Supplemental Figure Legends.

Figure S1. Identification of *MeXis* as an LXR target gene. **A**. Real-time PCR analysis of gene expression in mouse primary cell lines treated with GW3965 (GW, 0.5 μM). N=3 per group. Values are means ± SD. **B.** RNA-seq results for protein-coding genes in primary macrophages treated for 16 h with GW3965 (GW, 0.25 μM). Each dot is a single gene. Red dots, for both coding and non-coding genes, highlight genes that are expressed (FPKM>=1) and were at least two-fold unregulated after treatment. A single sample per group pooled from 3 different experiments sequenced. **C.** Network of ontology terms for GW3965-induced protein-coding genes in macrophages. Nodes with the same color are specific ontologies in the same GO generic class as labeled. Node size is proportional to statistical significance (hypergeometric p-value). Edge thickness is proportional to between-node similarity (computed using Kappa statistics, and reflects the overlap between the gene sets annotated in both ontology terms). **D.** RNA-seq results for noncoding RNAs in primary macrophages from experiments in A. Each dot is a single gene. Red dots, for both coding and non-coding genes, highlight genes that are expressed (FPKM>=1) and were at least two-fold unregulated after treatment. Neighboring protein-coding gene are shown in brackets for select genes. A single sample per group pooled from 3 different experiments sequenced.

Figure S2. Schematic of the *MeXis* gene locus and its RNA transcripts. UCSC genome browser view of RNA-seq transcriptional signatures at the *MeXis* locus in mouse primary peritoneal macrophages treated with GW3965 (GW, 0.25 μM). Structure of transcripts identified by RACE, aligned for comparison to existing annotation in the indicated databases.

Figure S3. Regulation of *MeXis* by LXR in macrophages. A. RNA copy number analysis of MeXis from primary macrophages (n= 8 samples). Values are mean ± SD. **B.** Gene expression from primary macrophages treated with endogenous ligand 22(R)-hydroxycholesterol (22R, 2.5 μM), or 25-hydroxycholesterol (25OH, 2.5 μM). (n= 3 samples per group). Values are mean ± SD. * $P < 0.05$, **** $P < 0.0001$ using one-way ANOVA followed by multiple comparisons test (Dunnett's). **C.** Gene expression from WAT isolated from WT mice treated with vehicle or GW3965 (40 mg/kg) by gavage for 3 days (n=5 samples per group). Values are mean ± SEM. **D.** Real-time PCR analysis of gene expression in primary mouse macrophages treated with GW3965 (GW, 0.5 μM). N=4 per group. Experiment repeated once with similar results. Values are means ± SEM. **E.** Gene expression analysis of iBMDM treated with GW3965 (GW, 0.5 μM). N= 4 samples per group from two independent experiments. All Values are means ± SD. ** $P < 0.01$ using two sample two-tailed student's t-test.

Figure S4. *MeXis* is a predominantly nuclear RNA. A. In vitro transcription/translation of *MeXis* (Mex), luciferase (luc), no plasmid (NP). Experiment was performed once. **B.** RNA FISH in mouse macrophages (MeXis green & DAPI blue). Representative image from three experiments. Scale bars, 25 μm. **C.** Primary mouse macrophages were treated with GW (1 μM GW3965). 24 h later cellular contents were separated. Transcripts in each fraction were analyzed by real-time PCR. N=4 samples/group. Values are means ± SD. **D.** Cellular fractionation from RAW-MeXis stable cell line. Transcripts in each fraction were analyzed by real-time PCR. N=4 samples/group. Values are means ± SD. **E.** Gene expression from primary mouse macrophages treated ASO (50 nM) for 24 h followed by GW (1 μM GW3965) (N=4 samples/group). Values are means ± SD. **F-G.**

No acceptor control for efflux experiments from Figures 2c and 2f. Experiments were conducted in triplicate. Values are means ± SD. **H.** Florescence signal in primary macrophages treated with acetylated Di-LDL for 4 h. Experiments were conducted in triplicate. Values are means ± SD. **I.** Quantification of foam cells from experiments in 2 h expressed as percent of cells showing any oil red staining. Results from 3 different fields per group. Mean ± SD. *** $P < 0.001$ using two sample two-tailed student's t-test.

Figure S5. **Generation of global *MeXis*$^{-/-}$ mice**. **A.** Schematic of knockout strategy. Vector construct designed to ablate entire *MeXis* transcript. Targeted mice were crossed with *Flp* mice to excise the Neo cassette since it contains an active bi-directional promoter. PCR genotyping strategy for *MeXis*. Representative blots from over 10 experiments. **B.** Real-time PCR analysis of gene expression 10 days after stable overexpression of *MeXis* in RAW cells treated with GW3965 (GW, 0.5 μM). Results are representative of three independent experiments. Values are means ± SD. **C.** Real-time PCR analysis of gene expression from primary macrophages treated with siRNA (50 nM) followed by GW3965 (GW, 0.5 μM) and the RXR ligand LG268 (LG, 50 nM) and harvested 36 h later. Results are representative of four independent experiments. Values are means ± SD. **** $P<0.0001$ by Two-way ANOVA followed by multiple comparisons test (Sidak's). **D.** Real-time PCR analysis of gene expression in primary mouse macrophages. Results are representative of four independent experiments. Values are means ± SD.

Figure S6. **Metabolic profile of *MeXis*$^{-/-}$ mice.** Total serum cholesterol and triglyceride levels in WT or *MeXis*$^{-/-}$ littermates maintained on western diet for 3 weeks. Lipids were measured using Wako kits. WT-M is WT male (n=5 animals). KO-M is *MeXis*$^{-/-}$ male (n=5 animals). WT-F is WT female (n=4 animals). KO-F is *MeXis*$^{-/-}$ female (n=4 animals). All values are means ± SEM.

Figure S7. Engraftment of WT or *MeXis*$^{-/-}$ bone marrow. A. Confirmation of engraftment by gene expression analysis of experiment in Figure 3A. Representative of 2 samples in WT and 4 samples in *MeXis*$^{-/-}$ mice. Representative of 3 samples per group for Abca1. Values are mean ± SEM. **B.** Total serum cholesterol and triglyceride levels from mice in experiment 3A from atherosclerosis bone marrow transplant experiment.. N=16 animals per group. Values are means ± SEM. **C.** Percent CD68-positive cells in lesions from LDLR animals transplanted with WT or *MeXis*$^{-/-}$. N= 8 animals per group. Values are means ± SEM. * $P < 0.05$ by two-sided student's t-test**.**

Figure S8. Mapping of enhancer sites at the *Abca1* locus. GRO-Seq and ChIP-seq data at the *Abca1* gene locus in mouse primary macrophages. Enhancer sites indicated by arrow and based on mouse mm9 genome build. Similar results were obtained with two biologic replicates.

Figure S9. Analysis of ATAC-seq in *MeXis*$^{-/-}$ macrophages. A. Schematic of mouse crossing strategy related to figure 4b. B. ATAC seq analysis showing genome-wide accessibility in WT or *MeXis*$^{-/-}$ macrophages with GW stimulation. **C.** Number of statistically significant peaks for established LXR target genes from experiment in Figure 4. **D.** Gene Ontology terms from differentially regulated access-sites from ATAC-seq

between WT or *MeXis*$^{-/-}$ macrophages classified by DAVID Functional Annotation Tools (Confidence Interval 95%). N=4 samples per group.

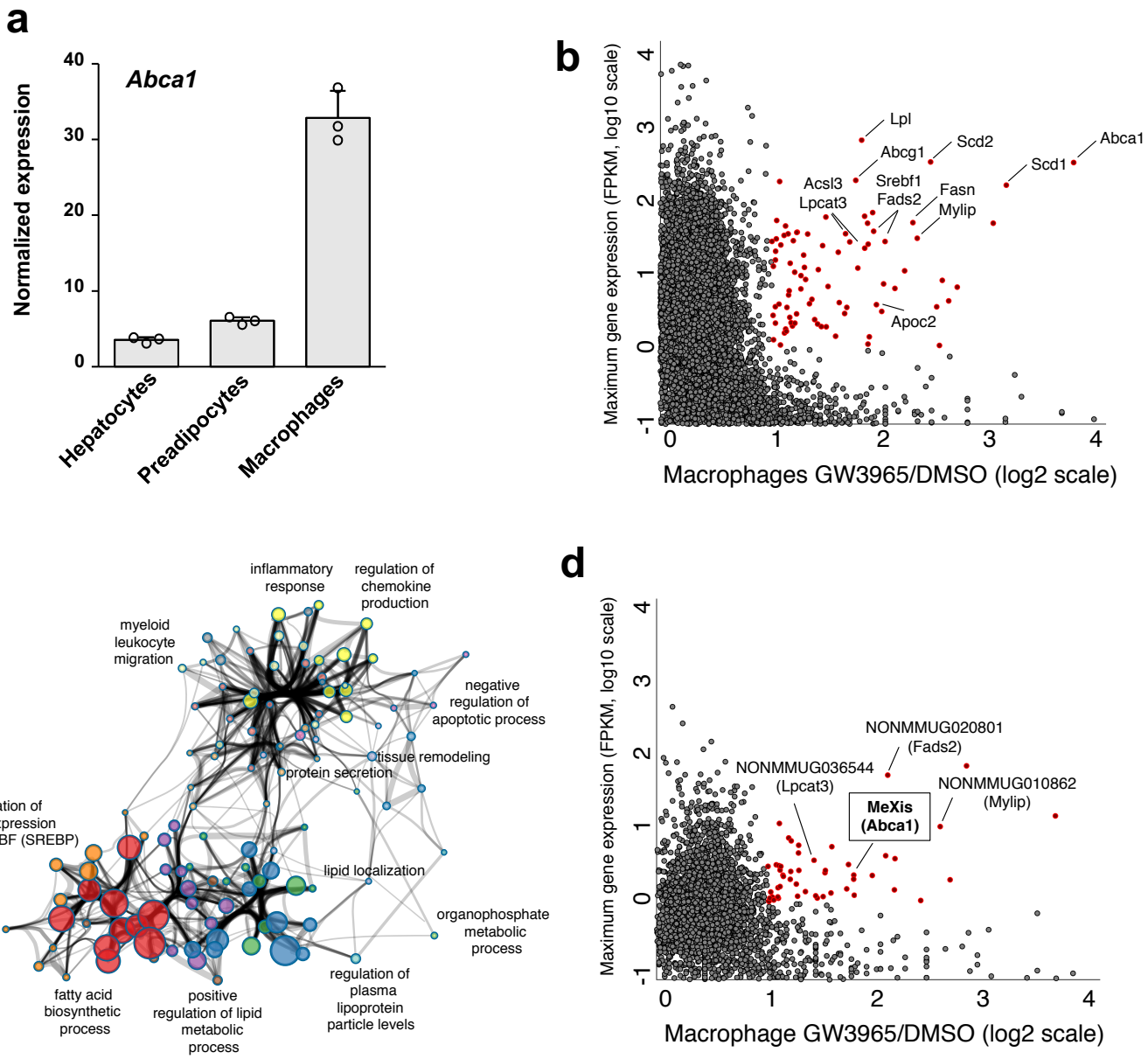
Figure S10. Retrieval of MeXis by ChIRP probes. A. Complimentary biotin-labeled tiling oligonucleotides were incubated with cellular extracts from mouse macrophages. Probes sets designed to retrieve MeXis or *LacZ*. Percent input of retrieved MeXis and *36b4* are shown. N=2 samples per group. Values are mean ± STD. **B.** ChIRP-Mass-spectrometry results at significance threshold of 0.05 for proteins differentially identified between MeXis or *LacZ* probes. **C.** Schematic of Crispr-cas targeting strategy of two different DDX17 exons using a single guide RNA.

Figure S11. Noncoding RNAs at human *ABCA1* gene locus. UCSC genome browser view of the human *ABCA1* gene showing location conservation of *MeXis* and intergenic transcription around *ABCA1* (Hg38 genome build).

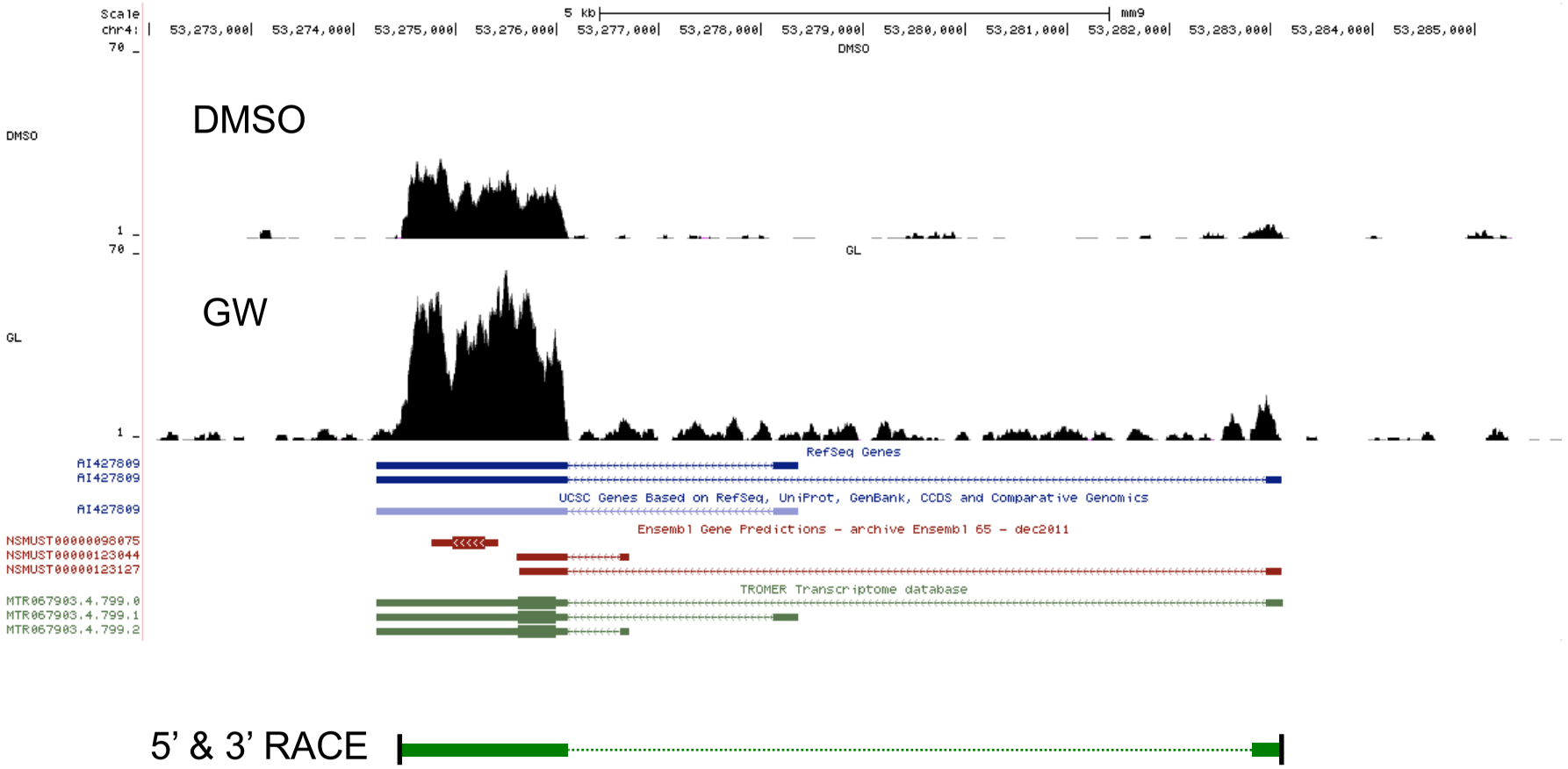
Figure S12. Primer and ASO sequences

Figure S13. Antibody information

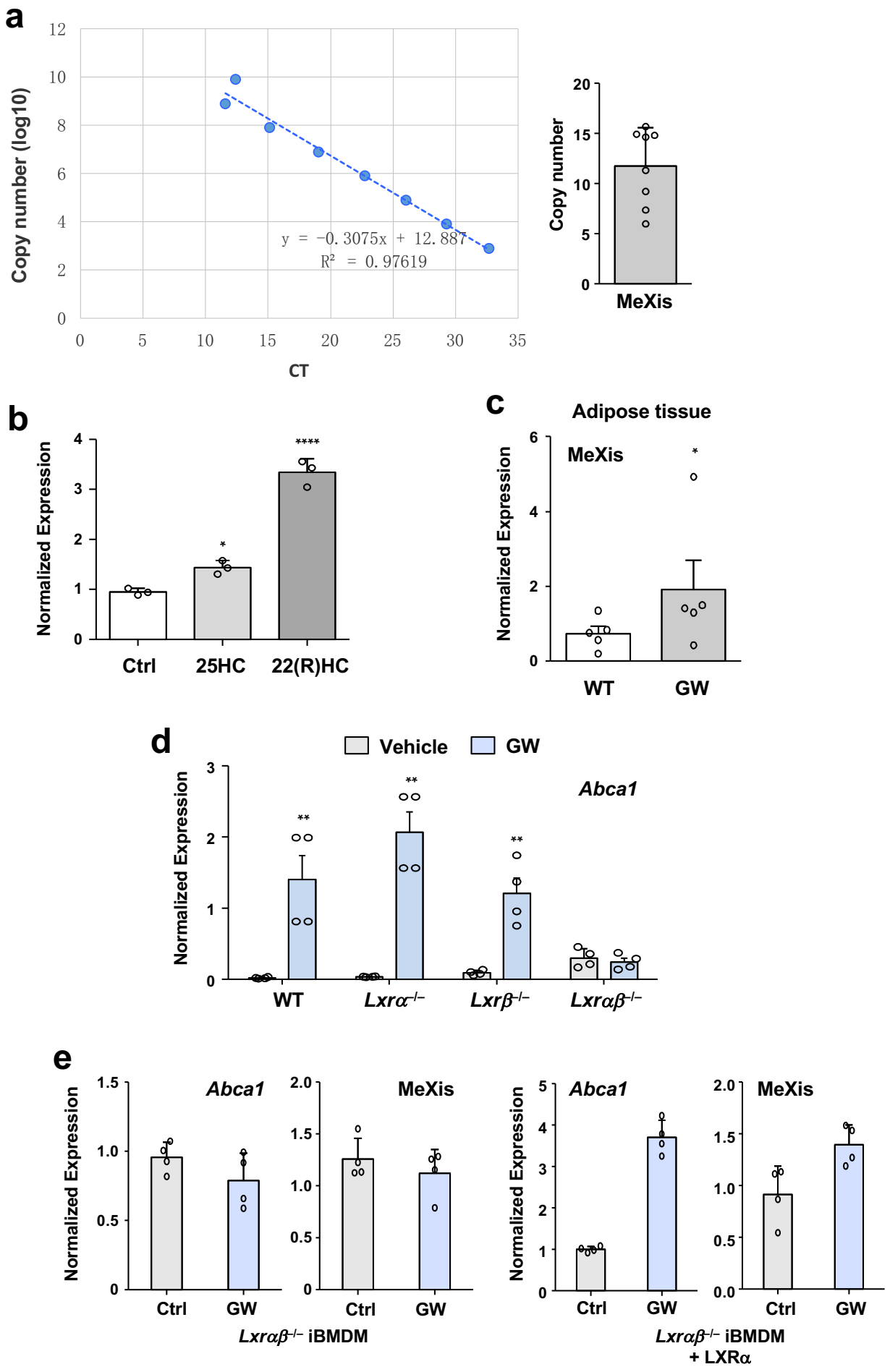
Figure S14. Full-length blots used in manuscript.



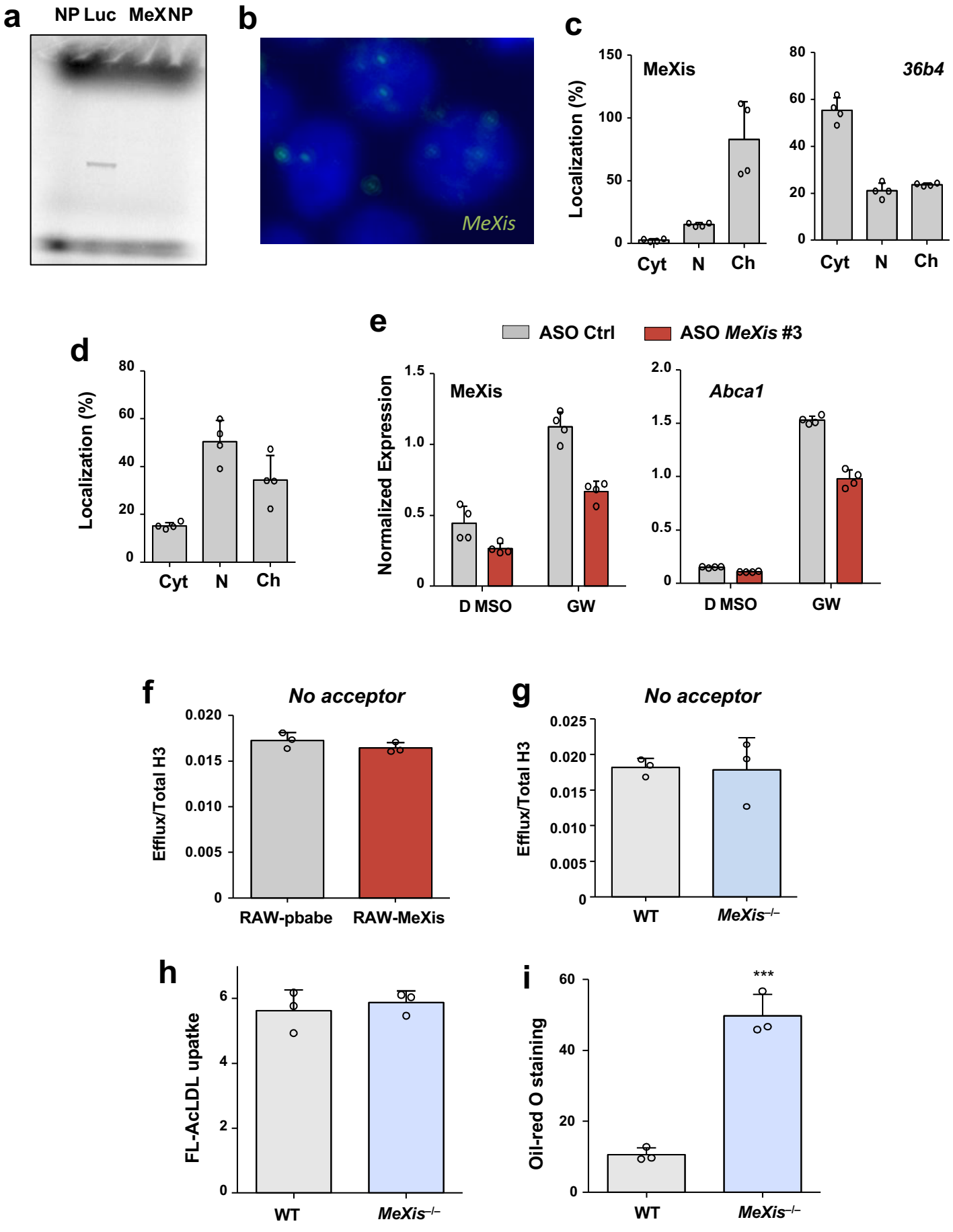
Supplemental Fig. 1



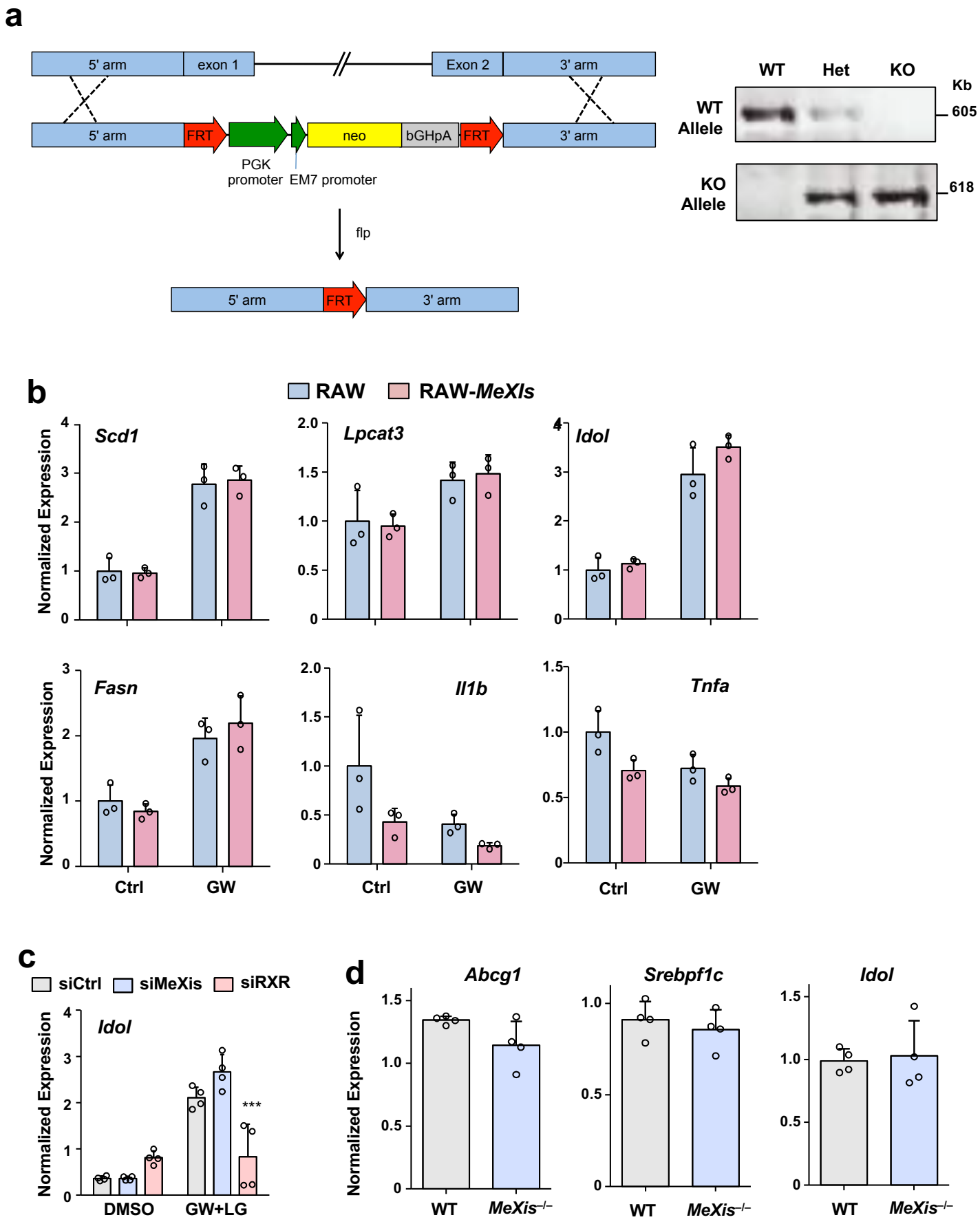
Supplemental Fig. 2



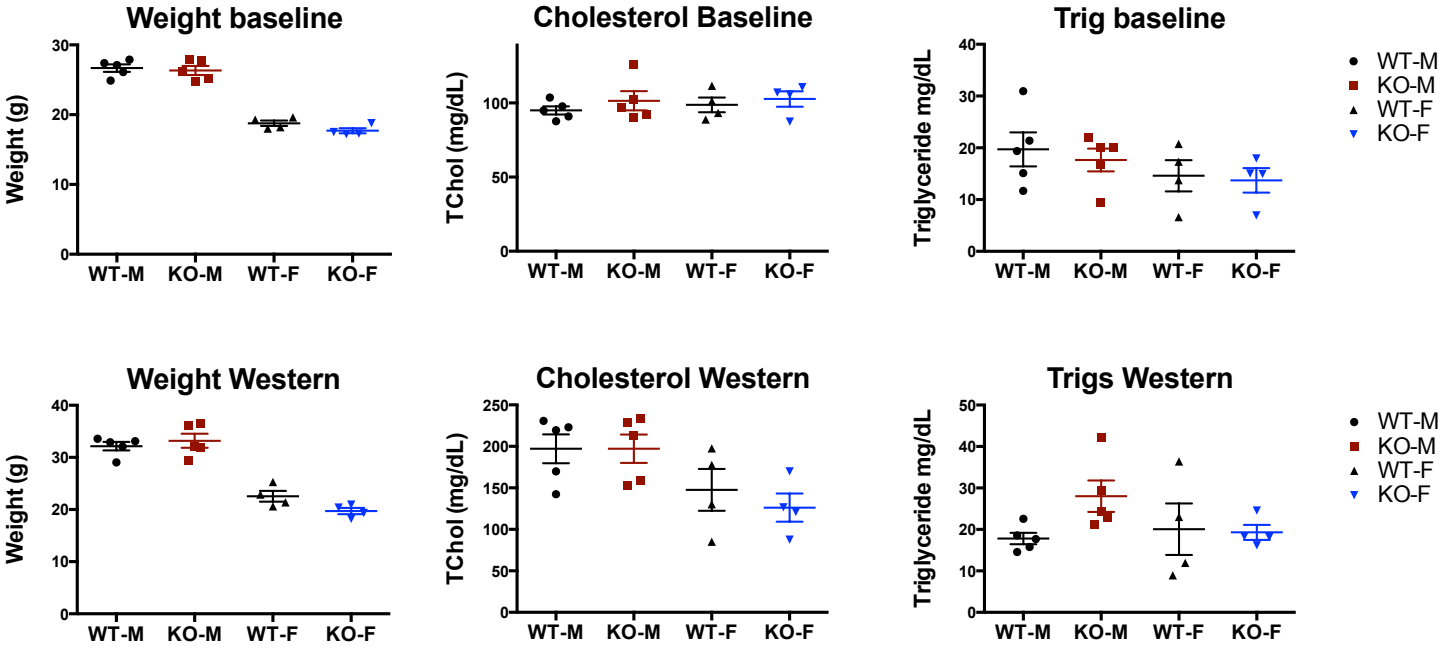
Supplemental Fig. 3



Supplemental Fig. 4



Supplemental Fig. 5



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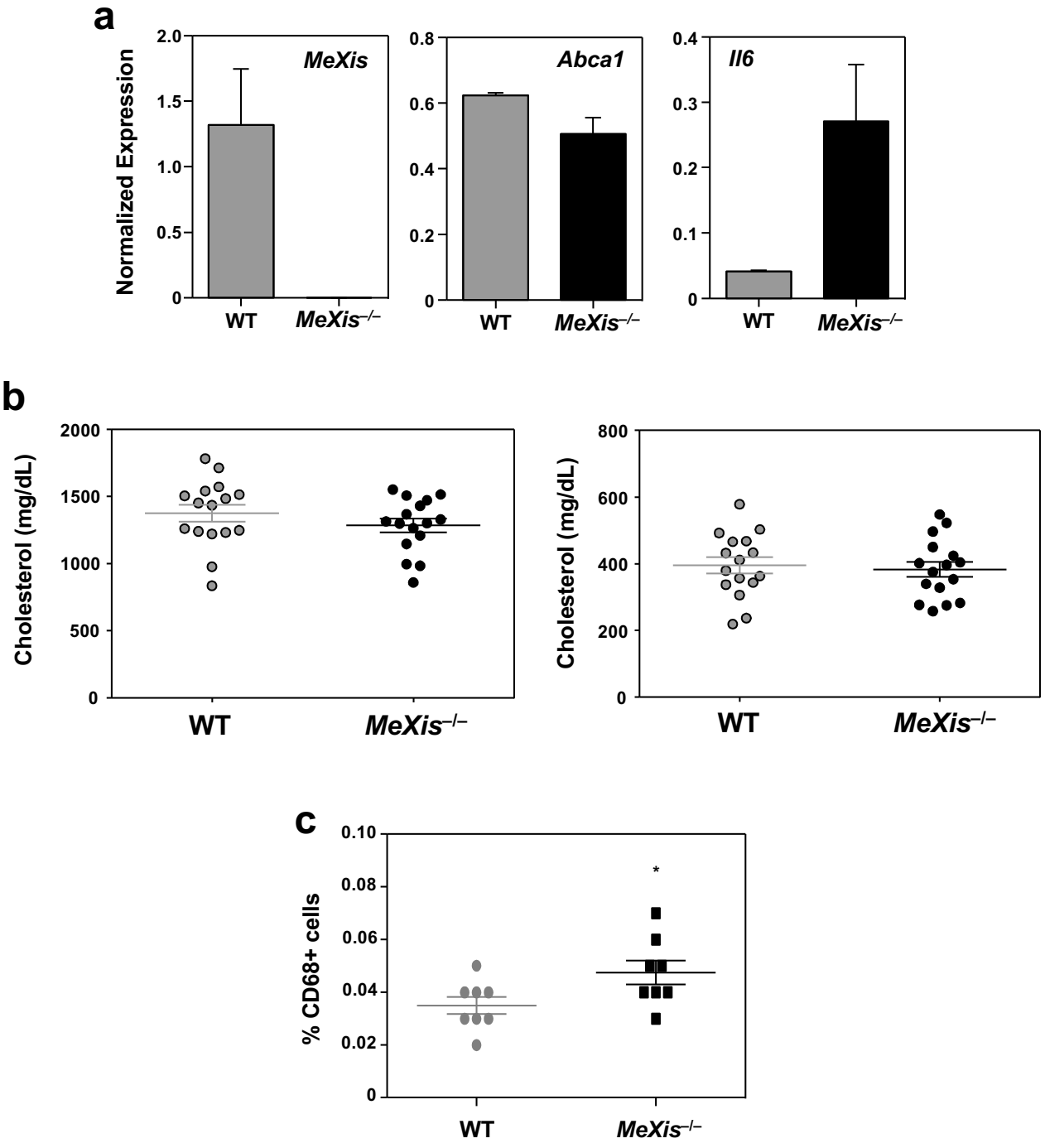

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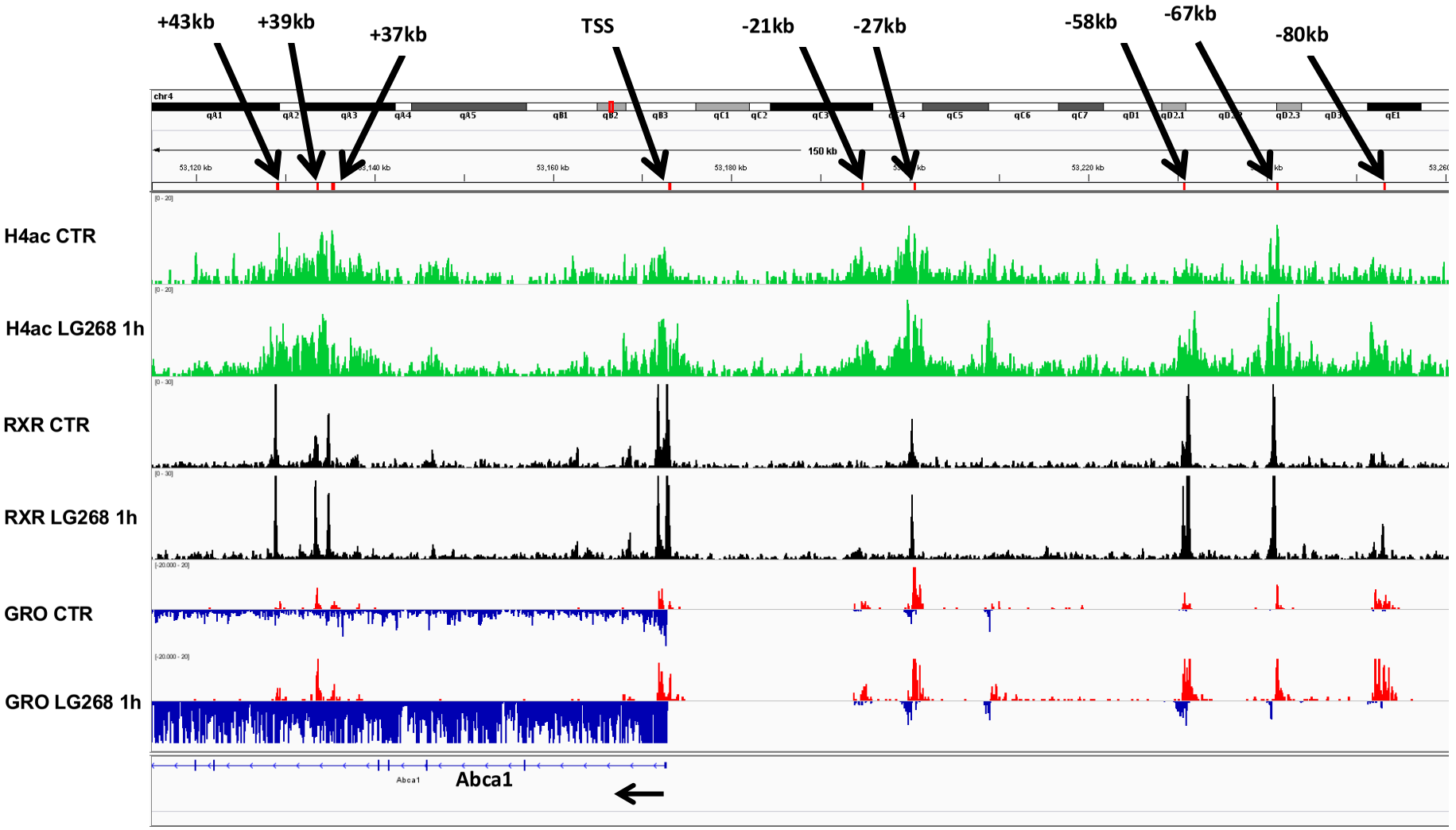
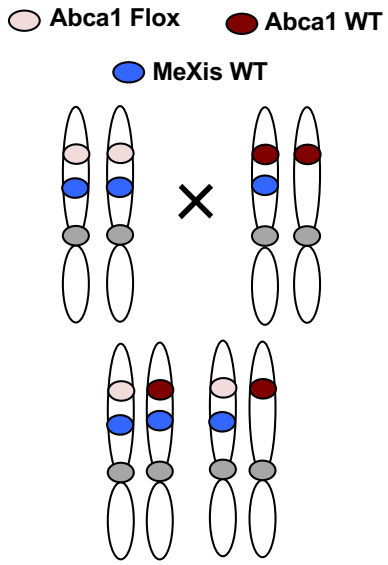


Supplemental Fig. 8

a



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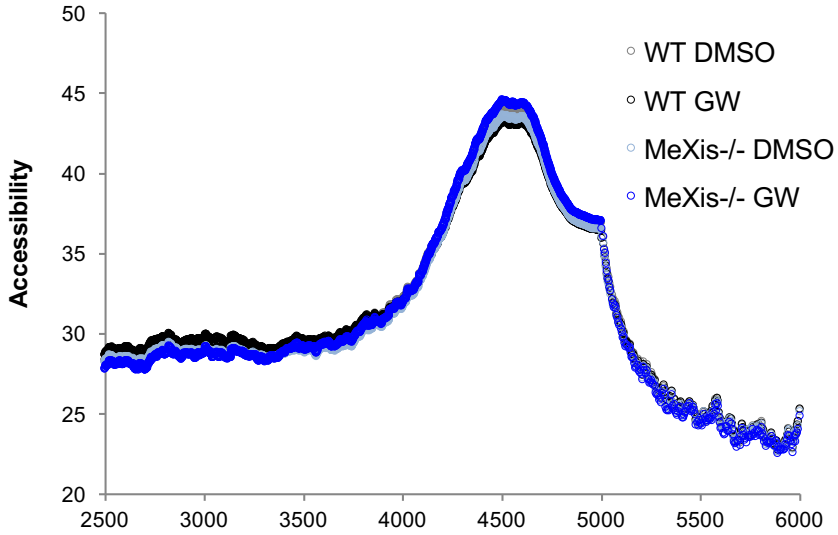


c

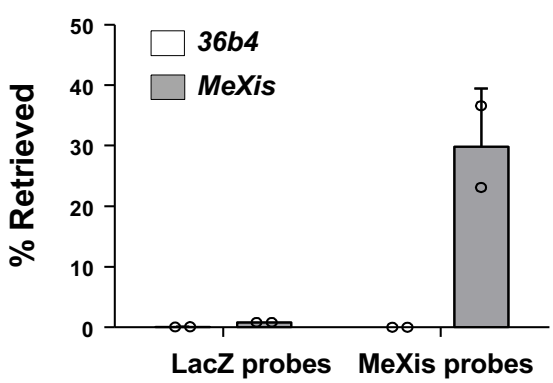
Feature	Number of peaks
Abca1	**6**
Abcg1	1
Mylip	1
Lbp	1
Pltp	1
MrtK	1

d

Rank	GO Term	P-Value
1	intracellular signaling cascade	5.50E-05
2	lipid localization	2.20E-04
3	protein kinase cascade	2.50E-04
4	cholesterol metabolic process	4.50E-04
5	activation of protein kinase activity	4.80E-04
6	sterol metabolic process	8.00E-04
7	regulation of steroid metabolic process	8.20E-04
8	response to protein stimulus	1.60E-03
9	lipid transport	2.50E-03
10	positive regulation of protein kinase activity	3.20E-03
11	regulation of steroid biosynthetic process	3.50E-03
12	reverse cholesterol transport	3.70E-03
13	glycerolipid metabolic process	4.00E-03

Supplemental Fig. 9

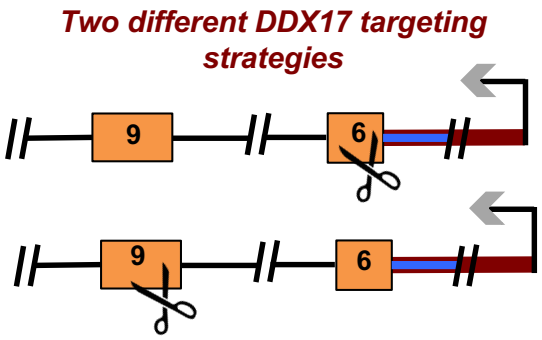
a



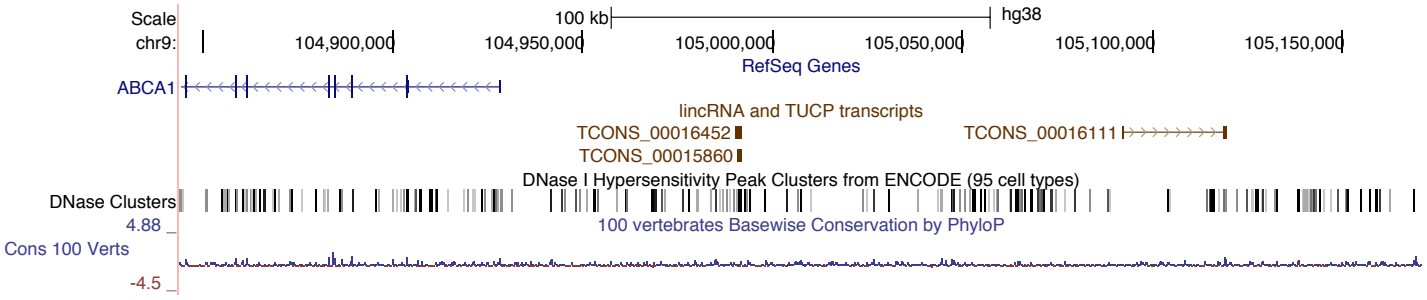
b

Description	Score	Mass	Pep(sig)
Heterogeneous nuclear ribonucleoproteins A2/B1 OS=Mus musculus GN=Hnrnpa2b1	63	37437	2
Heterogeneous nuclear ribonucleoprotein K OS=Mus musculus GN=Hnrnpk	61	51230	2
Splicing factor, proline- and glutamine-rich OS=Mus musculus GN=Sfpq	52	75508	3
Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8	51	71055	2
Serine/arginine-rich splicing factor 6 OS=Mus musculus GN=Srsf6	43	39116	1
40S ribosomal protein S3 OS=Mus musculus GN=Rps3	43	26828	1
Protein 9530053A07Rik OS=Mus musculus GN=9530053A07Rik	42	292361	5
GTP-binding nuclear protein Ran OS=Mus musculus GN=1700009N14Rik	31	24456	1
Desmoplakin OS=Mus musculus GN=Dsp	30	335158	1
Heterogeneous nuclear ribonucleoprotein F OS=Mus musculus GN=Hnrnpf	30	46043	2
Histone H3.3C OS=Mus musculus GN=H3f3c	29	15363	1
Protein 1700003H04Rik OS=Mus musculus GN=1700003H04Rik	22	22496	3
Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2	21	107992	1
Heterogeneous nuclear ribonucleoprotein A1 OS=Mus musculus GN=Hnrnpa1	21	34289	1
ATP-dependent RNA helicase DDX17 OS=Mus musculus GN=Ddx17	20	72981	1
60S ribosomal protein L12 OS=Mus musculus GN=Rpl12	20	17965	2
Heterogeneous nuclear ribonucleoprotein M OS=Mus musculus GN=Hnrnpm	19	77940	2
Vasohibin-1 OS=Mus musculus GN=Vash1	18	42020	1
Junction plakoglobin OS=Mus musculus GN=Jup	16	82490	1
Protein LKAAEAR1 OS=Mus musculus GN=Lkaaear1	16	22113	1
Adenylyltransferase and sulfurtransferase MOCS3 OS=Mus musculus GN=Mocs3	16	50313	1
Elongation factor 2 OS=Mus musculus GN=Eef2	15	96222	1

c



Supplemental Fig. 10



Supplemental Fig. 11

List of Probes used for ChIRP

LacZ (5' to 3')
CAAAAACAGAGAAAGGAAACGACAGAGGCCAAAAAGCTC
GTATCGGCGGAATTACAGCTGAGCGCCGGTCGCTACCATTACCAGTTG
CGCGGAAGAAGGCACATGGCTGAATATCGACGGTTTCCATATGGGGA
GACTTCCAGTTCAACATCAGCCGCTACAGTCAACAGCAACTGAT
CTTCCCGAGCGAAAACGGTCTGCGCTGCGGGACGCGCGAATTGA
GACCGCCTTACTGCCGCCTGTTTTGACCGCTGGGATCTGCCATTGTCA
CTGAACTGCCAGCTGGCGCAGGTAGCAGAGCGGGTAAACTGGCTCGGATT
ATACAAATCAGCGACACTGAATACGGGGCAACCTCATGTCCGA

MeXis (5' to 3')
GTGAGGAGCCTCACAGGAAGAGTCCAGTAAGATGGTAAGATGTAAACACCGCCTC
GATACTCCCGGCAAACAGGAAGCCGAGCTCACCTCTACATTTCACACGAGGGAA
TGTGCAGGATCTCTGATGTGCAGGATCTCTGATATGCAGGGTCTCTGATGTGCAGG
GCAGGGTCTCTGATTGCAGGATCTCTGATTGCAGGATCTCTGATGTGCAGGGTC
AGCAGGTAGAAACACTGAGGGATCGTGGAACCGCCAGATGCTGTGTG
CAGCCGCCCCTGAGCTCTATGCCAGCTGCAGCTAGATGTGTACAGAACA
GAGCTACACGGGCTGCGAAAGGCAAGGCAGGTGACAGACTGGTGTGGGAGGTGAGTGCC
CTGCTGCAAGAATTCTCTCGATGCCAGATAGATTGGAGGGCAAGGGCAGAG

Primers for ChIRP-qPCR

Related to figure 5c the sites below were differentially regulated between WT & *MeXis*$^{-/-}$ by ATAC-seq

Primer	Genomic Location	Forward Primer	Reverse Primer
site 1	chr4:53163326-53163798	AAACTGCGTGTATCTGCGGT	GTTGGACCTATTTCCCCGCT
site 2	chr4:53115888-53116119	GTCATGCCGACCCTTCTTCA	ACATATGTGTGCATGTAGGTCAGA
site 3	chr4:53043420-53043755	TTGAAGTAGCACCCCGAGTC	CTCTCATCGCTGGTGCAAGT
site 4	chr4:53121153-53121554	AAGCTTTCGGGGGAACAACA	GGCTTTGCATCTTAGGGTCC
site 5	chr4:53134685-53135226	GCCACACCACAGAACCGATA	TAGGGACAATCCCTCCGGTT
site 6	chr4:53101867-53102217	AAAGGCGACAGACACTGCAT	TAGGGGGCACTTGAAAGGGA

Primers for qPCR

Primers for enhancer RNA expression at ABCA1 related to figure 4a and S8

Primer	Forward	Reverse
E1	AAAGGGGCTGGAAATAATCACAC	GAATGAGGAATTGGAAGCCGTG
E2	GGGACCTCGTAGGTGTCAAG	ACGGCTGGCAAGAGTAGAAT
E3	TGAGCAGACAGGCTCACAAG	AGCCTCAAAGCAGTCCTTCC
E4 (TSS)	GCCTTCGGGAAACGGGAA	AGAGGAGTTTAGAGAACGAGCTTT
E5	GGATGGATGACTCGAGTGTTTG	CCTTCCTCTAAGTGGGTACTGC
E6	GCTACAAAGGGTCAGGTCGT	TAAACATCACCAAAAATCCAGTTGC
E7	TAGTTGTTAGATCCGGCTCCTC	GGAGCACATTCGAGCGAGA
E8	ACTATGATTCAAGGAAGGGTGTGAT	CCTTTCTGGTGACTACATCATCCT
E9	ACTGCCAGAAGCCAACGTAA	TCCTGTGCCACACAAAGTCTAA

Primers for ChIP-qPCR

Primers for LXR binding sites at Abca1 related to figure 5b

Primer	Forward	Reverse
site 1	GCCTTCGGGAAACGGGAA	AGAGGAGTTTAGAGAACGAGCTTT
site 2	GGGGAAAGAGGGAGAGAACAG	GAATTACTGGTTTTTGCCGC
site 3	AGTTTCCAACAACACCGGGA	CCCCTGGGTACAGGGGATTA

Antisense Oligonucleotides

ASO	Sequence
ASO#3 MeXis	mA*mU*mC*mU*mC*T*G*A*T*G*T*G*C*A*G*mG*mG*mU*mC*mU
ASO#2 TCONS00016111	mC*mU*mG*mG*mC*A*G*C*T*T*C*C*C*A*T*mC*mU*mC*mG*mU
ASO#3 TCONS00016111	mG*mU*mG*mU*mC*C*A*T*C*T*C*C*C*C*A*mU*mC*mG*mU*mA

Antibodies for ChIP

Antibody	Vendor	Catolog/Institution	Concentration
Flag	SIGMA	#F3165	3ug/IP
H3K27Ac	Abcam	#ab4729	3 ug/IP
LXR	Gift from Knut R. Steffensen	Karolinska	5 ug/IP
DDX17	Gift from Douglas Black	UCLA	5 ug/IP

Primary Antibodies

Antibody	Vendor	Catolog/Institution	Concentration
Abca1	Novus	NB400-105	1:000
Actin	Sigma	A2066	1:10000
CD68	AbD	MCA1957GA	1:4000
DDX17	Gift from Douglas Black	UCLA	1:500

Secondary Antibodies

Antibody	Vendor	Catolog/Institution	Concentration
biotin-SP-conjugated Goat anti-Rat IgG	Jackson ImmunoLabs	112-065-167	1:000 (CD68)
Goat anti-Rabbit Antibody HRP	Life Technologies	656120	1:4000

Figure 2k

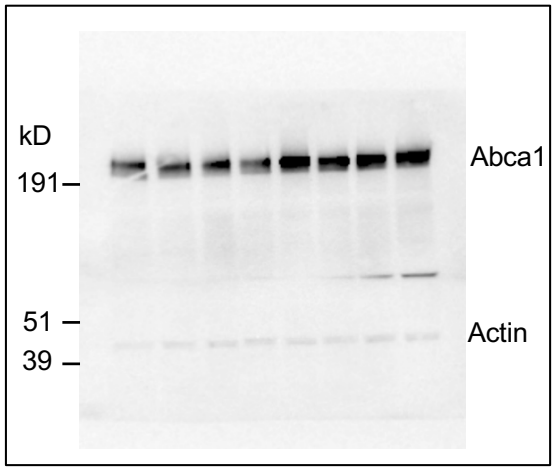


Figure 2e

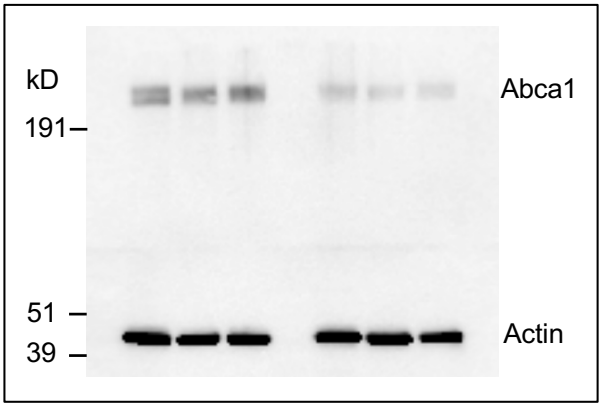


Figure 5a

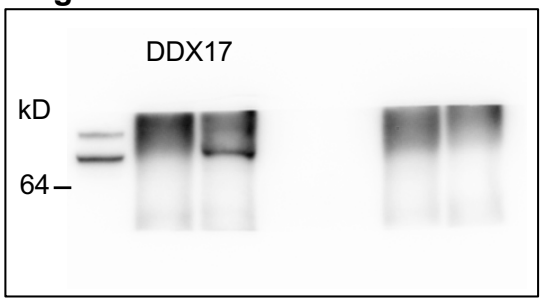


Figure 5d

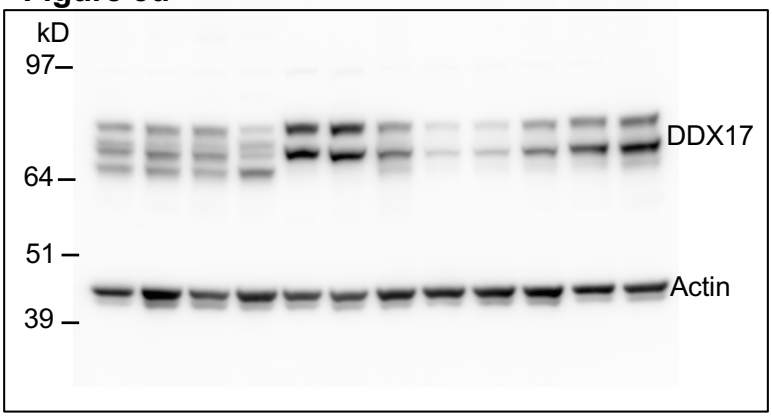


Figure 5g

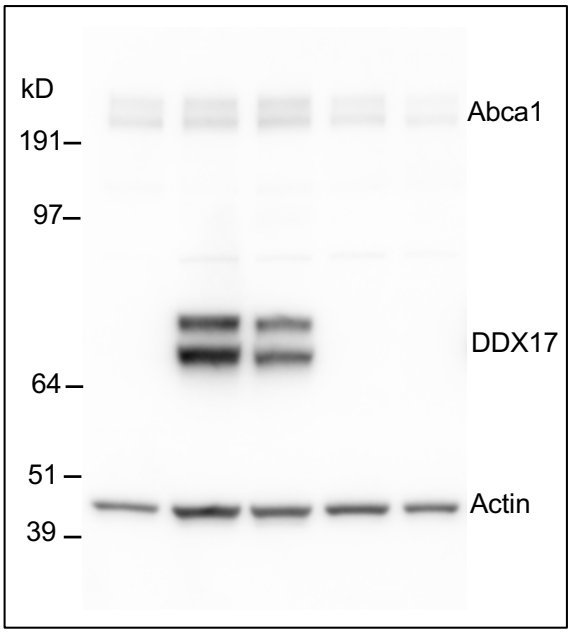


Figure S4a

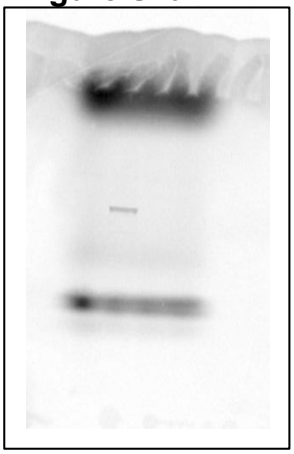
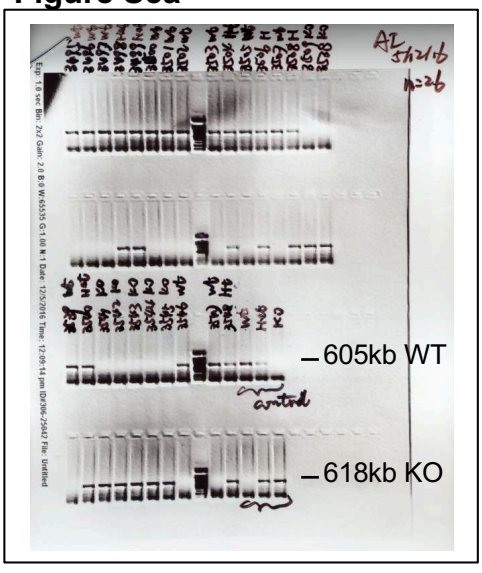


Figure S5a



Supplemental Table 1. LXR-Responsive LncRNAs

Coding potential: Coding potential (CP) score (in [0 1]) from CPAT. For mouse, CP<0.44 is used to classify non-coding nucleotide sequences
Exons: Maximal number of exons for transcripts in gene model
Macrophages, DMSO: Gene-level Expression estimates (FPKMs)
Macrophages, GW3965: Gene-level Expression estimates (FPKMs)
GW-induced fold, macrophages log2(fold-change) estimated from FPKM ratios (treated vs. control)

Gene id	Coding potential	Exons	Macrophages, DMSO	Macrophages, GW3965	GW-induced fold, macrophages
NONMMUG029258	0.14	1	1.17	14.16	3.60
NONMMUG021849	0.25	3	0.33	2.05	2.65
NONMMUG010862	0.03	1	1.74	10.26	2.56
NONMMUG020753	0.11	2	0.21	1.10	2.38
NONMMUG007384	0.33	2	0.88	3.89	2.15
NONMMUG031107	0.09	4	0.34	1.51	2.15
NONMMUG020801	0.03	1	11.46	48.64	2.09
NONMMUG044608	0.06	2	1.01	4.25	2.07
NONMMUG028796	0.08	1	0.61	2.34	1.95
NONMMUG040028	0.10	3	0.37	1.29	1.78
MeXis	0.11	2	0.69	2.36	1.78
NONMMUG014707	0.04	1	0.61	2.09	1.78
NONMMUG040696	0.01	1	0.98	3.26	1.73
NONMMUG025125	0.13	1	0.47	1.56	1.72
NONMMUG042323	0.07	1	1.86	5.58	1.58
NONMMUG020752	0.04	2	0.46	1.38	1.57
NONMMUG001098	0.17	2	0.89	2.54	1.52
NONMMUG002204	0.01	2	0.43	1.23	1.50
NONMMUG007882	0.07	1	0.43	1.18	1.45
NONMMUG036544	0.07	1	1.38	3.69	1.42
NONMMUG038049	0.10	2	0.56	1.43	1.34
4930426I24Rik	0.05	3	1.12	2.73	1.28
NONMMUG009249	0.00	1	2.40	5.84	1.28
NONMMUG000595	0.05	3	0.52	1.25	1.27
4833417C18Rik	0.02	3	0.75	1.80	1.26
NONMMUG038572	0.32	2	2.87	6.67	1.22
NONMMUG024603	0.01	1	1.14	2.64	1.21
NONMMUG008576	0.03	1	0.90	2.08	1.21
NONMMUG037641	0.02	1	3.19	7.28	1.19
NONMMUG020309	0.05	1	1.03	2.28	1.14
NONMMUG016240	0.07	1	1.07	2.36	1.14
NONMMUG041990	0.03	1	1.42	3.08	1.12
NONMMUG043449	0.02	1	0.77	1.67	1.11
NONMMUG002363	0.01	1	1.27	2.75	1.11
NONMMUG040304	0.01	1	5.23	11.27	1.11
NONMMUG041988	0.02	1	1.47	3.16	1.10
4930599N23Rik	0.33	4	0.55	1.17	1.10
NONMMUG035144	0.04	1	0.76	1.61	1.10
NONMMUG044541	0.01	1	0.57	1.22	1.09
NONMMUG007066	0.02	1	1.52	3.22	1.08
NONMMUG040149	0.02	1	0.53	1.11	1.06
NONMMUG008961	0.02	1	0.59	1.22	1.04
NONMMUG020822	0.06	1	0.69	1.42	1.03
NONMMUG038887	0.03	1	0.58	1.18	1.02
NONMMUG003326	0.02	1	0.54	1.10	1.02
NONMMUG037596	0.18	1	0.53	1.07	1.01
NONMMUG025132	0.17	1	1.53	3.08	1.01

Supplemental Table 3. Potential Open reading frames in the MeXis sequence.

Frame	Strand	Frame	Start	Stop	Length (nt | aa)
ORF1	+	1	118	204	87 | 28
ORF10	-	2	1277	1101	177 | 58
ORF11	-	2	1016	717	300 | 99
ORF12	-	2	200	>3	198 | 65
ORF13	-	3	868	692	177 | 58
ORF14	-	3	283	80	204 | 67
ORF2	+	2	170	253	84 | 27
ORF3	+	2	446	748	303 | 100
ORF4	+	2	1073	1387	315 | 104
ORF5	+	2	1460	1762	303 | 100
ORF6	+	3	147	356	210 | 69
ORF7	-	1	1866	1663	204 | 67
ORF8	-	1	798	667	132 | 43
ORF9	-	2	1580	1479	102 | 33

Supplemental Table 4. Analysis of MeXis-responsive pathways comparing WT and MeXis−/− primary mouse macrophages. Classified by DAVID Functional Annotation Tools (Confidence Interval 95%). One sample from each group pooled from 3 biologic replicates.

Ingenuity Pathway	-log (pvalue)
Enzyme linked receptor protein signaling pathway	4.05
Phosphorylation	3.84
Phosphate metabolic process	3.73
Positive regulation of cell proliferation	3.39
Protein amino acid phosphorylation	3.26
Transmembrane receptor protein tyrosine kinase signaling	3.21
Cation transport	2.77
Steroid metabolic process	2.67
Cholesterol metabolic process	2.21
Metal ion transport	2.11
Regulation of protein transport	1.95
Regulation of small GTPase mediated signal transduction	1.94
Sterol metabolic process	1.92
Ion transport	1.87
Lipid localization	1.84
Lipid transport	1.74
Di-, tri-valent inorganic cation transport	1.37
Regulation of DNA binding	1.22
Regulation of protein kinase cascade	1.22
Lymphocyte costimulation	1.14
T cell costimulation	1.14
Inflammatory response	1.03