Supplementary Figure 1

Glucose tolerance test (GTT) in chow **(A)** and WTD **(B)** fed *Ldlr-/-* and *L1^{B6}Ldlr-/-* mice. Blood samples were obtained at 0, 15, 30, 60, 90 and 120 minutes after i.p. injection of 2 g/kg body weight dextrose after 16hr fasting. Blood glucose values were determined using a Accu-Chek glucose monitor (Roche). (n=6-7, *p <0.05, ** p < 0.01). **(C)** Western analysis of InsR, pAKT, AKT, pGSK-3β, α Tubulin from chow fed *Ldlr-/-* and *L1^{B6}Ldlr-/-* mice. The lower panel is western analysis of SR-B1, MTP and α Tubulin from WTD fed *Ldlr-/-* and *L1^{B6}Ldlr-/-* mice. **(D)** VLDL cholesterol production in *Ldlr-/-* and *L1^{B6}Ldlr-/-* mice from Triton experiment in Figure 2(D). LPL activity **(E)** and LCAT **(F)** activity from chow and WTD fed *Ldlr-/-* and *L1^{B6}Ldlr-/-* mice (n=5). Plasma was collected after 5hr fasting. Plasma LDL and LCAT activity were determined using RB-LPL2 and RB-LCAT plasma assay kit (Roar Biomedical) according to manufacturer's instruction, respectively.

Supplementary Figure 2

Plasma lipoprotein lipid, apoB, VLDL production levels in chow fed mice injected with myrAKT or control empty adenovirus. **(A)** Plasma lipoprotein triglyceride and cholesterol levels in *Ldlr-/-* and *L1^{B6}Ldlr-/-* mice (10-11 weeks old, n=3) injected with either control empty (white bars) or myrAKT (black bars) adenovirus. Plasma was collected after 5hr fasting and VLDL and LDL were separated by ultracentrifugation. Statistics are performed with respect to the control adenovirus (*p <0.05, ** p < 0.01). **(B**) ApoB amount in VLDL and LDL in

mice injected with either empty or myrAKT adenovirus. ApoB-containing lipoproteins from (A) were resolved by SDS-PAGE and stained with Coomassie Blue. Representative results are shown. The lanes were run on the same gel but were noncontiguous. ApoB was quantified and normalized to the amount present in the mice injected with control adenovirus (*p<0.05, **<0.01). The lowest panel is western analysis for hepatic AKT expression. **(C)** ApoB amount in VLDL and LDL in *Ldlr-/-* mice injected with empty adenovirus or different dosages (x 10^7 PFU/g body weight) of myrAKT. The *Ldlr-/-* mice were 10-11 weeks old and fed on chow before viral injection. The lowest panel is western analysis for AKT expression. All data are representative of at least 3 independent experiments. **(D)** Triglyceride (Tg) and apolipoprotein B production in chow fed *Ldlr-/-* mice injected with empty or myrAKT adenovirus. Tg production was determined by measuring plasma Tg concentration at indicated times after Triton (WR1339) injection. The inset shows apoB levels at 2 hrs after Triton injection. VLDL Tg **(E)** and VLDL cholesterol **(F)** secretion were measured from the experiment (D). (n=3-4, *p < 0.05).

Supplementary Figure 3

Nuclear SREBP-1c protein expression. Western analysis of hepatic nuclear SREBP-1c and Lamin A expression in myrAKT **(A)** and dominant negative GSK-KM **(B)** injected *Ldlr-/-* mice. 10-11 weeks old chow fed *Ldlr-/-* mice were injected with either empty or myrAKT **(A)** or GSK-KM **(B)** adenovirus. **(C)** Western analysis of hepatic nuclear SREBP-1c and Lamin A expression in from

WTD fed ob/ob mice after injection with control empty or constitutively active GSK-S9A adenovirus. Four days after viral injection liver was collected after 5hr fasting.

Supplementary Figure 4

ApoB amount in VLDL and LDL in ob/ob mice injected with either scrambled control or InsR shRNA adenovirus. Plasma was collected after 5h fasting from *ob/ob* mice 10 days after shRNA virus injection. VLDL and LDL were separated by ultracentrifugation and apoB-containing lipoproteins were resolved by SDS-PAGE and stained with Coomassie Blue.

Supplementary Table 1. Phenotypic characterization of InsR knock-down in *Ldlr-/-* mice.

Ldlr-/- mice	Scrambled shRNA	InsR shRNA
Body weight, g	24.3 ± 0.4	25.5 ± 1.1
Glucose, mg/dl	98.2 ± 8.8	89.4 ± 4.2
Cholesterol, mg/dl	696.2 ± 72.2	573.4 ± 16.3
Non HDL Chol, mg/dl	639.4 ± 68.1	503.4 ± 11.4
HDL Cholesterol, mg/dl	56.8 ± 4.6	70.0 ± 5.8
Triglycerides, mg/dl	237.8 ± 42.3	123.6 ± 12.0*
Hepatic Tg (ug/mg liver)	9.7 ± 0.6	5.4 ± 0.4**
Hepatic Chol (ug/mg liver)	4.7 ± 0.08	5.1 ± 0.34
Relative Hepatic MTP mRNA	0.6 ± 0.08	0.5 ± 0.06
Relative Hepatic apoB mRNA	0.8 ± 0.09	0.9 ± 0.2

10-11 weeks old WTD fed *Ldlr-/-* mice were treated with scrambled shRNA or InsR shRNA adenovirus. 10 days after the treatment plasma and livers were collected from mice after 5 hr fasting (n=4, *<0.05, **<0.01)

Supplementary Table 2. Phenotypic characterization of InsR knock-down in *ob/ob* mice.

ob/ob mice	Scrambled shRNA	InsR shRNA
Body weight, g	51.8 ± 0.9	50.5 ± 1.7
Glucose, mg/dl	133.5 ± 24.0	117.0 ± 24.1
Cholesterol, mg/dl	164.3 ± 4.9	203.7 ± 21.5*
Non HDL Chol, mg/dl	71.1 ± 9.0	132 ± 27.1*
HDL Cholesterol, mg/dl	92.0 ± 4.9	76.6 ± 1.8
Triglycerides, mg/dl	88.3 ± 8.2	90.7 ± 11.0
Hepatic Tg (ug/mg liver)	50.4 ± 7.2	26.8 ± 3.6*
Hepatic Chol (ug/mg liver)	5.5 ± 0.2	5.6 ± 0.5
Relative Hepatic MTP mRNA	1.4 ± 0.2	1.2 ± 0.1
Relative Hepatic apoB mRNA	1.6 ± 0.3	1.7 ± 0.3

10-11 weeks old ob/ob mice were treated with scrambled shRNA or InsR shRNA adenovirus. 10 days after the treatment plasma and livers were collected from mice after 5 hr fasting (n=4-5, *<0.05)

Supplementary Table 3. Probe and primer sequences used for mRNA quantification by real-time PCR

mRNA	Type	Sequence 5' to 3'
SREBP1c	Forward	GGAGCCATGGATTGCACATT
	Reverse	CCTGTCTCACCCCCAGCATA
	Probe	CAGCTCATCAACAACCAAGACAGTGACTTCC
FAS	Forward	GGCATCATTGGGCACTCCTT
	Reverse	GCTGCAAGCACAGCCTCTCT
	Probe	CCATCTGCATAGCCACAGGCAAC
36B4	Forward	AGATGCAGCAGATCCGCAT
	Reverse	GTTCTTGCCCATCAGCACC
	Probe	CGCTCCGAGGGAAGGCCG
ACC	Forward	TTATCTCTGGAGAACCTCTCTAATGG
	Reverse	AGACACTTAGCAAGAGCAAAAATGA
SCD1	Forward	CTGCAGGTTGTGCTAGATGGGATGG
	Reverse	GCCTGGGGTCTTTGGTAAGTAGGC
Acox1	Forward	GTGCAGCTCAGAGTCTGTCCAA
	Reverse	TACTGCTGCGTCTGAAAATCCA
SREBP2	Forward	GTGCGTCTATCAAGTCCAGAATG
	Reverse	GAGACTGTCTCCTTTCTGCCTCT
HMG-CoA Syn	Forward	CAGCCATTTGTTACAGCTTATTCTC
	Reverse	TCTTTTTAATTGCCACATATTATTTTAGAA
HMG-CoA Red	Forward	CTTTCAGAAACGAACTGTAGCTCAC
	Reverse	CTAGTGGAAGATGAATGGACATGAT
IGFBP1	Forward	AGATCGCCGACCTCAAGAAAT
	Reverse	CTCCAGAGACCCAGGATTTT
PEPCK	Forward	CCACAGCTGCTGCAGAACA
	Reverse	AAAGACTTCTTGTGTGTCTGTC
UCP2	Forward	From SupperArray (Cat No. PPM03034A)
	Reverse	From SupperArray (Cat No. PPM03034A)
MTP	Forward	From supperarray (Cat No. PPM24881A)
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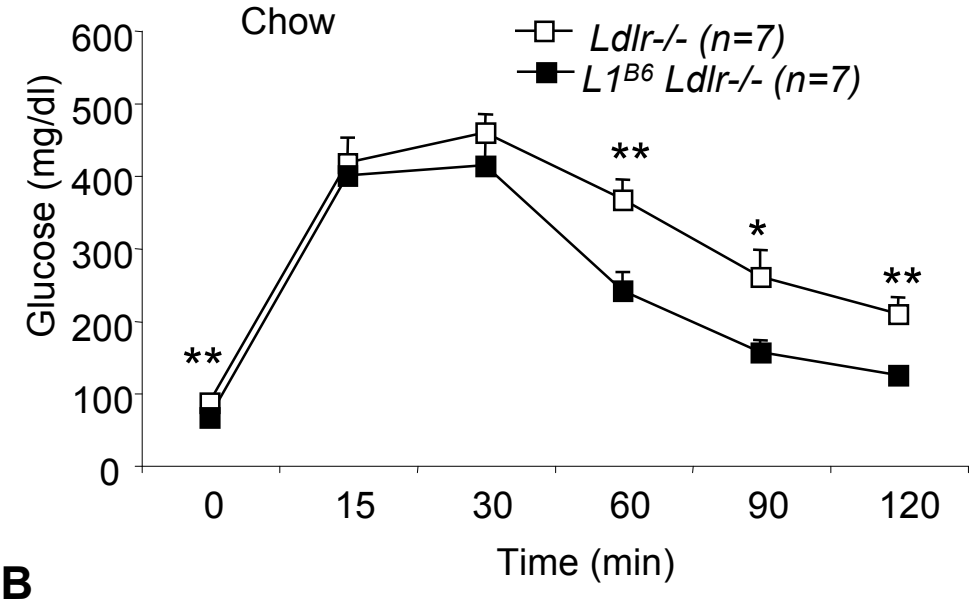
Intraperitoneal GTT

A



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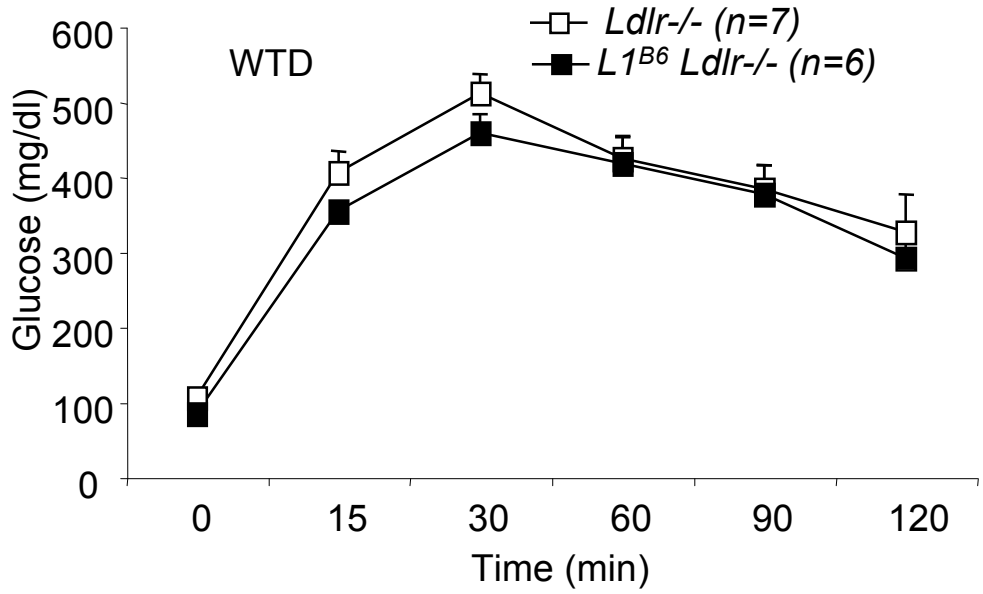
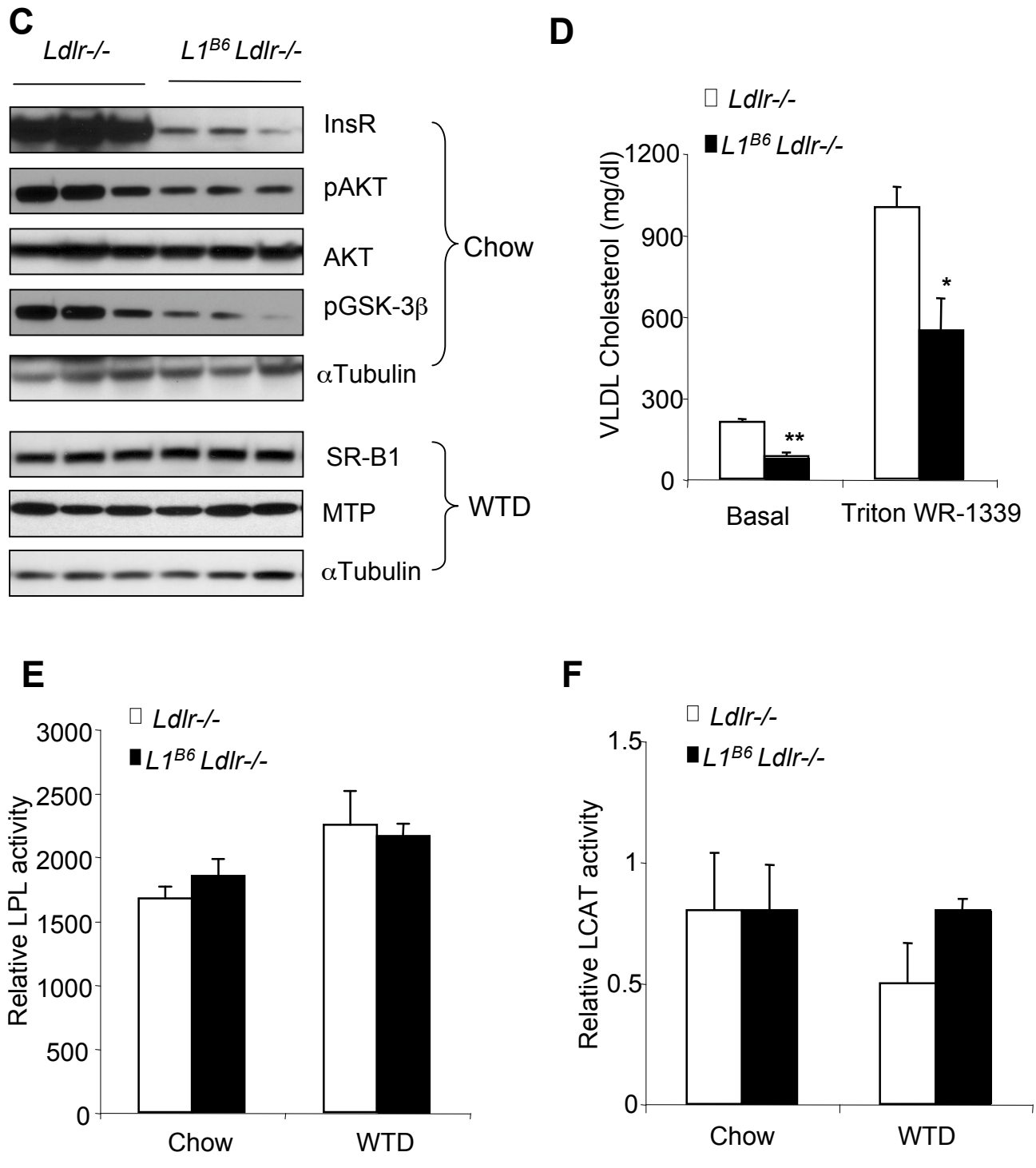


Supplementary figure 1



Supplementary figure 1 (continued)

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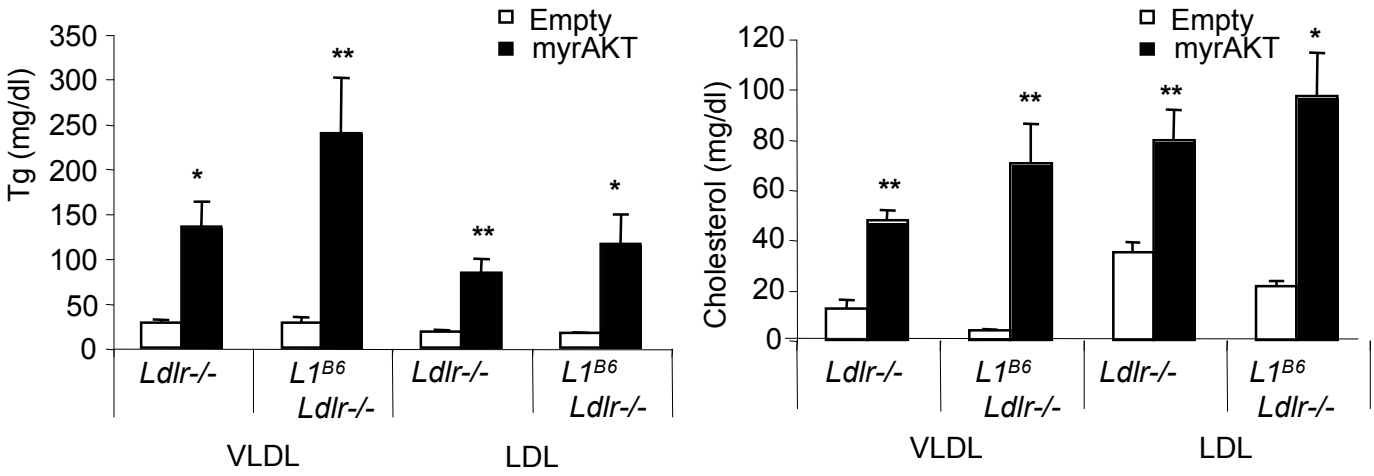

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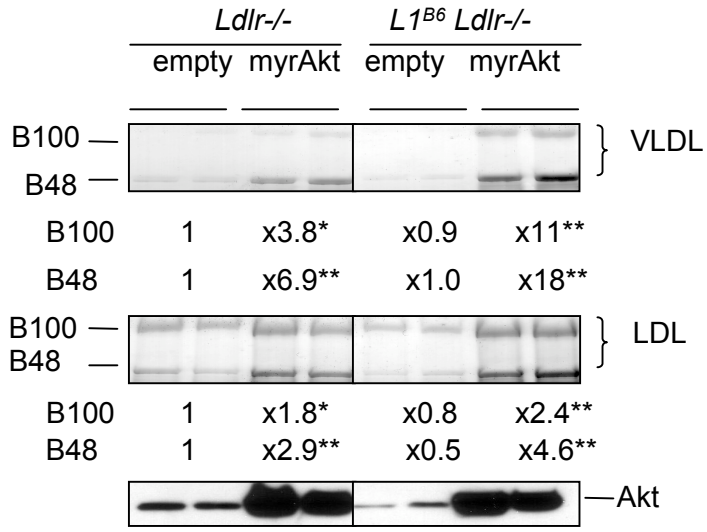

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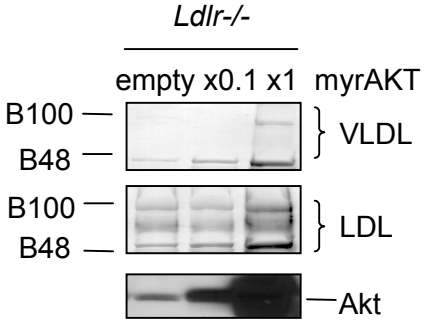
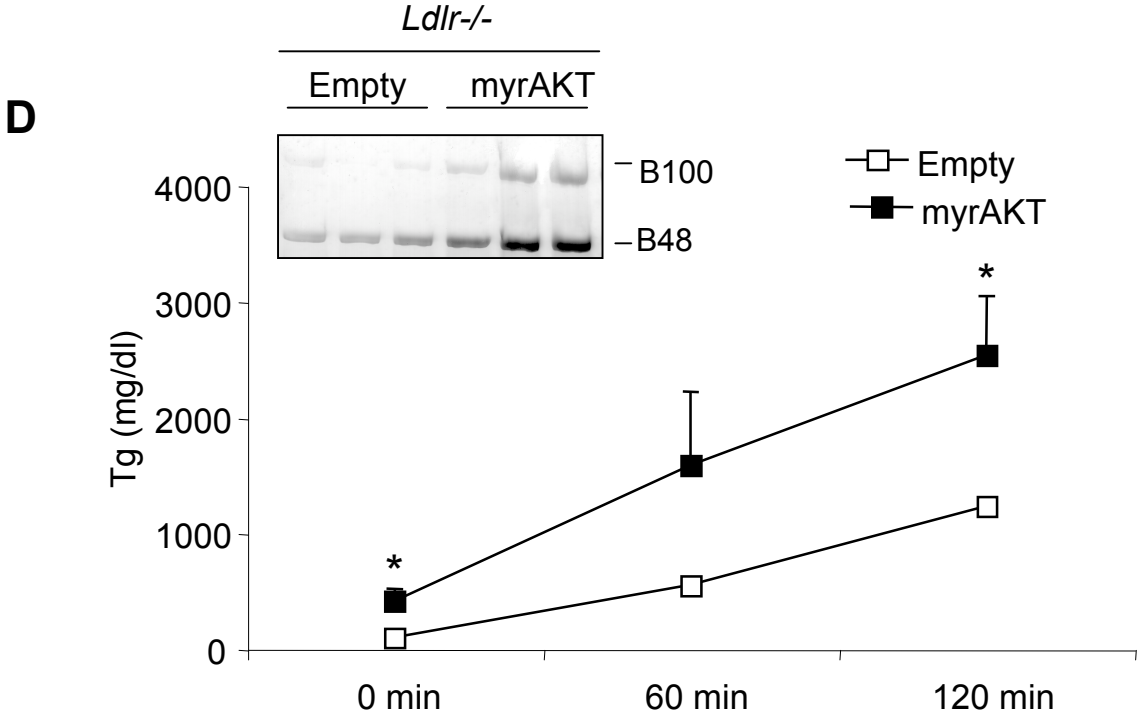
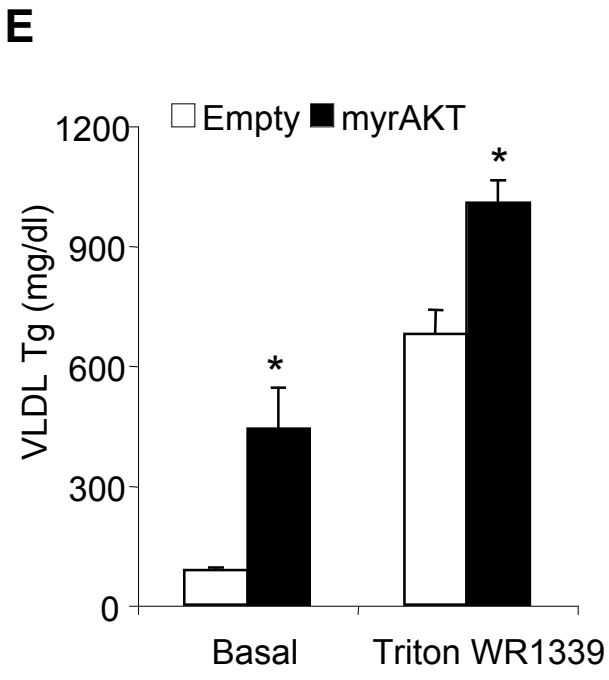
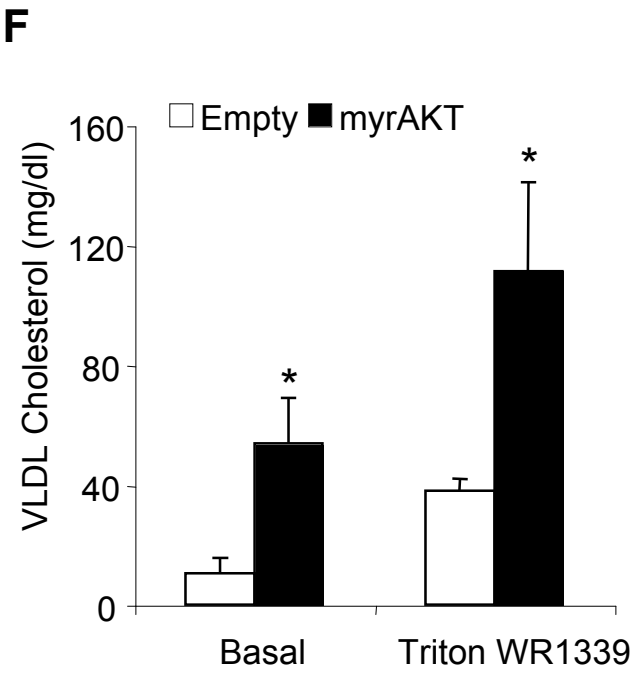


Supplementary figure 2







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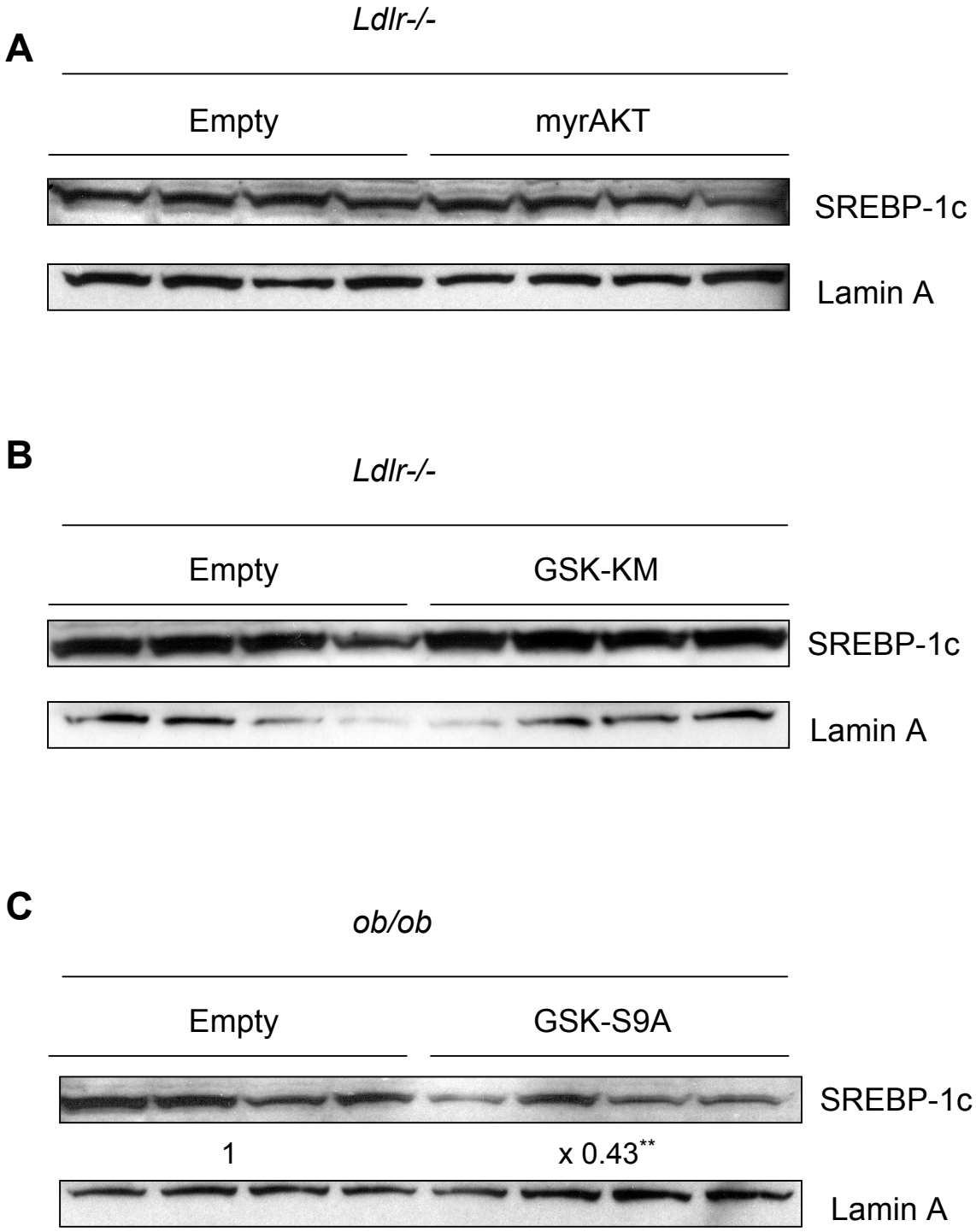

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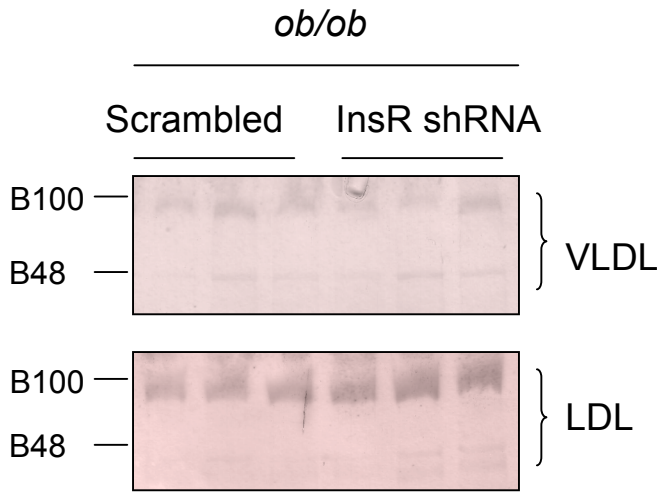

Supplementary figure 4