measured. (**c**,**d**) GTTs were performed two weeks after AAV infection (**c**), summarized by the areas under curves (AUC) (**d**). (**e**,**f**) ITTs were performed four weeks after AAV infection (**e**), summarized by the areas under curves (AUC) (**f**). (**g**) Expression of hepatokine mRNAs assessed by qPCR on total liver RNA from $hepatokine^{AAV \cdot TBG}$- and $GFP^{AAV \cdot TBG}$-infected mice (cohort 1; *n* = 5-7). (**h**) Expression of hepatokine mRNAs assessed by qPCR on total liver RNA from $hepatokine^{AAV \cdot TBG}$- and $GFP^{AAV \cdot TBG}$-infected mice (cohort 2; *n* = 3). (**i-k**) Five-week old C57BL6 mice maintained on high fat diet (45% fat) for 2 months were infected with lower dose of $GFP^{AAV \cdot TBG}$ or $Fst315^{AAV \cdot TBG}$ ($0.5x10^{11}$ GC/mouse). Serum Fst was measured two weeks after infection (**i**) (*n* = 7); GTTs (**j**) and fasting blood glucose levels (**k**) were performed 10 days after infection (*n* = 7-8). Data were analyzed by one-way ANOVA (**a**, **b**, **d**, **f**), two-way ANOVA (**c**, **e**) and unpaired Student's t-test (**g**, **h**, **i**, **j**, **k**). Data are reported as the mean±SEM. *$P<0.05$; **$P<0.01$; ***$P<0.001$; ****$P<0.0001$.

Supplemental Figure 5

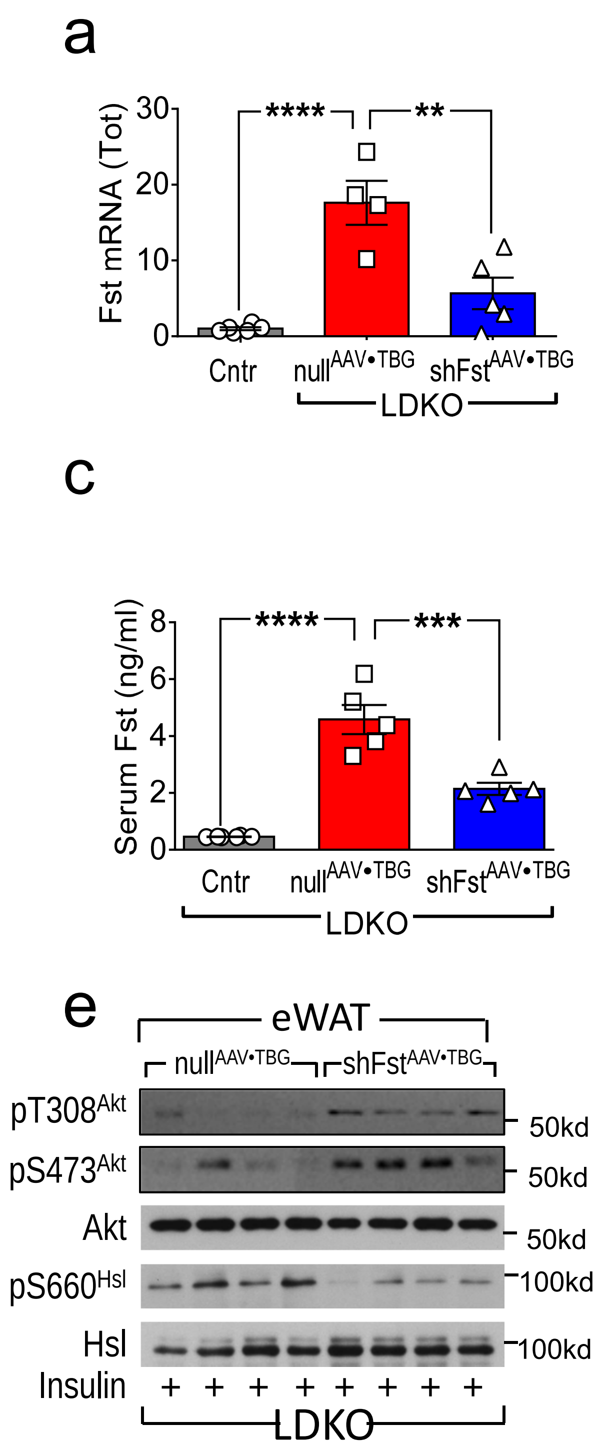


j

Human	- 603	GGGAGACCGGGCCTGAGGTGTTAAACATTTTTGTTTGCTTCCGACTAGTCCAGACGAA	- 546
Mouse	- 629	GGGCGGCCGGCTCCGAGGTGTTAAACATTTTTGTTTGCTTCTGACTTGTGGAGCCCGA	- 568
Rat	- 603	GGGCGGCCGGCTCCGAGGTGTTAAACATTTTTGTTTGCCTCTGACTTGTGGAGACCGA	- 572
Human	- 1614	GAGAGACAGCGAGACAGAAACAGACAGAATGATTCTGGAAAGATTAAG	- 1566
Mouse	- 1660	AACGGGCAGACAGACAGAAACAGACAAAATGAATCTGGCAAGATTAAG	- 1618
Rat	- 1443	GACAAACAGACAGACAGAAACAGACAAAATGAATCTGGAAAGATTAAG	- 1395
Human	- 1895	CTGCCATTAGAGGGCACTAAACAACTCTACATTAATGAGTTGGAGGGAA	- 1847
Mouse	- 1874	CTACCATTAGAGGGCACTAAACAACTCCACATTAATGCGTTGGAGGGAA	- 1826
Rat	- 1640	CTACCATTAGAGGGCACTAAACAACTCCACATTAATGCGTTGGAGGGAA	- 1592

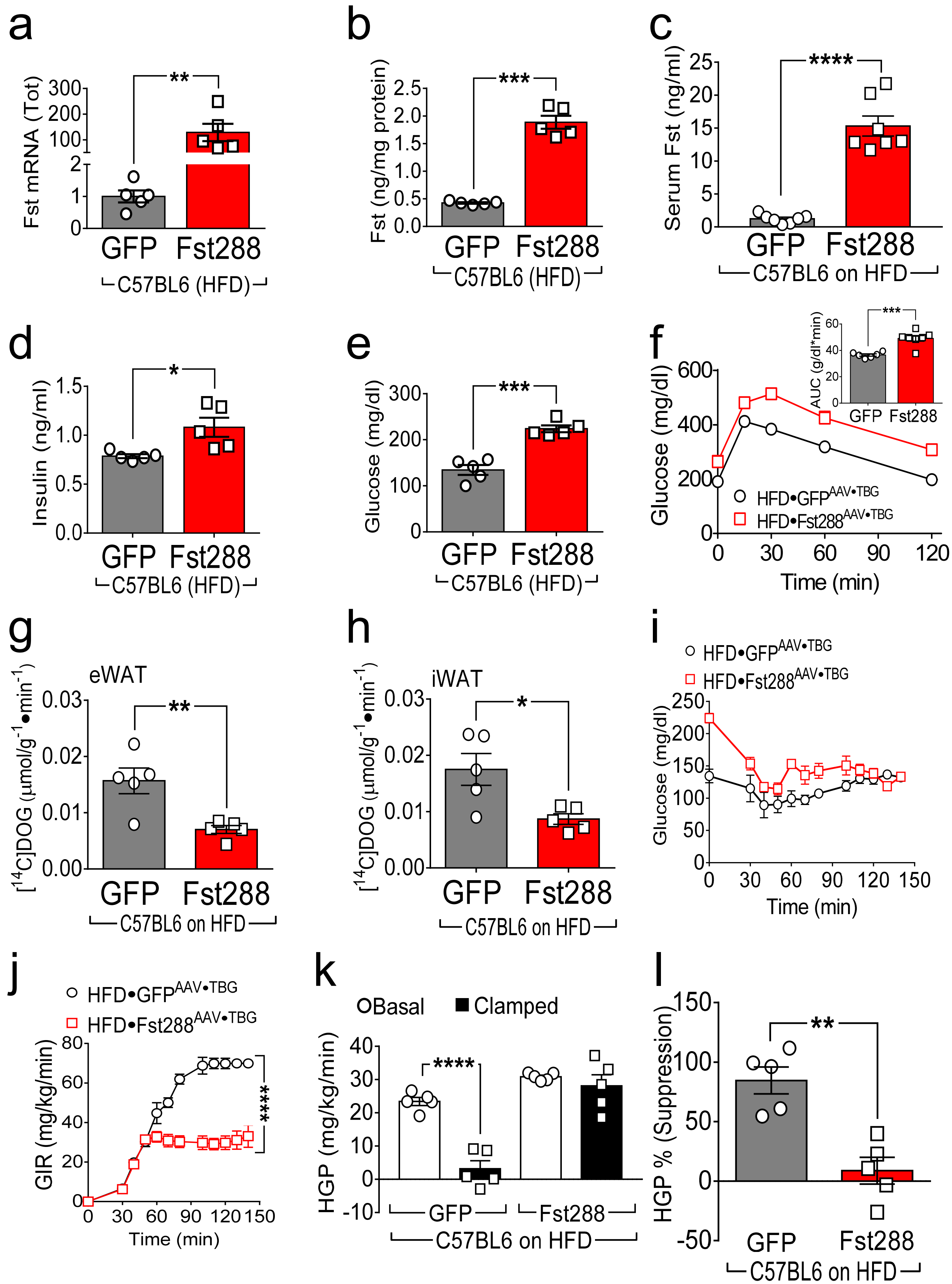
Supplemental Fig. 5. Related to Figure 3. Effect upon Fst expression and secretion of fasting/feeding, glucagon-to-insulin ratio, insulin insufficiency, and diet-induced or genetic obesity. (**a**,**b**) Hepatic Fst mRNA expression (**a**) and serum Fst concentration (**b**) in two-month old C57BL6 mice, with or without four hours refeeding after an overnight fast (n = 6). (**c**-**e**) Two-month old C57BL6 mice were treated with streptozotocin (STZ, 150mg/kg i.p.), 10 days after which (**c**) serum insulin concentration, (**d**) hepatic Fst mRNA expression, and (**e**) serum Fst concentration were measured after overnight fasting (n = 5-7). (**f**,**g**) Fasting serum glucagon (**f**) and insulin concentration (**g**) in 3-4-month old LDKO and Cntr mice (n = 10-14). (**h**) Total and Fst315 mRNA expression in the liver of LIRKO and floxed control mice (n = 3-4). (**i**) Serum total Fst concentration in four-month old high fat diet-fed mice (3 months HFD) and in 4-month old genetically obese *ob/ob* mice (n = 5). (**j**) Conservation of consensus FoxO1 binding sites within the promoter region of human, mouse and rat Fst gene sequences. Data were analyzed by one-way ANOVA (**a**, **i**) and unpaired Student's t-test (**b**, **c**, **d**, **e**, **f**, **g**, **h**). Data are reported as the mean±SEM. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

Supplemental Figure 6



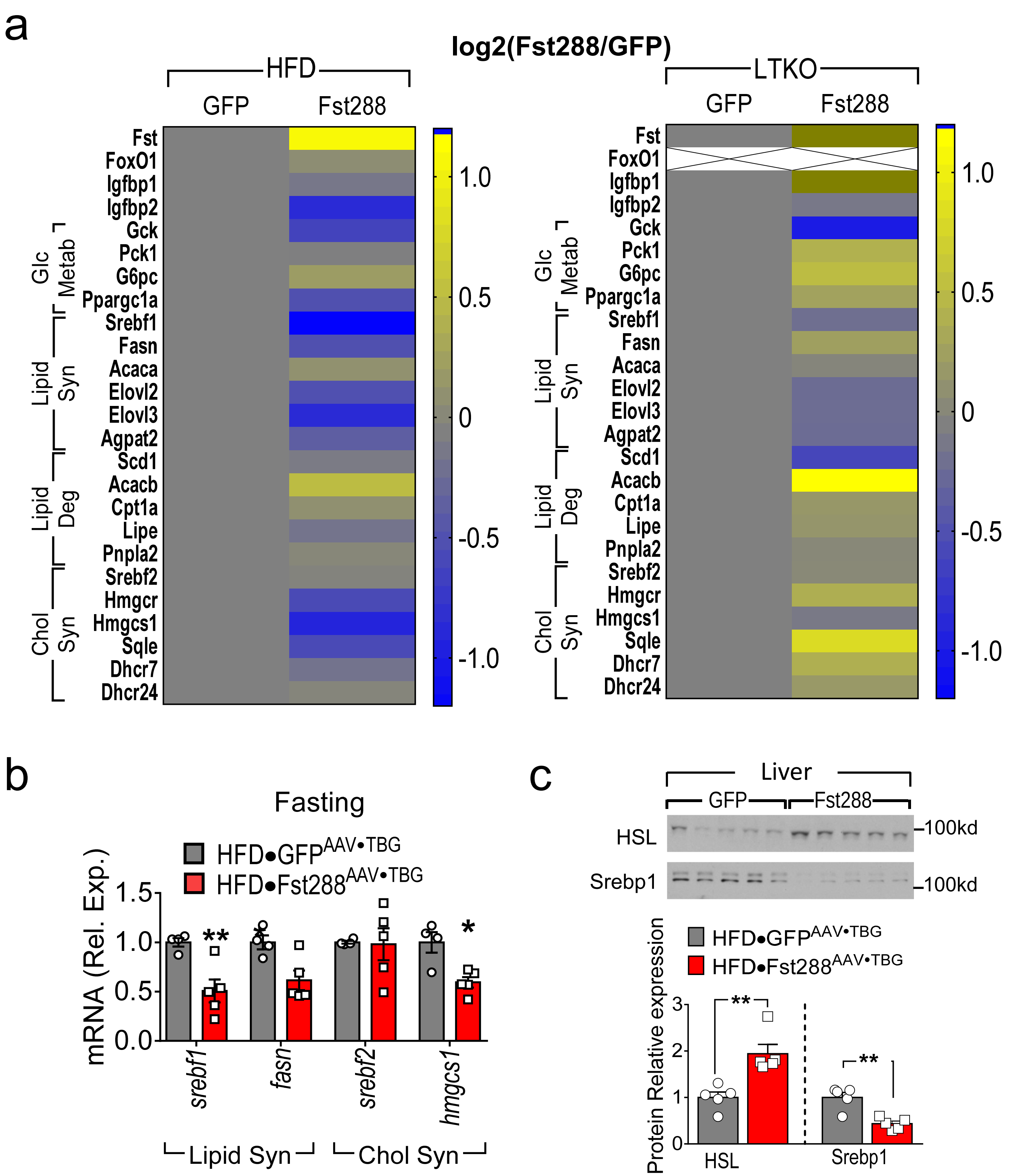
Supplemental Fig. 6. Related to Fig 4. Additional data on shFst$^{AAV•TBG}$-mediated knockdown of hepatic Fst in LDKO mice. (**a**,**b**) Hepatic Fst mRNA expression (**a**) (*n* = 4-6) and Fst protein content (**b**) (*n* = 5-6) two weeks after infection of five-month old LDKO mice with shFst$^{AAV•TBG}$ or null$^{AAV•TBG}$. (**c**) Serum total Fst concentration in the control and infected mice two weeks after infection (*n* = 5-6). (**d**) Glucose tolerance of the infected mice measured one week after infection and summarized by the areas under curves (*n* = 7-8). (**e**,**f**) Insulin-mediated regulation of Akt and HSL phosphorylation in eWAT was analyzed two weeks after infection by Western blotting (**e**) and quantitated by densitometry (**f**). Data were analyzed by one-way ANOVA (**a**, **b**, **c**, **d**) and unpaired Student's t-test (**f**). Data are reported as the mean±SEM. **P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001.

Supplemental Figure 7



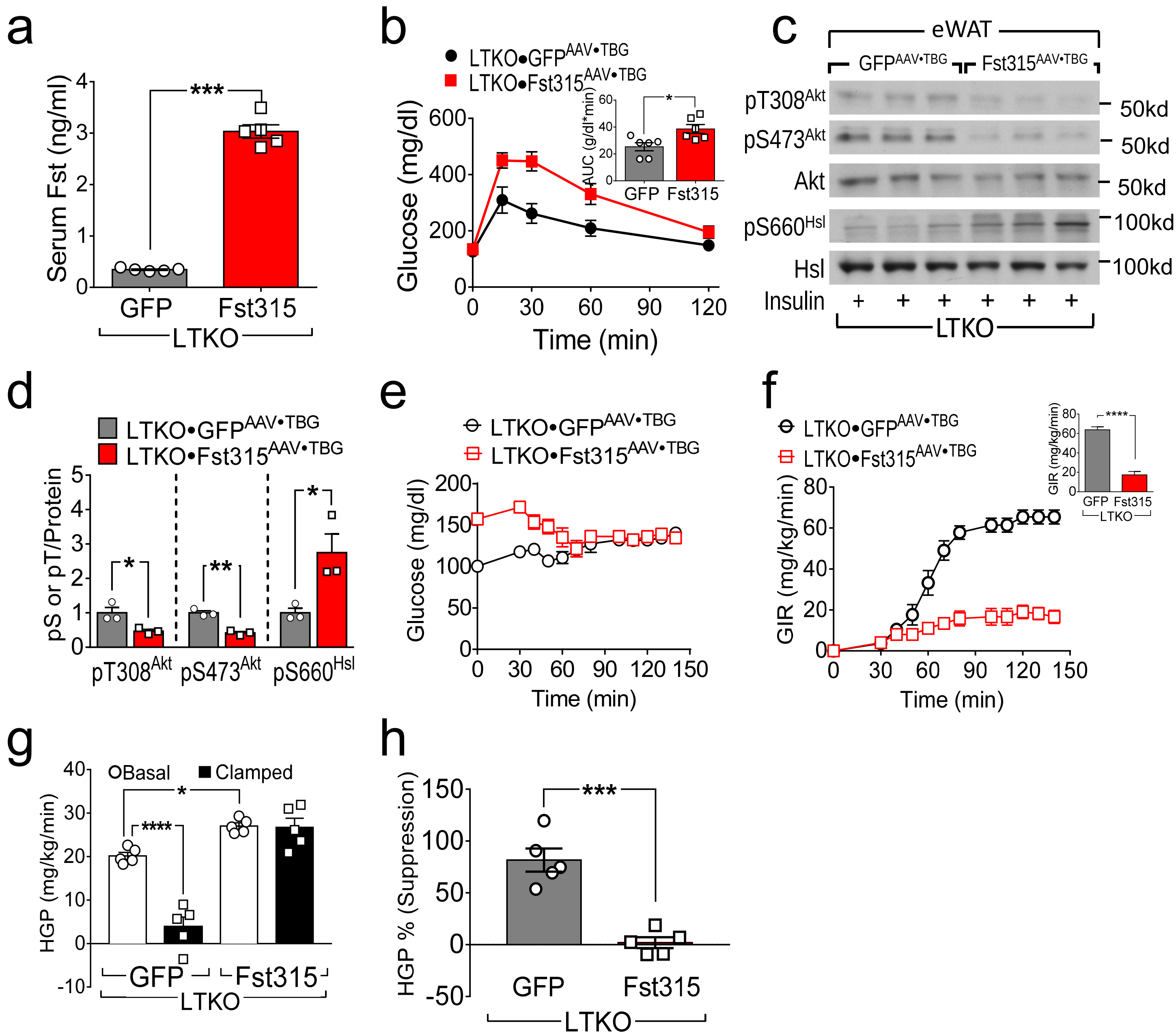
Supplemental Fig. 7. Related to Fig 5. Fst288 promotes WAT insulin resistance, hepatic glucose production, and glucose intolerance in C57BL6 mice. *Panels* ***a-l:*** C57BL6 mice challenged with high fat diet (45% fat) for 2 months were infected with Fst288$^{AAV•TBG}$ or GFP$^{AAV•TBG}$. (**a**,**b**) Hepatic Fst mRNA expression (**a**) and protein levels (**b**) were measured four weeks after infection (*n* = 5). (**c**) Serum total Fst concentration was measured one week after infection (*n* = 7). (**d**,**e**) Fasting (5 h) plasma insulin (**d**) and glucose concentrations (**e**) were measured two weeks after infection (*n* = 5). (**f**) Glucose tolerance of the infected mice was measured two weeks after infection and summarized by the areas under curves (*n* = 6-7). (**g**,**h**) Hyperinsulinemic-euglycemic clamps were conducted four weeks after infection and uptake of 2DOG ([1-^{14}C] 2-deoxy-D-glucose) tracer into (**g**) eWAT and (**h**) iWAT, was measured at the end of the clamp (*n* = 5). (**i** and **j**) Blood glucose concentrations (**i**) and glucose infusion rates (**j**) before and at steady state during hyperinsulinemic-euglycemic clamp (*n* = 5). (**k** and **l**) Basal and clamped hepatic glucose production (**k**) and calculated suppression of HGP by insulin during the clamp (**l**) (*n* = 5). Data were analyzed by unpaired Student's t-test (**a**, **b**, **c**, **d**, **e**, **f**, **g**, **h**, **l**), one-way ANOVA (**k**) and two-way ANOVA (**j**). Data are reported as the mean±SEM. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

Supplemental Figure.8



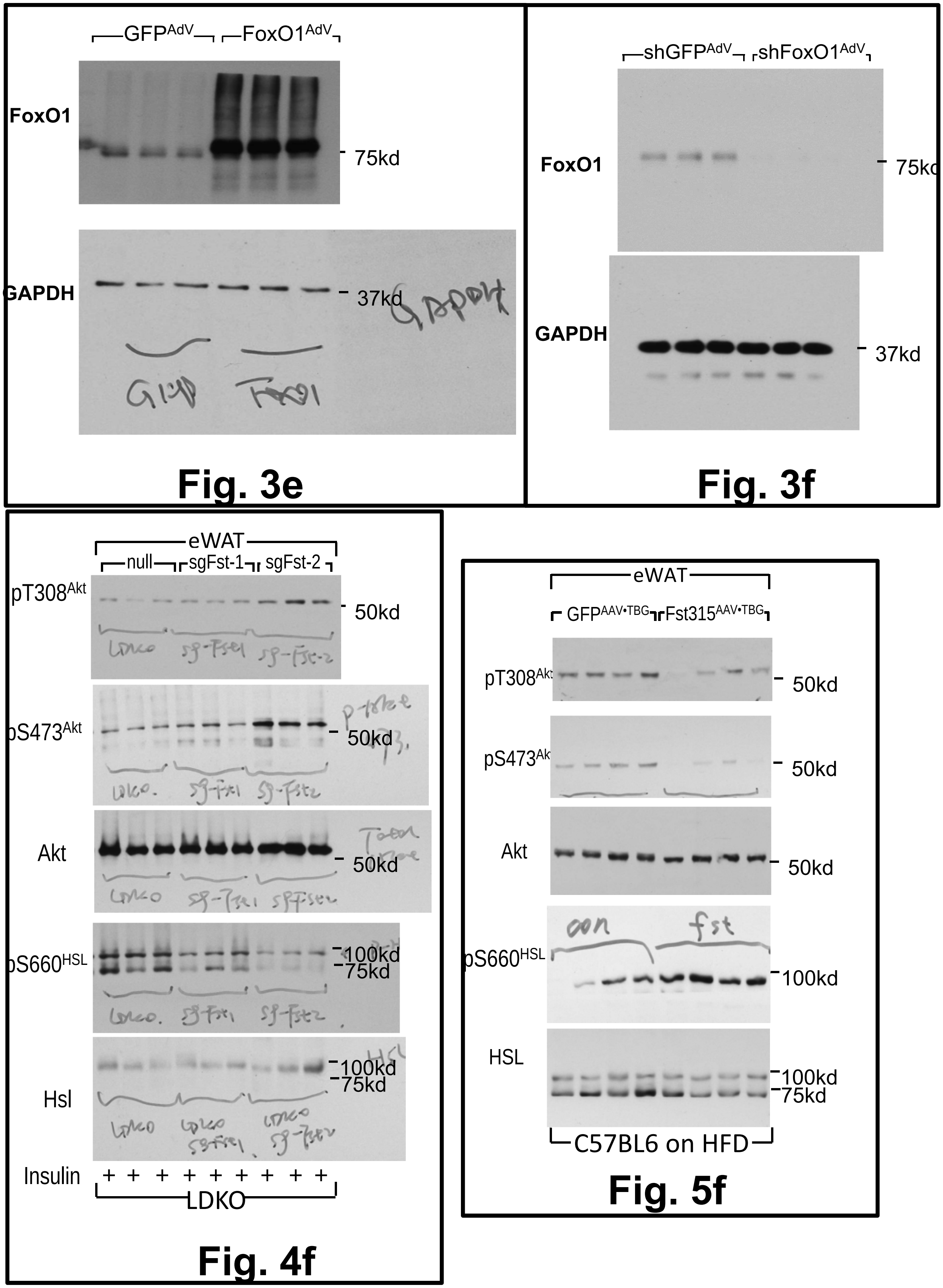
Supplemental Fig. 8. Related to Fig 6. (**a**) Expression of selected hepatic genes measured by Affymetrix array (Mo_Gene 2.0) on liver RNA from wild-type C57BL6 mice maintained on high fat diet for 2 months (n = 3) and from LTKO mice one week after infection with Fst288$^{AAV\cdot TBG}$ or GFP$^{AAV\cdot TBG}$ (n = 2). (**b**) C57BL6J mice maintained on high fat diet (45% fat) for 2 months were infected with Fst288$^{AAV\cdot TBG}$ or GFP$^{AAV\cdot TBG}$ and mRNA expression was measured one week later (after a 16h overnight fast) by qPCR on total liver RNA. (**c**) Western blotting and densitometric quantitation of Srebp1 (long form) and HSL protein expression in liver of the mice in '**b**' (For loading control see actinin blot, Fig. 6d). Data were analyzed by unpaired Student's t-test (**b**, **c**). Data are reported as the mean±SEM. *$P<0.05$; **$P<0.01$; ***$P<0.001$; ****$P<0.0001$.

Supplemental Figure 9



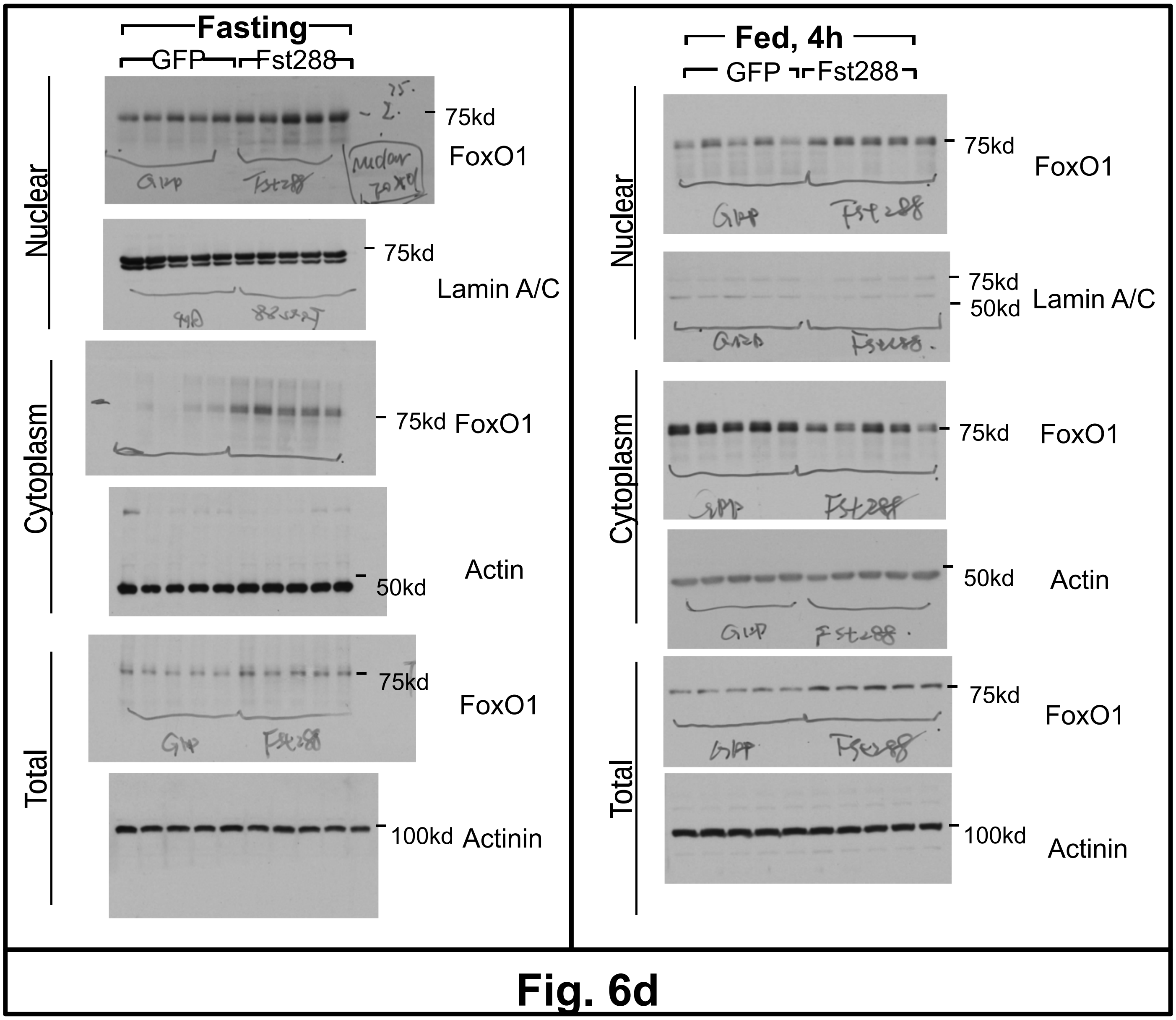
Supplemental Fig. 9. Related to Fig 6. Data from LTKO mice infected with Fst315$^{AAV•TBG}$ or GFP$^{AAV•TBG}$. (**a**) Serum Fst concentration was measured two weeks after infection of LTKO mice with Fst315$^{AAV•TBG}$ or GFP$^{AAV•TBG}$ (*n* = 5). (**b**) GTTs were performed two weeks after infection and summarized by the areas under curves (*n* = 6). (**c**,**d**) Western blot analysis (**c**) and densitometric quantitation (**d**) of insulin-stimulated signaling (1 U/kg, i.v.) in eWAT three weeks after infection (*n* = 3). *Panels **e-h**:* Hyperinsulinemic-euglycemic clamps were conducted four weeks after infection of LTKO mice with GFP$^{AAV•TBG}$ or Fst315$^{AAV•TBG}$. (**e**,**f**) Blood glucose concentrations (**e**) and glucose infusion rates (**f**) before and at steady state during hyperinsulinemic-euglycemic clamp (*n* = 5). (**g**,**h**) Basal and clamped hepatic glucose production (**g**) and calculated suppression of HGP by insulin during the clamp (**h**) (*n* = 5). Data were analyzed by unpaired Student's t-test (**a**, **b**, **d**, **f, h**) and one-way ANOVA (**g**). Data are reported as the mean±SEM. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

Supplemental Figure 10a



Supplemental Fig. 10a. Uncropped immunoblot pictures of main Figures.

Supplemental Figure 10b



Supplemental Fig. 10b. Uncropped immunoblot pictures of main Figures.

Supplemental Figure 11a

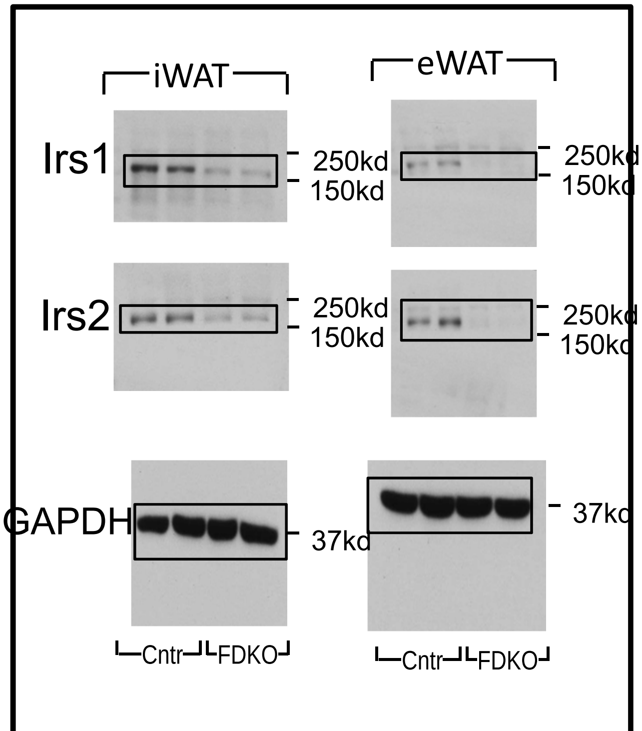


Fig. s1a

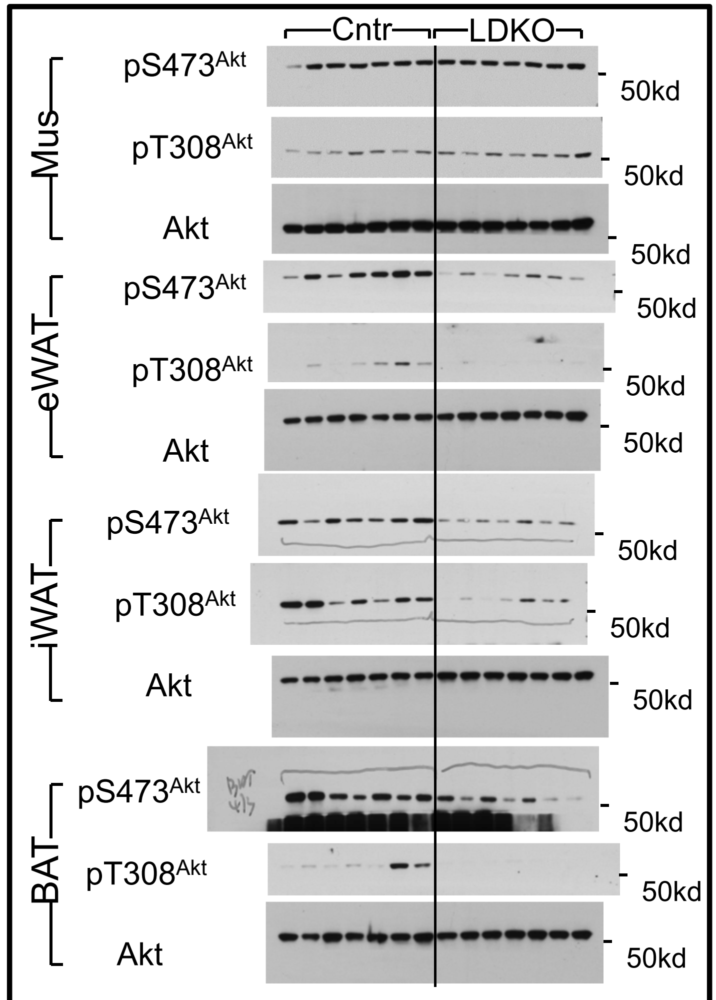


Fig. s1d

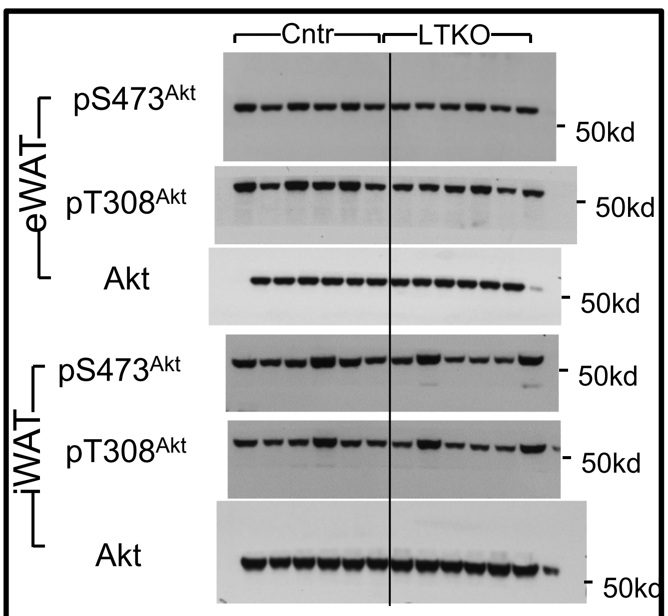


Fig. s1g

Supplemental Fig. 11a. Uncropped immunoblot pictures of supplementary Figures.

Supplemental Figure 11b

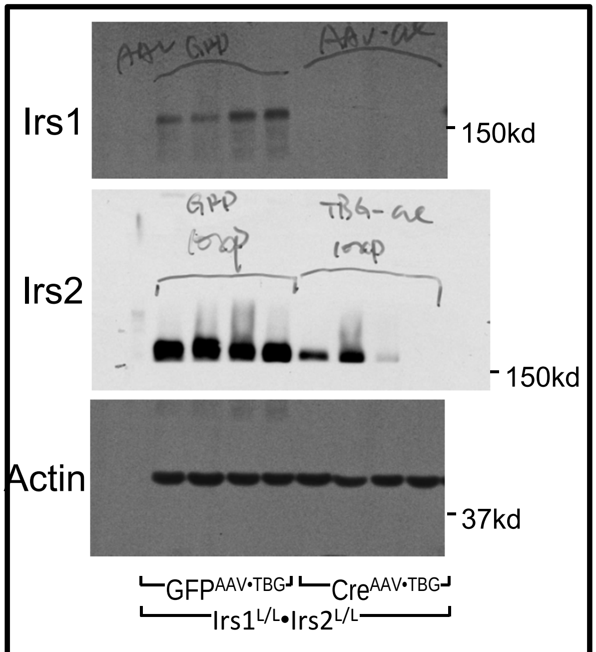


Fig. s2a

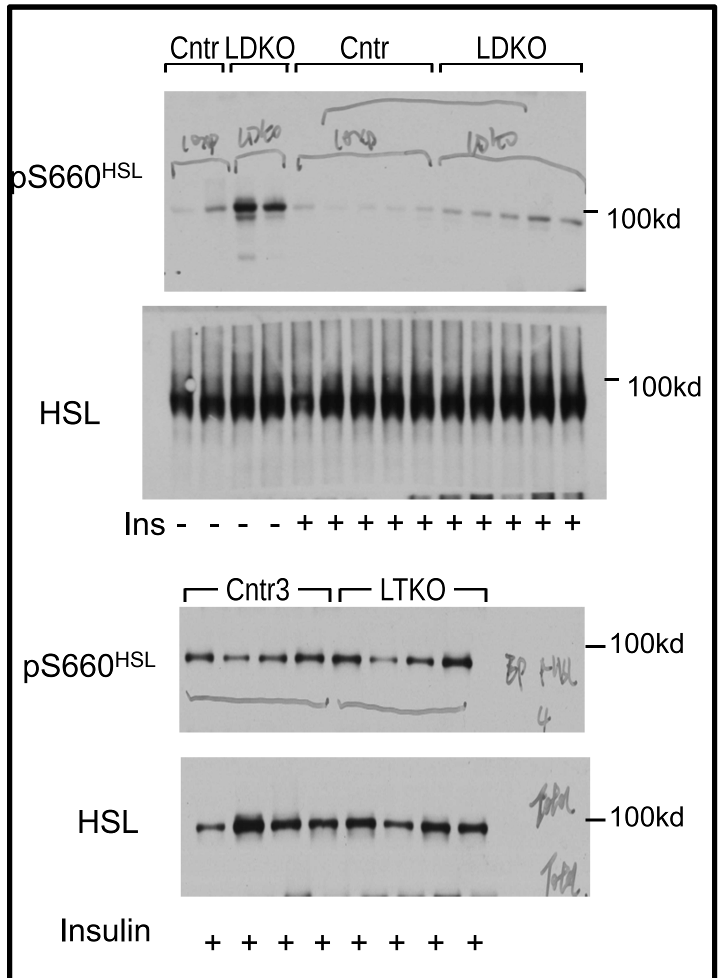


Fig. s2e

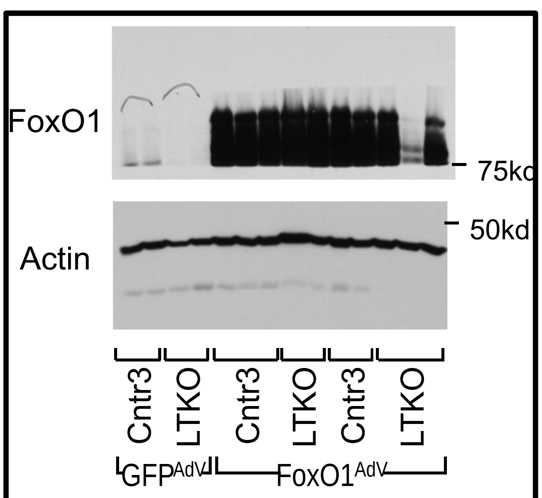


Fig. s2c

Supplemental Fig. 11b. Uncropped immunoblot pictures of supplementary Figures.

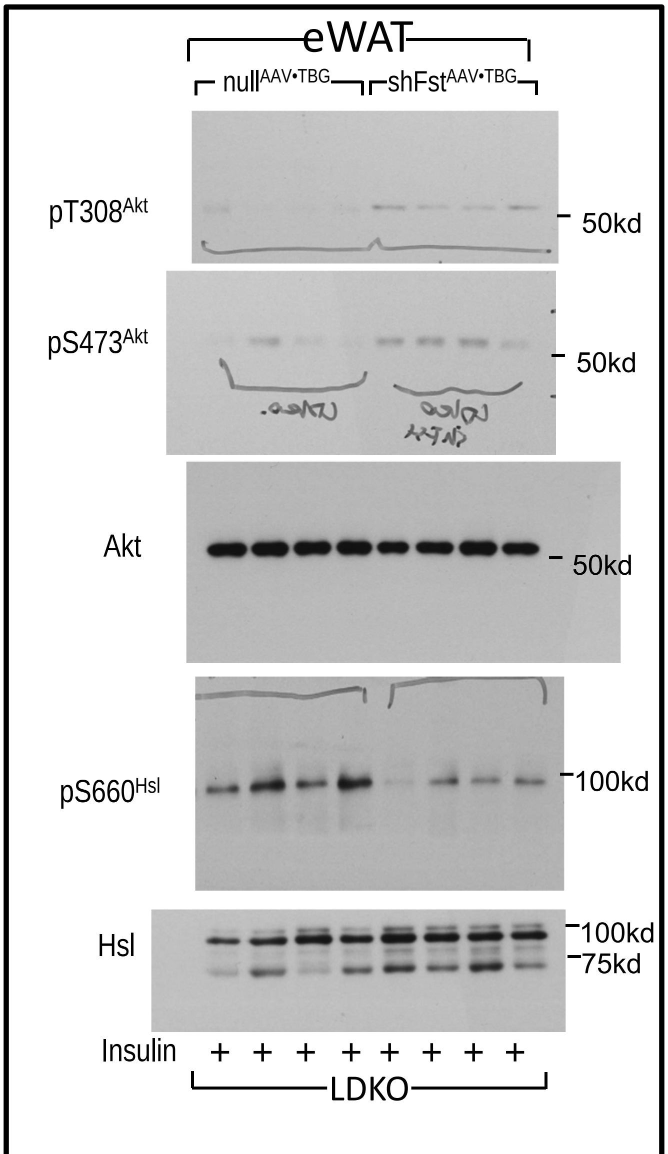


Fig. s6e

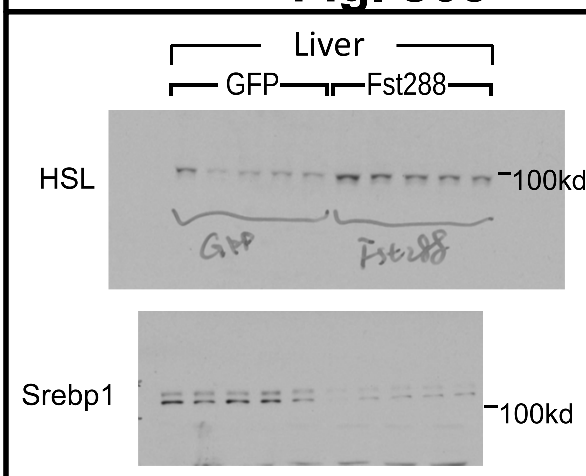


Fig. s8c

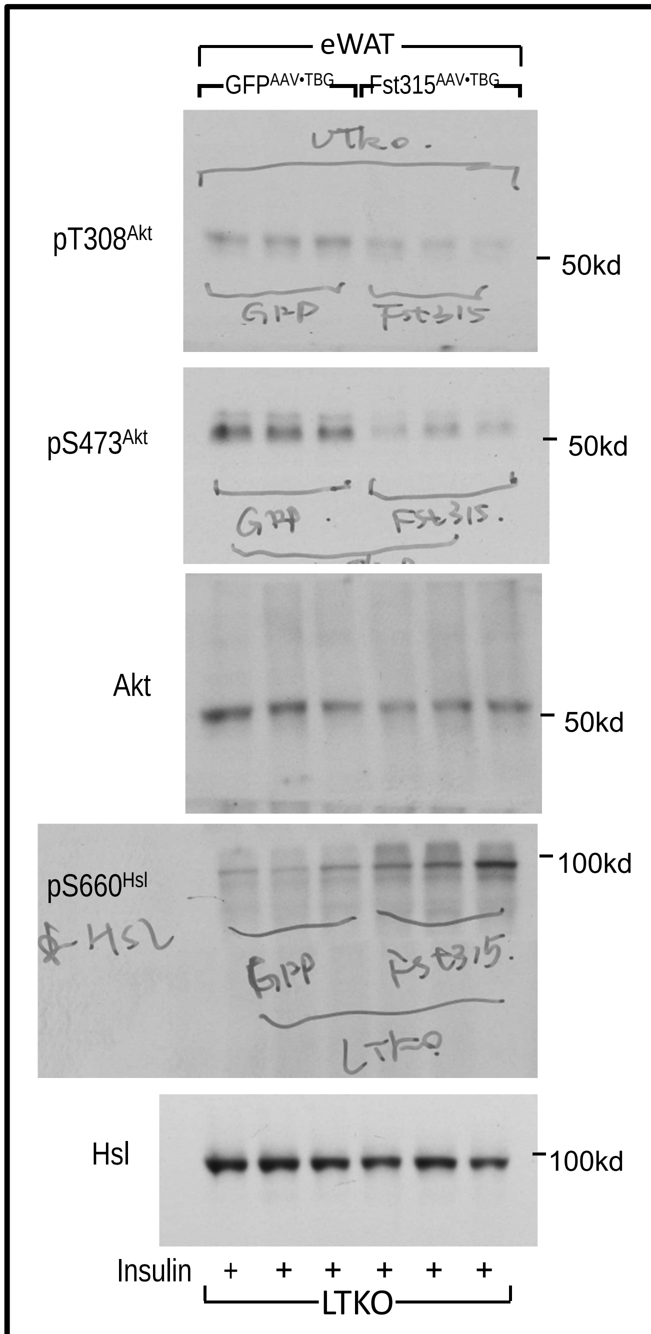
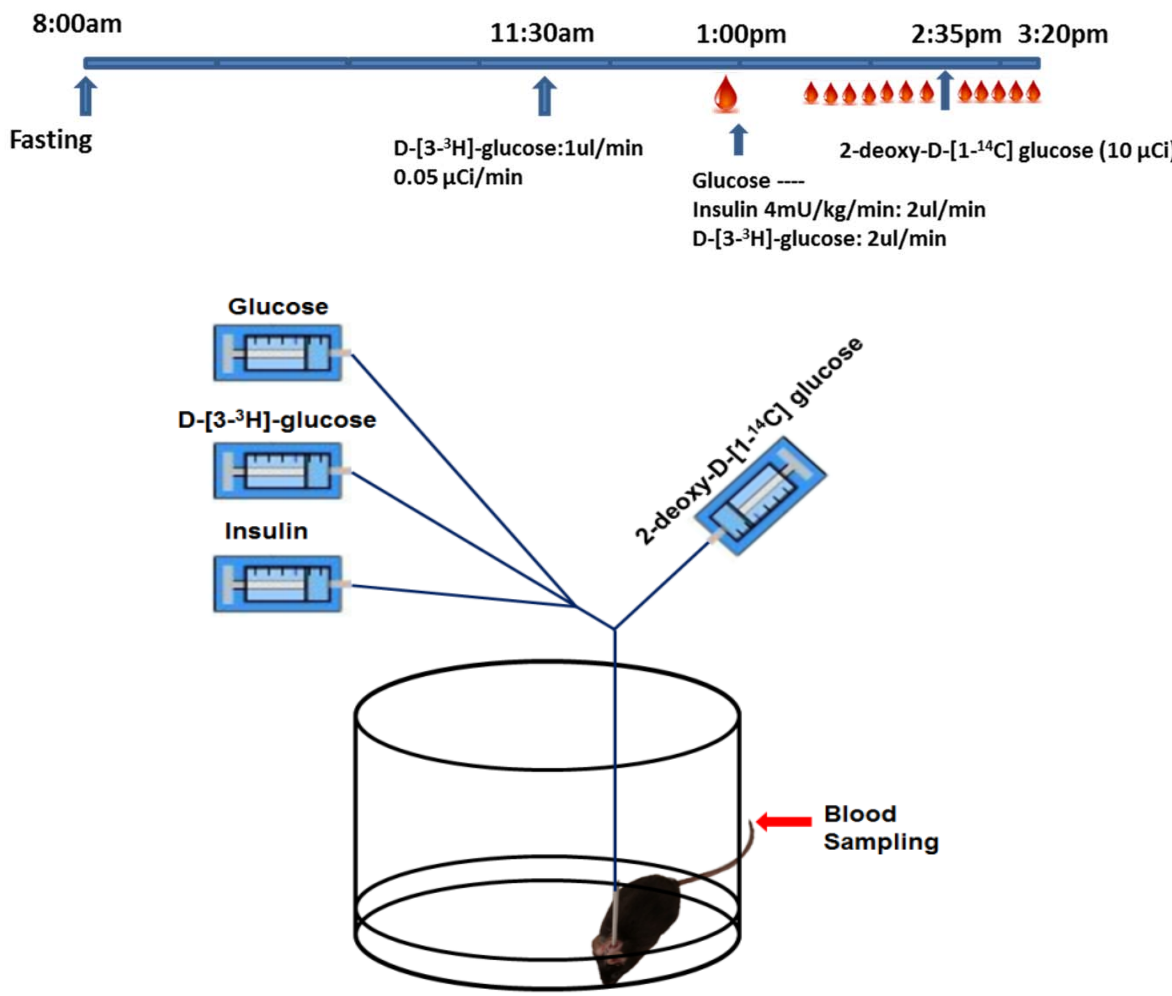


Fig. s9c

Supplemental Fig. 11c. Uncropped immunoblot pictures of supplementary Figures.

Supplemental Figure 12



Supplemental Fig. 12. Hyperinsulinemic euglycemic clamp in conscious and unrestrained mice.

Table S1. Genes down-regulated (n=83) or upregulated (n=82) more than 2-fold in eWAT of LDKO-mice relative to Cntr-mice, determined by Affymetrix whole-gene hybridization microarray. Related to Fig S1I.

Gene Symbol	LDKO/Cntr (log2)	LTKO/Cntr3 (log2)	Gene Symbol	LDKO/Cntr (log2)	LTKO/Cntr3 (log2)
Zim1	-3.750882	-1.060452	Agpat2	1.011359	-0.211748
Thbs2	-3.341744	-0.299111	Als2cr12	1.015465	-0.213349
Irf4	-2.665674	-0.020737	Me1	1.020324	0.04369
Myh4	-2.622508	8.7E-05	Gm6936	1.021918	0.363874
Vnn1	-2.612773	0.02966	Krt17	1.022862	0.007546
Sgcg	-2.508807	-0.391135	Slc2a4	1.032405	-0.448542
Gprin3	-2.334664	-0.021941	Fam158a	1.038836	-0.350579
Peg3	-2.281393	-0.15645	Igfals	1.03957	-0.190863
St6galnac5	-2.073522	-0.407297	Anxa2	1.044121	0.198786
Adap2	-1.997105	0.13894	Ndufb3	1.045308	-0.02219
Acsm3	-1.956618	-0.789405	Igkv5-43	1.065802	-0.020398
Cmklr1	-1.932594	0.351213	Isoc1	1.070155	0.028488
Fam134b	-1.889569	0.628968	Ces1f	1.083565	-0.521765
Mest	-1.871339	-0.30097	Prkcb	1.092713	-0.099269
Fmo3	-1.789893	0.087459	Gm5478	1.097924	0.0013
Sox7	-1.732821	-0.010626	Hacl1	1.101691	-0.117984
Serpine1	-1.685798	1.320124	Frmd3	1.106228	-0.19534
Cd209g	-1.679933	-0.984515	Orm1	1.112044	0.128644
Acta1	-1.524203	0.130079	Tmem48	1.112212	-0.053385
Zbtb38	-1.507172	0.349885	Paqr9	1.113859	0.217467
Zfp97	-1.501514	0.1367	Olfml1	1.122106	-0.251061
Ddit4	-1.479044	0.235045	Tmem45b	1.12837	0.037968
Nr4a3	-1.47829	-0.018749	Niacr1	1.129761	-0.321957
Cxx1c	-1.449717	-0.637689	Olfr735	1.139459	0.438534
Trp53inp1	-1.408767	-0.261547	Scd2	1.141974	0.710061
Sfrp5	-1.376056	0.331588	Rps13	1.142351	0.029374
Cd209b	-1.348736	-0.678531	Igh-VJ558	1.156482	0.119508
Ifi205	-1.33307	-0.083752	Arxes2	1.156819	-0.343099
Chst4	-1.325169	-0.629263	Echdc1	1.168727	0.095472
Gadd45g	-1.297371	-0.645331	Gadd45a	1.174995	-0.060268
Usp54	-1.292655	0.162856	Smyd1	1.181049	0.229666
Gm10851	-1.289769	0.322124	Lpgat1	1.194236	0.218342
Ttn	-1.28747	-0.050697	Pilrb2	1.19673	-0.049056
Scg3	-1.27993	0.289235	Gpd1	1.19771	-8E-05
Tnfrsf11b	-1.274319	0.361824	Mir708	1.208718	-0.469499
Hmgcs2	-1.269165	-0.294503	Psat1	1.216498	-0.404853
Scara5	-1.244959	-0.241542	Aldh3b2	1.221689	-0.283578

Gene Symbol	LDKO/Cntr (log2)	LTKO/Cntr3 (log2)	Gene Symbol	LDKO/Cntr (log2)	LTKO/Cntr3 (log2)
Gm765	-1.229286	-0.140589	Cdkn2c	1.222999	-0.280405
Upk3b	-1.215553	-0.18891	Igh-VJ558	1.22309	-0.993101
Pmepa1	-1.213588	0.063275	Ighg	1.226966	0.389438
Muc16	-1.185351	-0.178132	Insig1	1.23774	0.135081
Tat	-1.183446	1.38603	Tmem182	1.25233	-0.02209
Eif4ebp3	-1.180897	-0.444907	Aqp11	1.254241	0.418556
Hspb7	-1.180063	0.071223	Gm4871	1.263588	0.445477
Sult1d1	-1.178718	1.633916	Ranbp3l	1.2676	0.32603
Errfi1	-1.167395	0.164898	Rab9b	1.288028	-0.036487
Chchd10	-1.16603	-0.460054	Krt79	1.288732	0.398722
Folr2	-1.16338	-0.449826	Gm4981	1.28999	-0.256478
Cyp2d22	-1.155034	-0.1382	Zdhhc2	1.290149	-0.145371
Pnpla7	-1.14804	-0.088138	Thrsp	1.293625	-0.265227
Stoml3	-1.136987	1.670174	Slc25a35	1.295351	-0.270091
Sdc4	-1.133649	0.43363	Gys2	1.297301	-0.943828
Fbxo31	-1.13251	-0.174988	Tpi1	1.320515	0.130083
Thbs1	-1.128532	0.005496	Steap4	1.347646	-0.205538
Npc1	-1.123717	-0.454949	Hgf	1.359002	-0.473704
Acot4	-1.119273	0.000398	Bmp3	1.409767	-0.05818
Mirlet7f-1	-1.11543	-0.35102	Odz4	1.417978	-0.218266
Clmn	-1.112631	0.125017	Cidea	1.463163	-0.291937
Sema3e	-1.087111	0.082412	Angpt1	1.472583	-0.322284
Atp2a1	-1.083525	-0.373867	Fasn	1.475002	0.0772
Nova1	-1.080522	-0.211836	Adam12	1.515543	-0.127497
Mir32	-1.073457	0.05281	Ifi27l2a	1.527095	-0.211772
Snord37	-1.06746	0.038432	Cycs	1.593572	0.292203
Plcl2	-1.066159	0.13596	Fabp5	1.619399	-0.650746
Gpr133	-1.063816	-0.705936	Fgf13	1.697856	0.249057
Arrdc3	-1.061551	0.32479	Chi3l3	1.698056	-0.202853
Tle3	-1.061188	0.192375	Obfc2a	1.738146	-0.433351
Pcsk6	-1.060444	-0.190266	Gpt	1.738472	0.09216
Gfpt2	-1.060165	-0.435801	Col15a1	1.776894	-0.132135
Il6ra	-1.05944	-0.124717	Igkv15-103	1.834551	0.643843
Mir103-2	-1.058341	-0.246584	Lctl	1.871293	0.138932
Ifnz	-1.049604	0.430439	Pnpla3	1.920606	-0.38938
Gm11827	-1.035381	-0.083388	Ncam2	1.954447	0.406999
Adrb2	-1.034939	-0.111871	Arxes1	1.983407	-0.003941
Fcna	-1.02841	-0.668016	Lrrc39	2.01118	-0.132343
Slc7a8	-1.02199	-0.402419	Sycp3	2.042756	-0.391121
Cmah	-1.019949	-0.132184	Aldh1a7	2.058233	-0.174981

Gene Symbol	LDKO/Cntr (log2)	LTKO/Cntr3 (log2)	Gene Symbol	LDKO/Cntr (log2)	LTKO/Cntr3 (log2)
Ms4a4a	-1.009563	0.009008	Slc25a10	2.069263	-0.090003
Pla1a	-1.005094	-0.568851	Ear11	2.110067	0.716328
Cuzd1	-1.004164	0.898065	Serpina3b	2.192778	0.499345
Defb7	-1.002875	0.212596	Igh-VJ558	2.248472	0.282009
Apol9b	-1.000961	-1.690716	Gpr81	2.480955	-0.551443
			Cyp2f2	2.835013	1.073235

Table S2. Obese diabetic individuals' data. Related to Fig 4H-I.

Sex	Study Group	BMI BL	BMI 6 mo	%HbA1c BL	%HbA1c 6 mo	FBG BL	FBG 6 mo	Fst BL	Fst 6 mo
Male	Diabetic	37	32	9.7	8.0	162	122	2.32	1.33
Female	Diabetic	52	38	9.2	6.1	172	108	1.02	0.58
Female	Diabetic	43	27	8.5	5.4	128	89	1.47	0.75
Female	Diabetic	51	32	7.0	5.2	83	82	1.31	1.14
Male	Diabetic	27	32	9.8	7.4	182	174	1.31	1.20
Female	Diabetic	60	29	7.7	5.5	135	88	1.10	0.97
Female	Diabetic	40	30	9.5	6.6	198	134	4.31	1.14
Female	Diabetic	51	36	6.6	5.1	130	96	2.01	0.70
Female	Diabetic	47	34	7.2	5.1	217	123	1.10	0.43

BMI: Body Mass Index, weight in kilograms divided by the square of height in meters. BL: Baseline before the surgery. 6 mo: 6 months after surgery. HbA1c: hemoglobin A1c. FBG: fasting blood glucose (mg/dl). Fst: Serum follistatin level (ng/ml).

Table S3. Materials

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Phospho-Akt (Ser473)	Cell Signaling Technology	CST#4058
Phospho-Akt (Thr308)	Cell Signaling Technology	CST #4056
Akt	Cell Signaling Technology	CST #9272
Phospho-HSL (Ser660)	Cell Signaling Technology	CST #4126
HSL	Cell Signaling Technology	CST #4107
FoxO1	Cell Signaling Technology	CST #2880
β-Actin	Cell Signaling Technology	CST #4967
Phospho-Smad2 (Ser465/467)	Cell Signaling Technology	CST #3101
Smad2 (D43B4)	Cell Signaling Technology	CST #5339
GAPDH (D16H11)	Cell Signaling Technology	CST #5174
Lamin A/C	Cell Signaling Technology	CST #2032
Actinin	Santa Cruz Biotechnology	SC-15335
Irs1 mouse polyclonal	Produced in our laboratory	
Irs2 mouse polyclonal	Produced in our laboratory	
Srebp1	Abcam	#3259
Prolong Antifade Gold with DAPI	Life Technologies	#1652731
Fst primary antibodies for immunostaining	Abcam	#203131
Fst primary antibodies for cell culture	R&D Systems	#AF669 (Fig 5a)
Goat anti-rabbit secondary antibody	Molecular Probes	#A11012
Chemicals		
D-[3-3H]-glucose	PerkinElmer	NET331C005MC
Recombinant human insulin	Eli lilly	#HI-210
Bovine Serum Albumin (Fatty acid-free)	Sigma Aldrich	#A8806
2-deoxy-D-[1-14C] glucose	PerkinElmer	NEC495A001MC
Barium hydroxide solution	Sigma Aldrich	#B4059
Zinc sulfate solution	Sigma Aldrich	#Z2876
3-Isobutyl-1-methylxanthine	Sigma Aldrich	#I5879
Streptozocin	Sigma Aldrich	#S1030

Experimental Models: Organisms/Strains	SOURCE	IDENTIFIER
C57BL6 mice	The Jackson Laboratory	#000664
Ob/ob mice	**The Jackson Laboratory**	#000632
B6;FVB-Tg(Adipoq-cre)1Evdr/J	**The Jackson Laboratory**	#010803
Irs1-flox	Generated in our laboratory	
Irs2-flox	Generated in our laboratory	
FoxO1-flox	From Ronald DePinho's lab	
B6.129S2-Il6^{tm1Kopf}/J	The Jackson Laboratory	#002650
Experimental Models: Cell Lines		
3T3-L1 adipocyte	Evan Rosen's lab	
HEK293	ATCC	CRL-1573
Recombinant DNA		
pShuttle-IRES-hrGFP-2 vector	Agilent	#240082
pAdEasy vector	Agilent	#240005
pENTR/U6 vector	Life Technologies	#45-0511
pAd/BLOCK-iT vectors	Life Technologies	#V49220
Paav2 backbone LSP with promega intron vector	Dr. Umut Ozcan's lab	
AAV8.TBG.PI.eGFP (AAV-GFP)	Penn Vector Core	#cs0397dl
AAV8.TBG.PI.Cre (AAV-Cre)	Penn Vector Core	#cs0725-dl
pX602-AAV-TBG::NLS-SaCas9-NLS-HA-OLLAS-bGHpA;U6::BsaI-sgRNA	Addgene	#61593
Software		
Alpha Innotech FluorChem 5500		
GraphPad Prism 7		