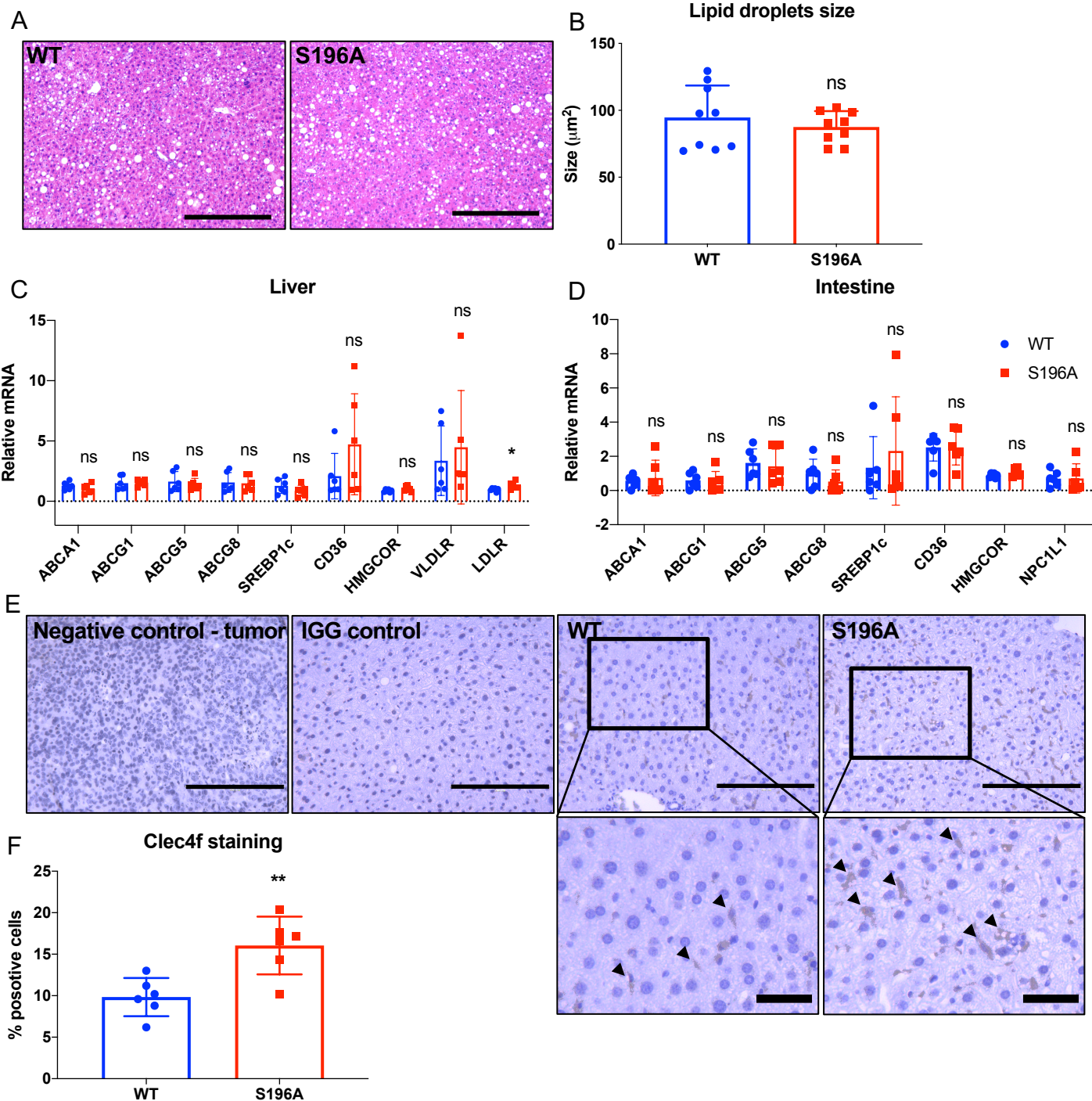
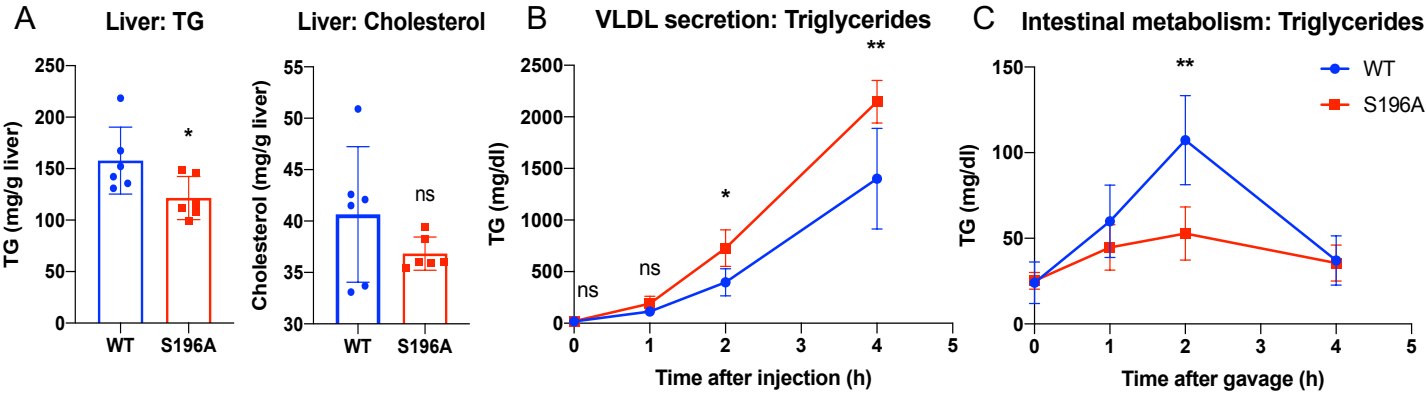


Supplementary Figure 1: LXR α S196A increases Clec4f staining in livers without affecting lipid accumulation, or genes expression



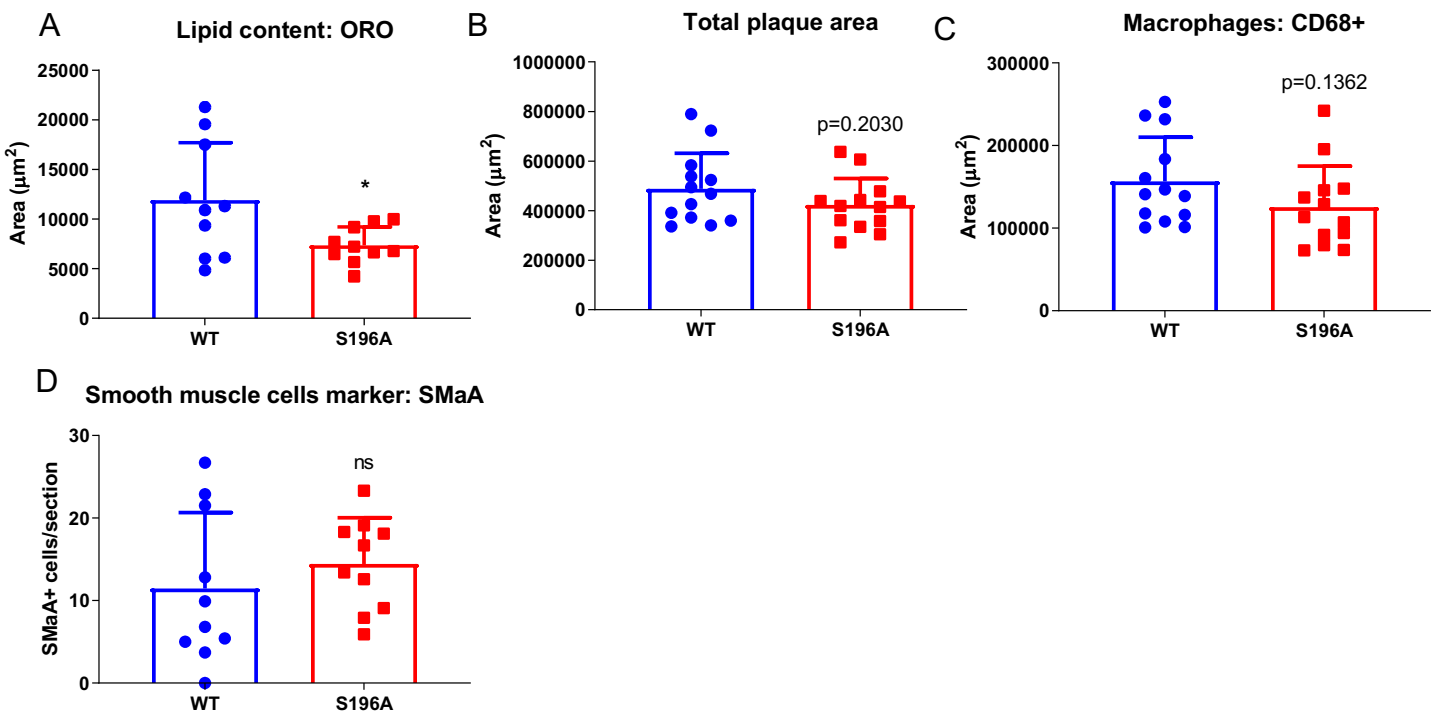
(A) Representative hematoxylin and eosin image of liver sections from LXR α WT and LXR α S196A (scale bar = 400 μ m), and (B) quantification of lipid droplets in liver sections. (C-D) Expression of cholesterol homeostasis genes by qPCR: cholesterol secretion (*Abca1*, *Abcg1*), cholesterol excretion (*Abcg5*, *Abcg8*), fatty acid metabolism (*Srebp1c*), fatty acid uptake (*Cd36*), cholesterol biosynthesis (*Hmgcor*), and lipoproteins uptake (*Vldlr*, *Ldlr*), and intestinal cholesterol uptake (*Npc1l1*) in (C) the liver, and (D) the intestine. (E-F) Representative image of Clec4f staining, and quantification of positive cells in liver sections (scale bars: 200 μ m and 50 μ m). Data are expressed as mean \pm SD (n=9 for lipid droplet quantification in liver, n=5 for gene expression, and n=7 for Clec4f quantification) and obtained from independent samples. T test; *P<0.05 and **P<0.01.

Supplementary Figure 2: LXR α S196A shows decreased TG in the liver, and full body LXR α S196A increased VLDL secretion and plasma TG clearance



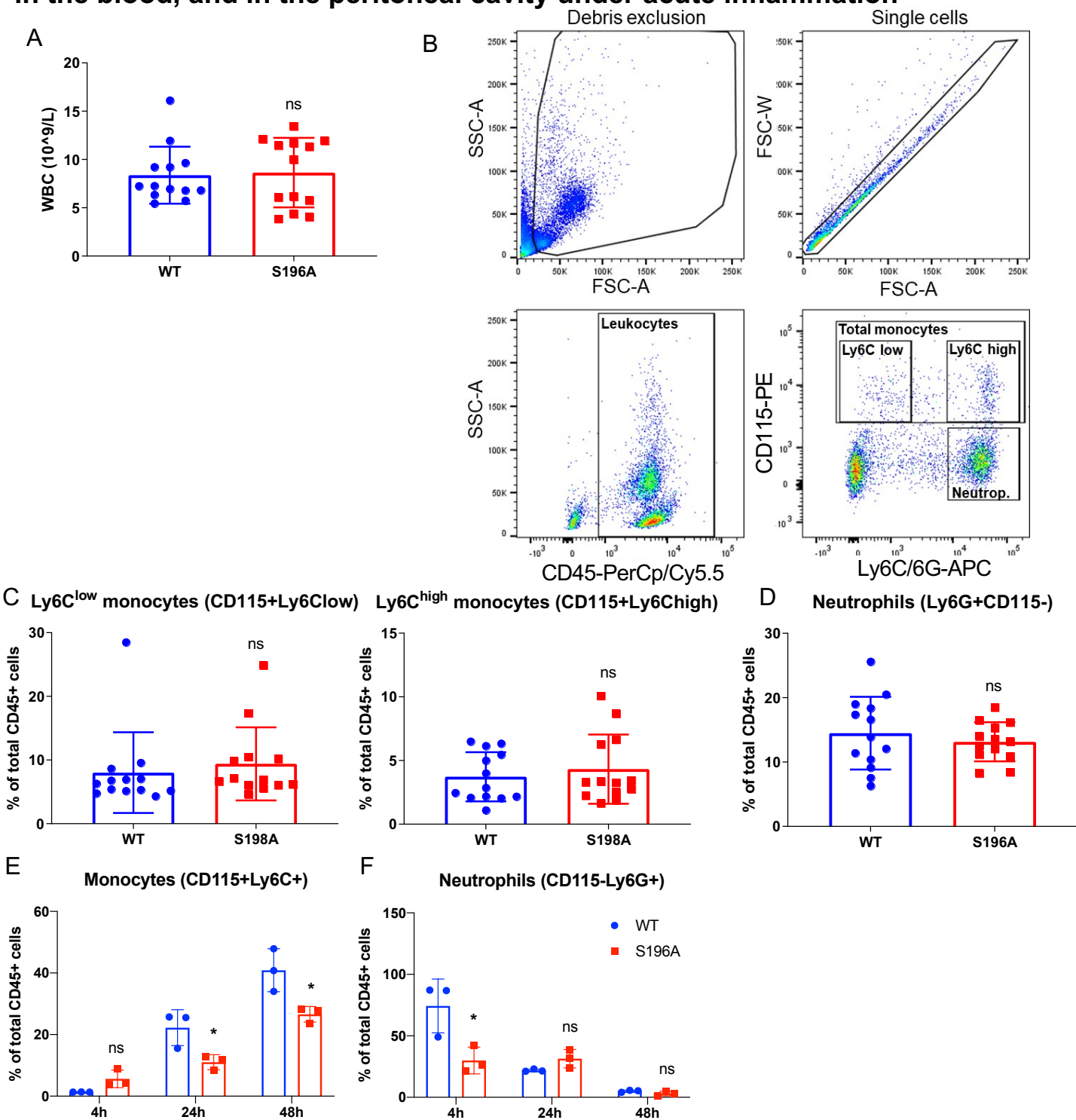
(A) Measurements of TG and total cholesterol from the livers of the *Ldlr*^{-/-} LXR α WT and S196A mice on western diet for 16 weeks. (B-C) VLDL secretion and intestinal metabolism in LXR α WT and LXR α S196A mice on chow diet. (B) VLDL secretion was measured in fasted mice (4 h) by monitoring plasma TG following oral gavage of olive oil at the indicated time points. (C) Intestinal metabolism measured by TG plasma on overnight fasted mice and treated with the LPL inhibitor poloxamer 407 to inhibit lipolysis of TG-rich lipoprotein particles. Data are expressed as mean \pm SD (n=6) and obtained from independent samples. T test; *P<0.05 and **P<0.01.

Supplementary Figure 3: Effect of LXR α S196A on aortic plaque characteristics



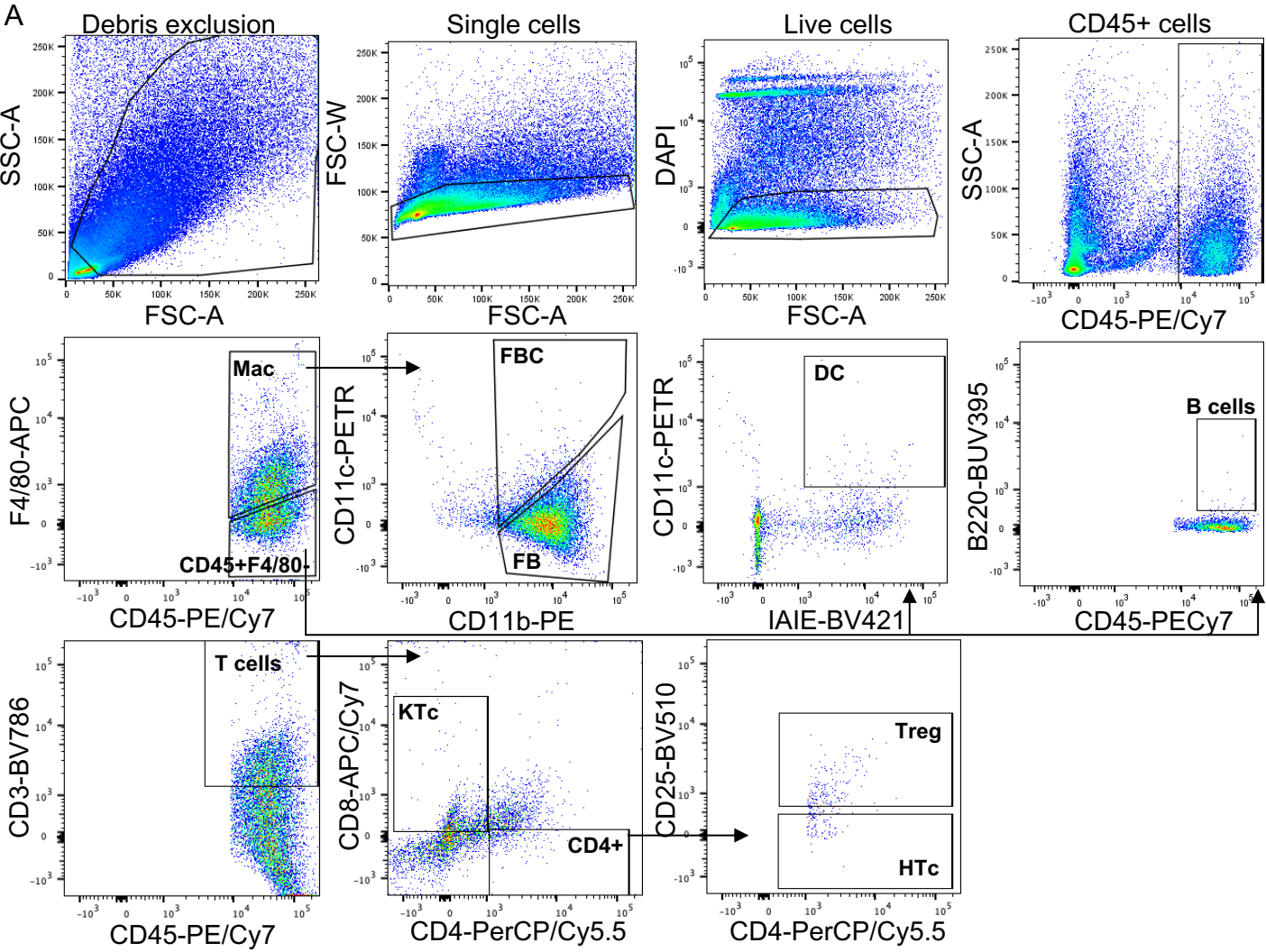
(A) Lipid content (Oil Red O), (B) total plaque area quantification, (C) area of macrophages (CD68⁺), and (D) number of cells per section expressing SMAA (smooth muscle cell actin marker) were measured after staining of aortic sections. Data are expressed as mean \pm SD (n=13 per group, except for ORO, and SMAA n=10) and obtained from independent samples. T test; *P<0.05.

Supplementary Figure 4: Effect of LXR α S196A on monocytes and neutrophils in the blood, and in the peritoneal cavity under acute inflammation



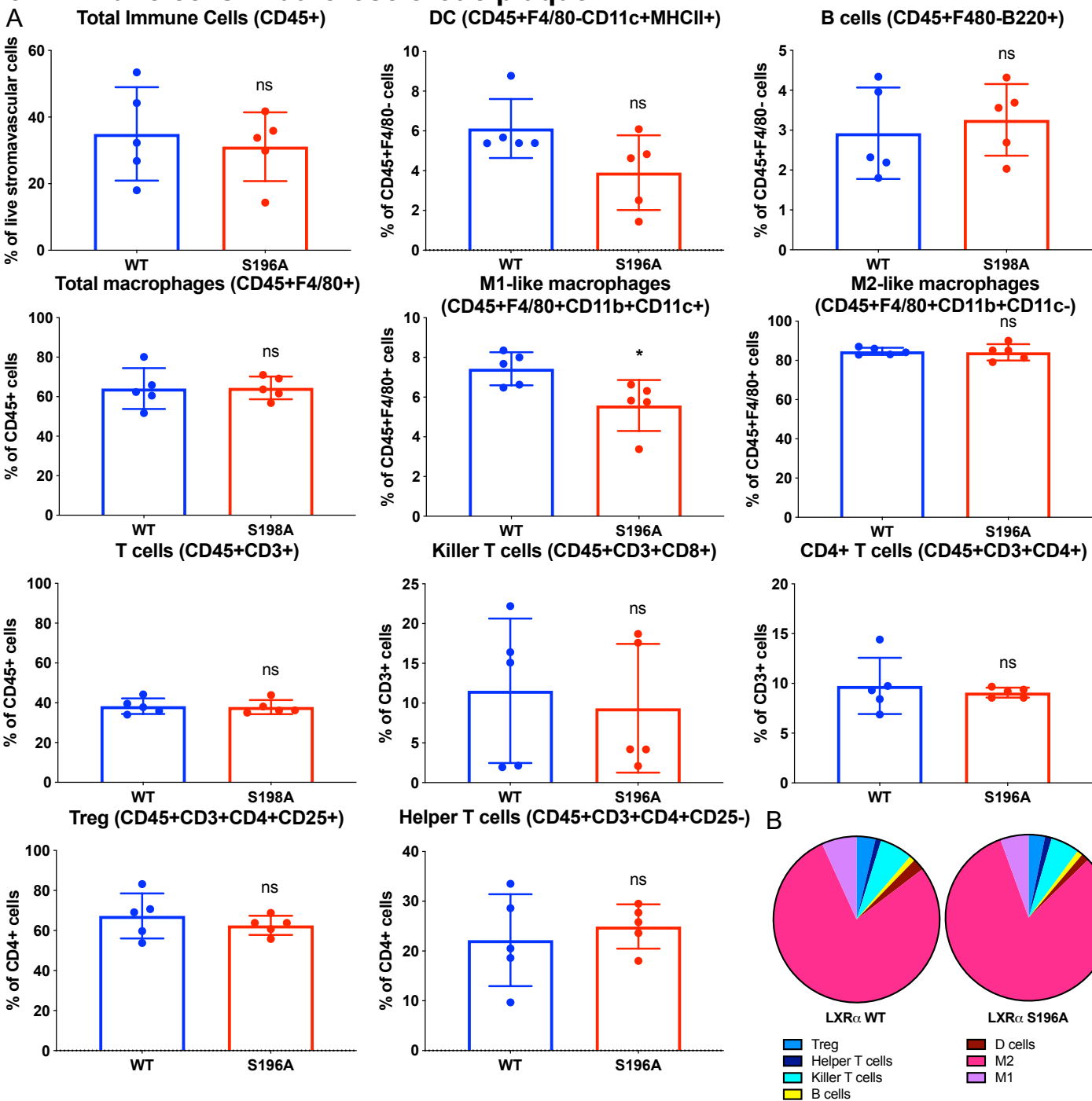
(A) Total number of white blood cells in the circulation (WBC) (WT; 8.375 ± 2.954 , S196A: 8.642 ± 3.600 10^9 cells/L, $p=0.8380$). (B) Gating strategy for monocytes and neutrophils quantification by flow cytometry. (C) Ly6C^{low} (WT; 8.0 ± 6.3 , S196A: 9.4 ± 5.7 %, $p=0.5640$) and Ly6C^{high} monocytes (WT: 3.7 ± 1.9 , S196A: 4.3 ± 2.7 % of total CD45⁺ cells, $p=0.5237$), and (D) neutrophils (WT: 6.3 ± 5.7 , S196A: 8.3 ± 3.0 % of total CD45⁺ cells, $p=0.4564$) were measured by flow cytometry. (E-F) Full body LXR α S196A and WT mice on chow diet were injected intraperitoneally with zymosan A, and (E) monocytes and (F) neutrophils recruitment was measured at 4, 25, and 48 hours. Data are expressed as mean \pm SD ($n=13$ per group, or $n=3$ for zymosan A-injected monocytes and neutrophils recruitment) and obtained from independent samples. T test; * $P < 0.05$.

Supplementary Figure 5: Flow cytometry of immune cells in atherosclerotic plaque



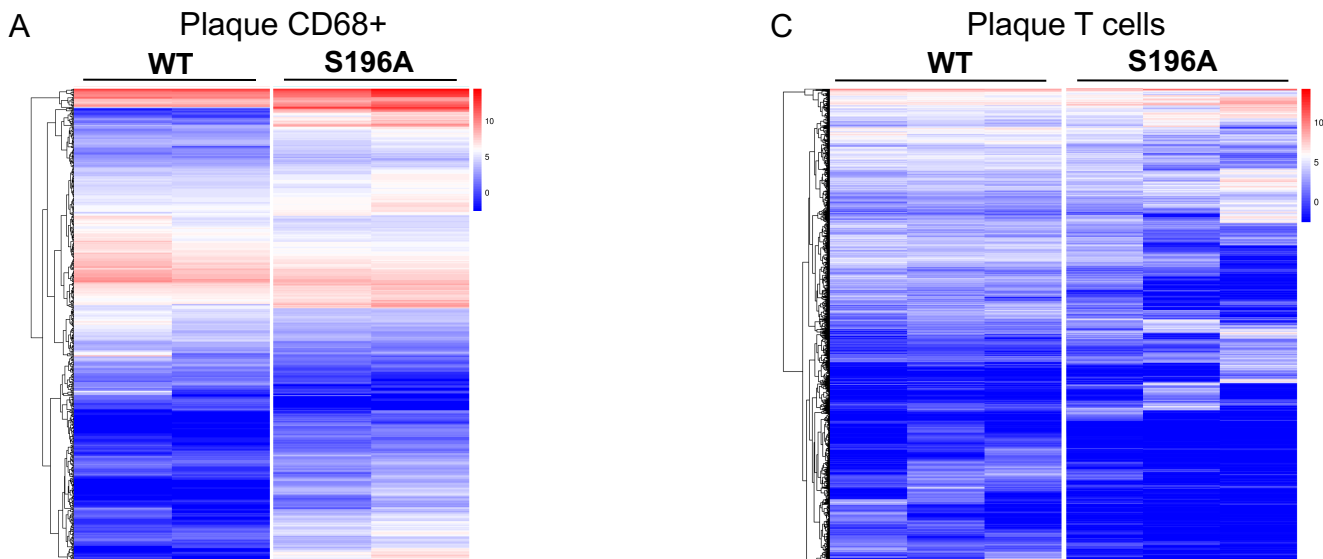
(A) Gating strategy for immune cells population from aortic digestions of atherosclerotic plaque from *Ldlr*^{-/-} mice reconstituted with WT and S196A bone marrow and fed a western diet for 16 weeks.

Supplementary Figure 6: Effects of LXR α S196A bone marrow transplantation on immune cells in atherosclerotic plaque



(A) Quantification of immune cells by flow cytometry in digested aortas from WT and S196A mice. Total immune cells (CD45⁺ WT:34.94±14.02, S196A:31.12± 10.32%, p=0.6370), dendritic cells (DC WT:6.12±1.48, S196A:3.90±1.88 %, p=0.0723), B cells (Bc WT:2.92±1.15, S196A:3.26±0.90 %, p=0.6198), total macrophages (F4/80⁺ WT:64.12±10.35, S196A:64.46± 5.76 %, p=0.9504), M1-like macrophages (CD11b⁺CD11c⁺ WT:7.43±0.83, S196A:5.58±1.28 %, p=0.0269), M2-like macrophages (CD11b⁺CD11c⁻ WT:84.60±1.83, S196A:84.10±4.17 %, p=0.8122), total T cells (CD3⁺ WT:38.28±3.90, S196A:37.86±3.56 %, p=0.8631), Killer T cells (CD8⁺ WT:11.55±9.09, S196A:9.35±8.08 %, p=0.6965), CD4⁺ T cells (CD4⁺ WT:9.75±2.82, S196A:9.07±0.50 %, p=0.6144), Treg (CD4⁺C25⁺ WT:67.30±11.27, S196A:62.58±4.77 %, p=0.4135), and Helper T cells (CD4⁺CD25⁻ WT:22.17±9.24, S196A:24.92±4.45 %, p=0.5659) populations. (B) Pie chart representing the percentage of different cell population of immune cells in the plaque. Data are expressed as mean ± SD (n=5 per group) and obtained from independent samples. T test; *P<0.05.

Supplementary Figure 7: Heatmap of plaque CD68⁺ and T cells.

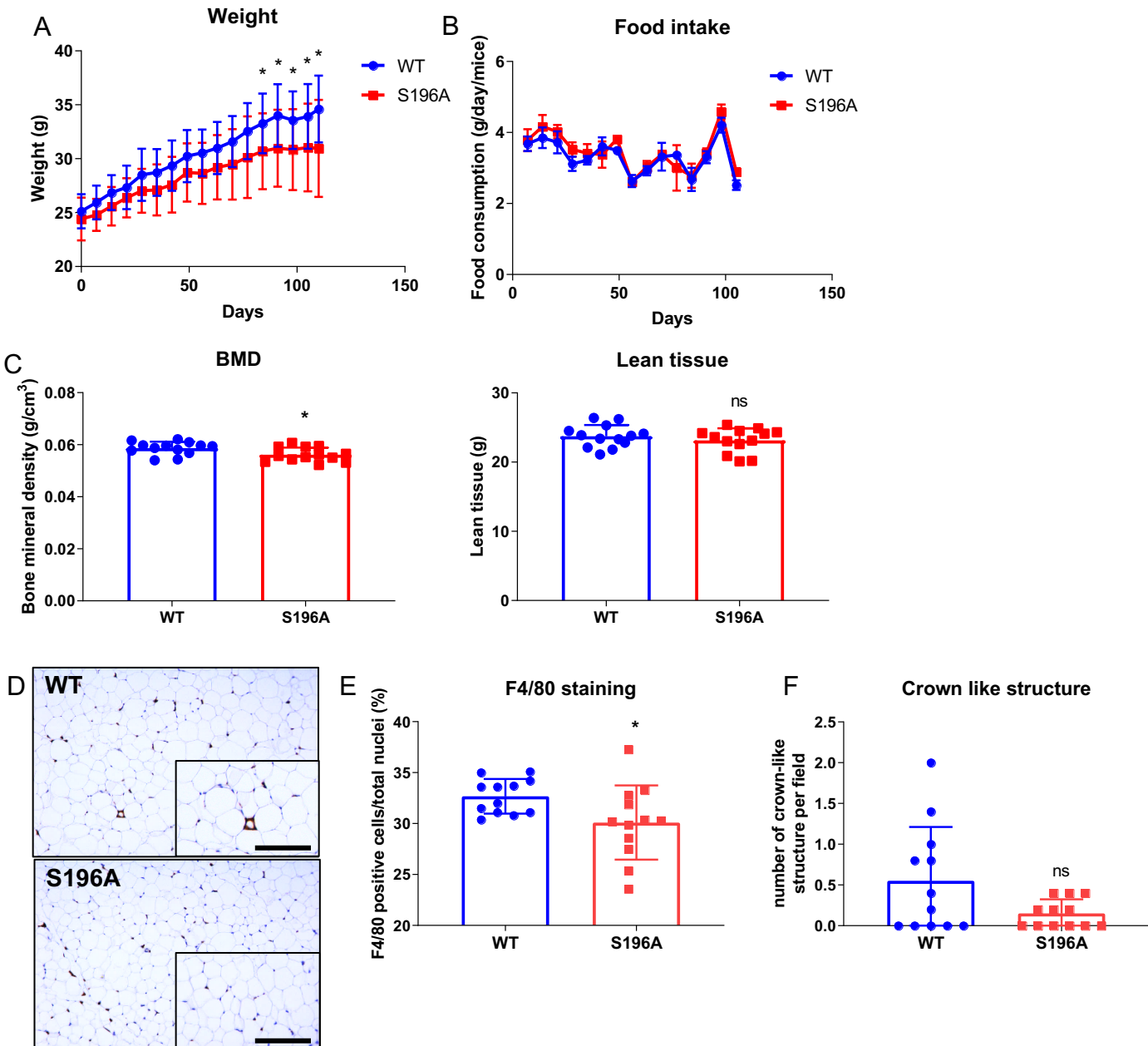


B

| Gene | Log(FC) | Gene | Log(FC) |
|----------------|-------------|----------------|---------|
| Cox7a1 | 8.54 | Atp5j2 | 1.09 |
| Cox8b | 6.8 | Atp5b | 1.08 |
| Cox6a2 | 6.78 | Cox7a2 | 1.07 |
| Cpt1b | 4.8 | Atp5c1 | 1.07 |
| Mapk10 | 4.09 | Ndufb4 | 1.04 |
| Ndufa5 | 1.84 | Ndufs3 | 1.04 |
| Atp5g1 | 1.5 | Atp5a1 | 0.95 |
| Atp5o | 1.42 | Pink1 | 0.92 |
| Ndufb9 | 1.41 | Prdx3 | 0.91 |
| Ndufa4 | 1.41 | Atp5h | 0.9 |
| Aco2 | 1.38 | Ndufs1 | 0.89 |
| Cox7b | 1.29 | Cox4i1 | 0.88 |
| Pdha1 | 1.29 | Ndufa13 | 0.87 |
| Uqcrrs1 | 1.25 | Atp5g3 | 0.86 |
| Cycs | 1.2 | Vdac1 | 0.85 |
| Ndufb11 | 1.18 | Ndufs2 | 0.83 |
| Cox6c | 1.17 | Atp5l | 0.62 |
| Atp5j | 1.11 | Ogdh | 0.62 |

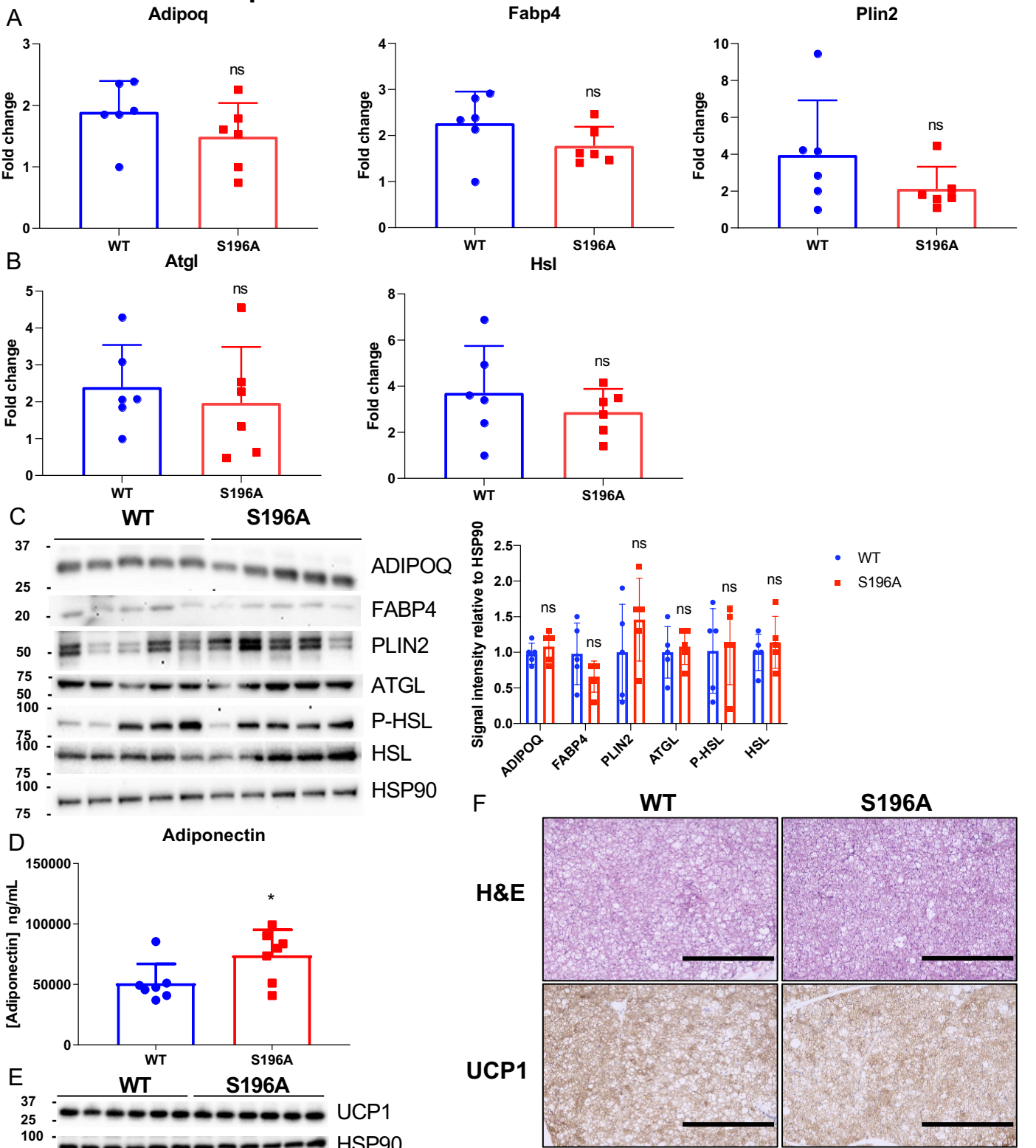
(A) Heatmap of plaque CD68⁺ cells captured by LCM from LXR α WT and S196A by RNA seq: 570 significant genes; LogFC> 0.6; pvalue<0.05). (B) Genes and fold change of upregulated mitochondrial function-associated genes in CD68⁺ RNA seq. Genes in bold are involved in mitochondrial oxidative phosphorylation pathway. (C) Heatmap of plaque T cells collected by flow cytometry from LXR α WT and S196A by RNA seq: 3970 significant genes; LogFC> 1; FDR<0.05).

Supplementary Figure 8: Effects of LXR α S196A bone marrow transplantation on diet induced obesity



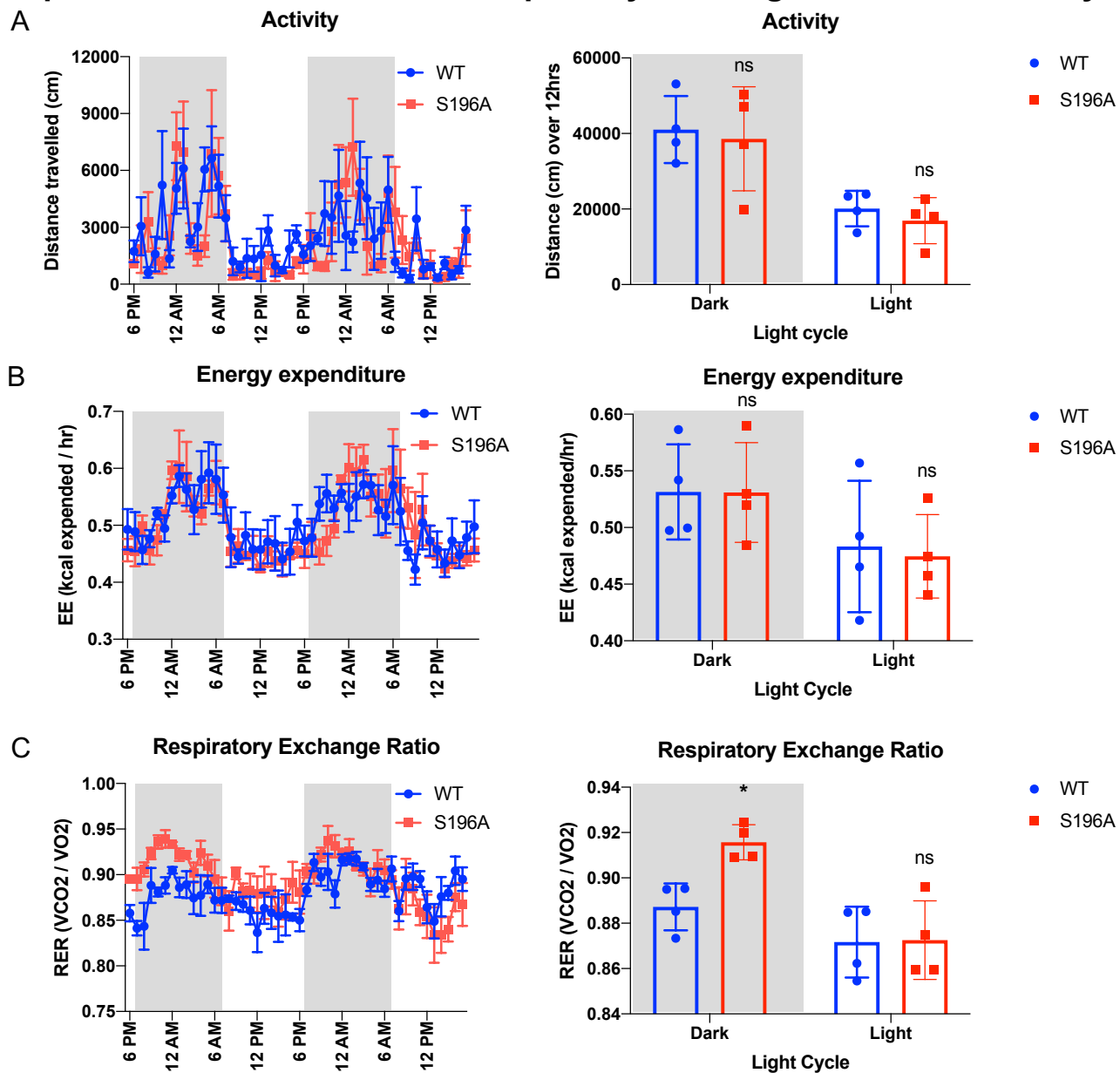
(A) Mouse body weight, (B) food intake, (C) bone mineral density and lean tissue quantification by DEXA scan were determined from *Ldlr*^{-/-} mice reconstituted with bone marrow from WT and S196A mice. (D) Representative F4/80 staining images (scale bar = 400 μ m), (E) quantification of F4/80 staining and (F) of crown-like structures of pWAT sections. Data are expressed as mean \pm SD (n=13 per group except for F4/80 staining and crown-like structure n=12) and obtained from independent samples. T test; *P<0.05.

Supplementary Figure 9: LXR α S196A increases adiponectin levels but does not affect UCP1 expression in BAT



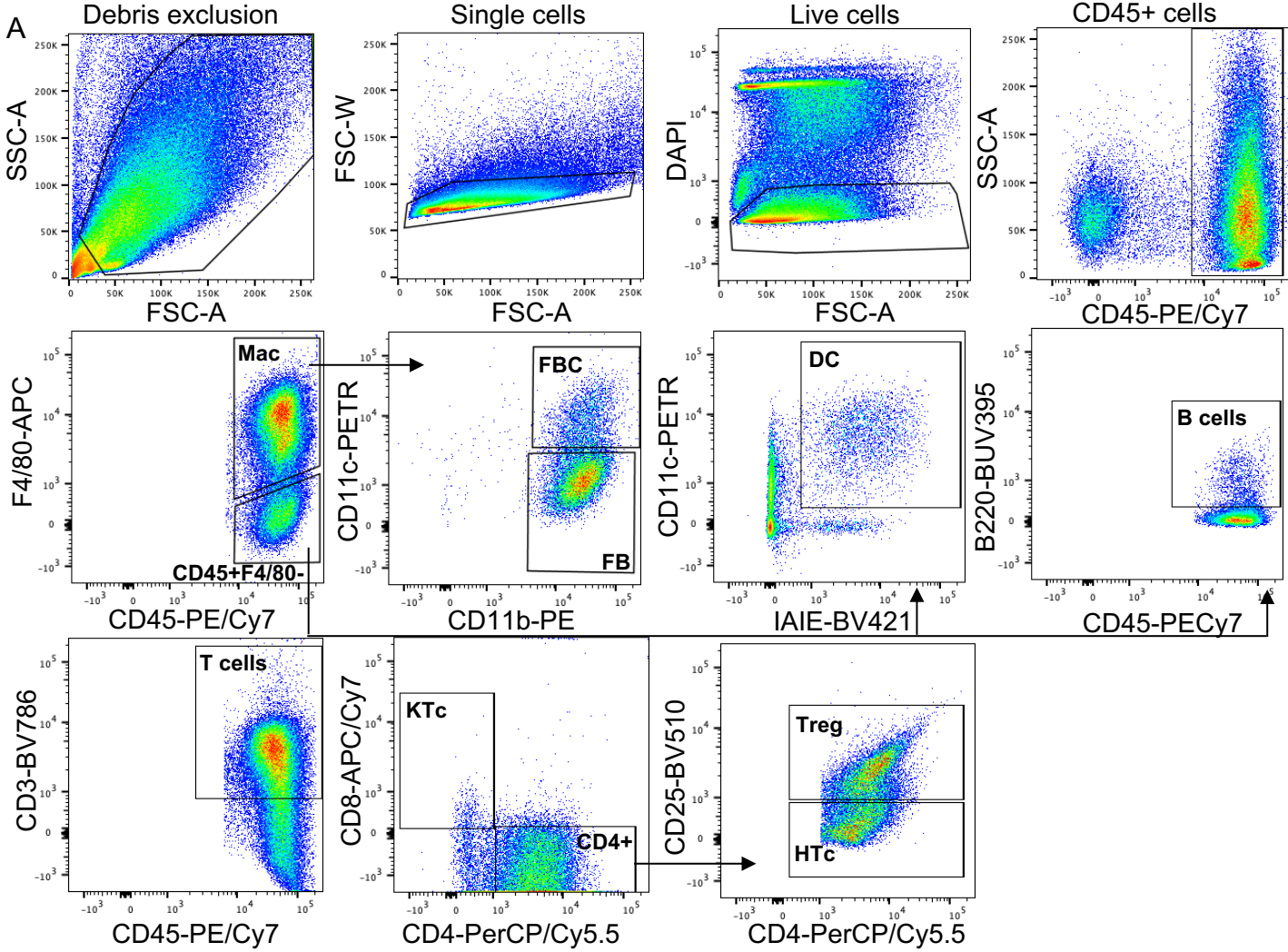
(A) Gene expression of adipocyte differentiation marker in pWAT adipocytes: *Adipoq* (Adiponectin), *Fabp4* (Fatty acid binding protein 4) and *Plin2* (Perilipin2), and (B) lipolysis activators: *Atgl* (Adipose triglyceride lipase) and *Hsl* (Hormone-sensitive lipase). (C) pWAT protein expression assessed by western blot and quantification of the adipocyte differentiation markers. (D) Plasma adiponectin level. Protein expression of UCP1 in brown adipose tissue (BAT) by (E) western blot, and (F) immunohistochemistry. Representative image of hematoxylin and eosin and UCP1 staining in BAT (scale bars: 400 μ m). Data are expressed as mean \pm SD ($n=6$ for gene expression and BAT protein expression, $n=5$ for pWAT protein expression, and $n=7$ for adiponectin level) and obtained from independent samples. T test; * $P<0.05$.

Supplementary Figure 10: LXR α S196A does not affect activity or energy expenditure but increases the respiratory exchange ratio in the dark cycle



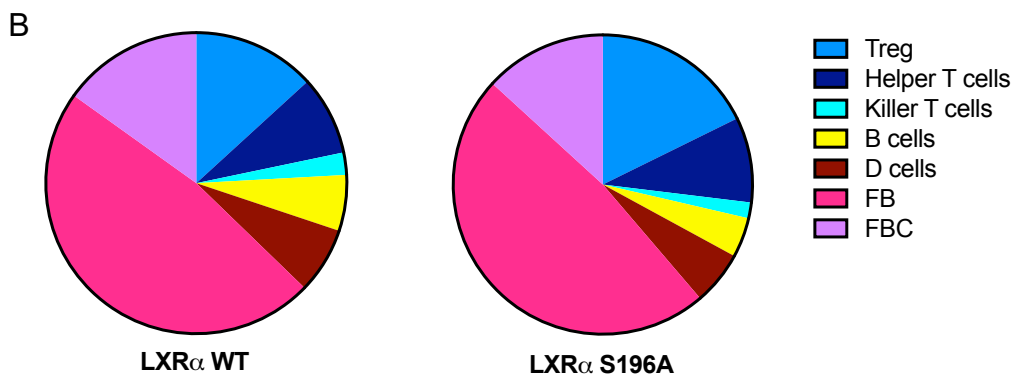
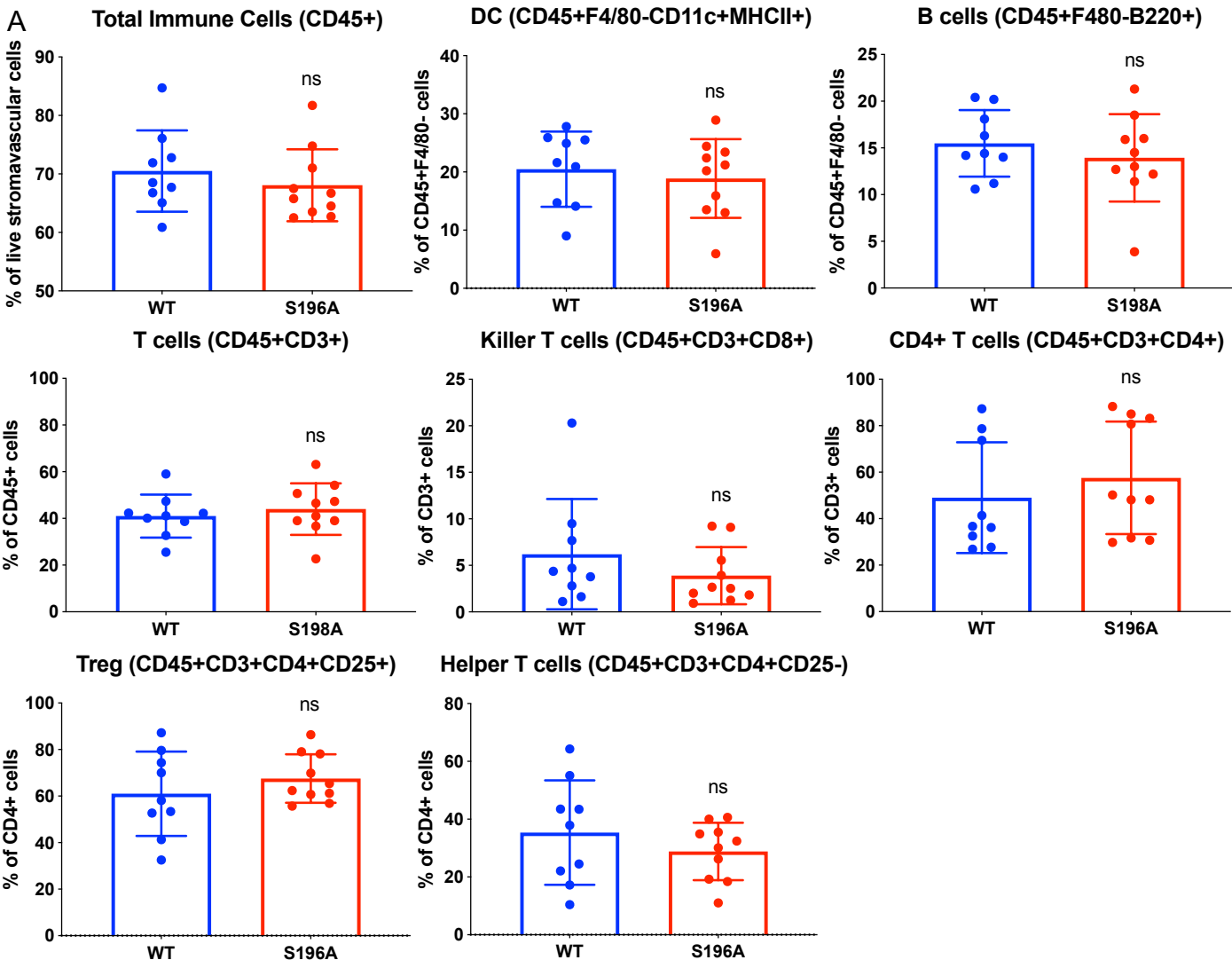
(A) Activity, (B) energy expenditure (EE), and (C) respiratory exchange ratio (RER) in LXR α WT or S196A fed a western diet for 16 weeks. Data are expressed as mean \pm SD (n=4) and obtained from independent samples. T test; *P<0.05.

Supplementary Figure 11: Flow cytometry of immune cells in pWAT



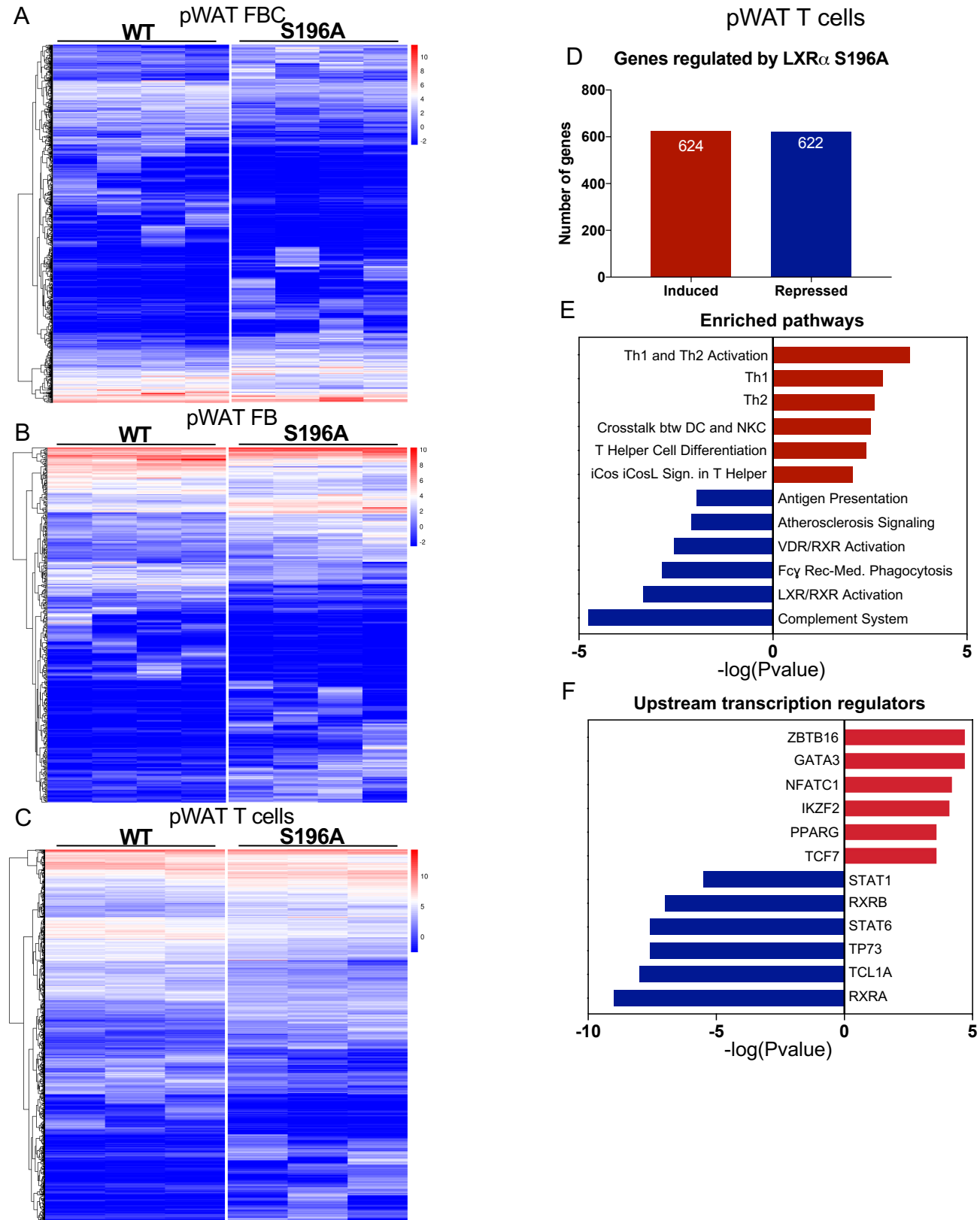
(A) Gating strategy for immune cells population in pWAT from mice expressing WT or S196A from the bone marrow.

Supplementary Figure 12: Effects of LXR α S196A on immune cells in adipose tissue



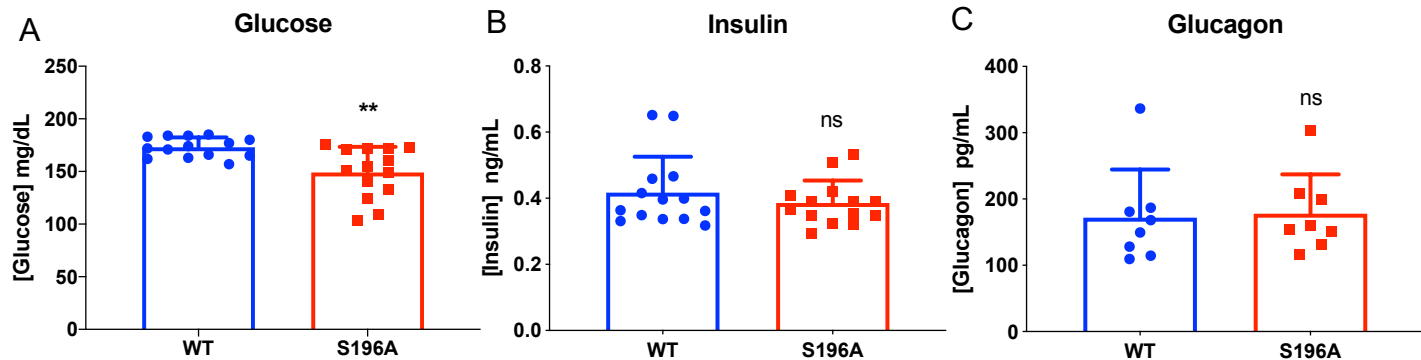
(A) Quantification of immune cells by flow cytometry in digested pWAT from *Ldlr*^{-/-} mice reconstituted bone marrow from WT and S196A mice. Total immune cells (CD45⁺ WT:70.50±6.96, S196A:68.07±6.15 %, p=0.4300), dendritic cells (DC WT:20.49±6.46, S196A:18.88±6.75%, p=0.6038), B cells (Bc WT:15.49±3.55, S196A:13.94±4.672%, p=0.4310), total T cells (CD3⁺ WT:41.00±9.24, S196A:44.02±11.04%, p=0.5292), Killer T cells (CD8⁺ WT:6.21±5.93, S196A:3.90±3.07%, p=0.2947), CD4⁺ T cells (CD4⁺ WT:49.01±23.84, S196A:57.58±24.23%, p=0.4487), Treg (CD4⁺C25⁺ WT:61.02±18.13, S196A:67.57±10.41%, p=0.3414), and Helper T cells (CD4⁺CD25⁻ WT:35.38±18.07, S196A:28.83±9.92 %, p=0.3343) populations. (B) Pie chart representing the percentage of different populations of immune cells in the pWAT. Data are expressed as mean ± SD (n=9/10 per group) and obtained from independent samples. T test.

Supplementary Figure 13: LXR α S196A ATMs regulate genes in pWAT T cells



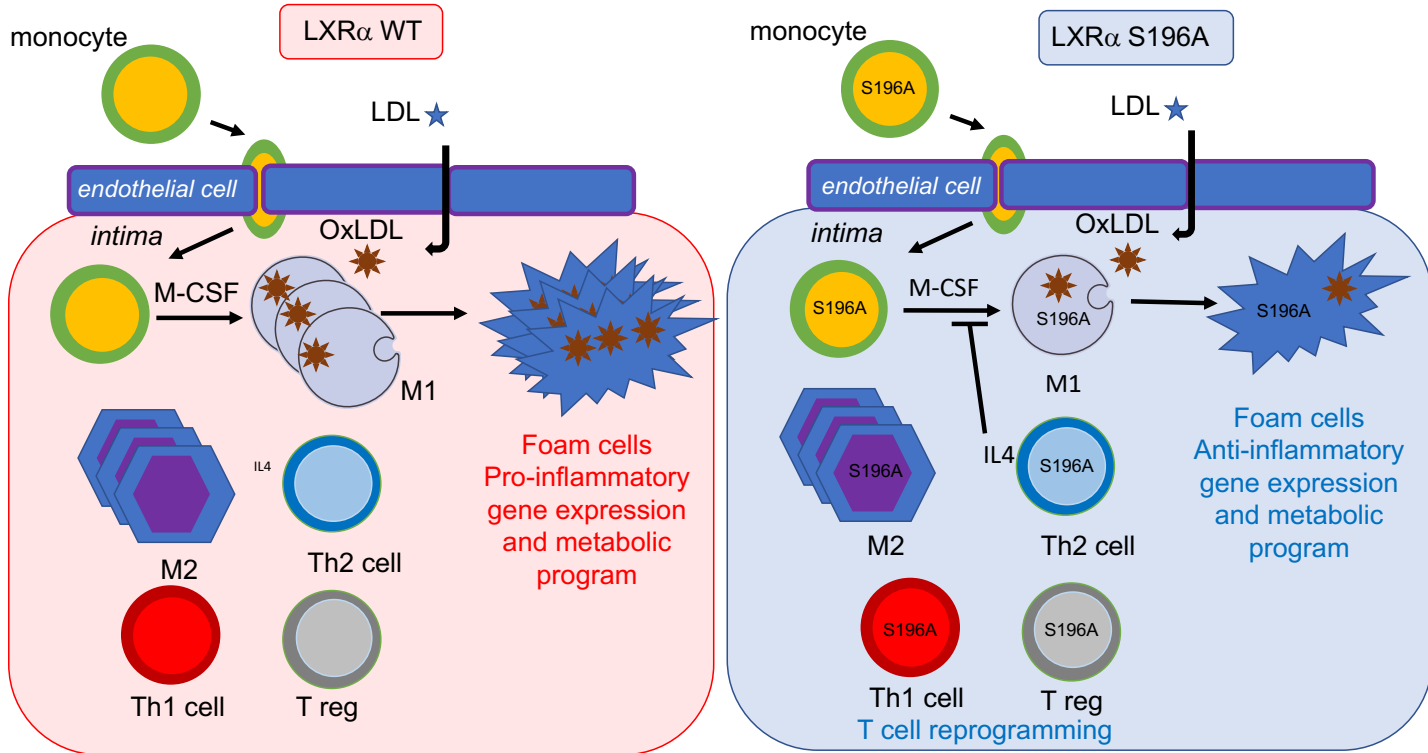
RNA seq analysis of pWAT T cells sorted by flow cytometry from LXR α S196A vs WT mice. (A) Heatmap of pWAT FBC cells from LXR α WT and S196A (RNA seq: 798 significant genes; LogFC > 1, FDR < 0.05). (B) Heatmap of pWAT FB cells from LXR α WT and S196A (RNA seq: 410 significant genes; LogFC > 1, FDR < 0.05). (C) Heatmap of pWAT T cells from LXR α WT and S196A (RNA seq: 1246 significant genes; LogFC > 1, FDR < 0.05). (D) Number of genes regulated in pWAT T cells by LXR α S196A versus WT (LogFC > 1, FDR < 0.05). (E) Enriched pathways in pWAT T cells in S196A after DGE analysis with IPA. (F) Transcriptional regulators controlling the upregulated or downregulated genes in pWAT T cells.

Supplementary Figure 14: Steady state blood glucose, insulin and glucagon levels in LXR α WT and S196A mice.



(A) Steady-state blood glucose levels from WT and S196A mice on western diet for 16 weeks was determined. Steady state (B) insulin and (C) glucagon levels were also determined from the same cohort of mice as the blood glucose measurements. Data are expressed as mean \pm SD (n=14 for glucose and insulin, and n=8 for glucagon) and obtained from independent samples. T test; **P<0.01.

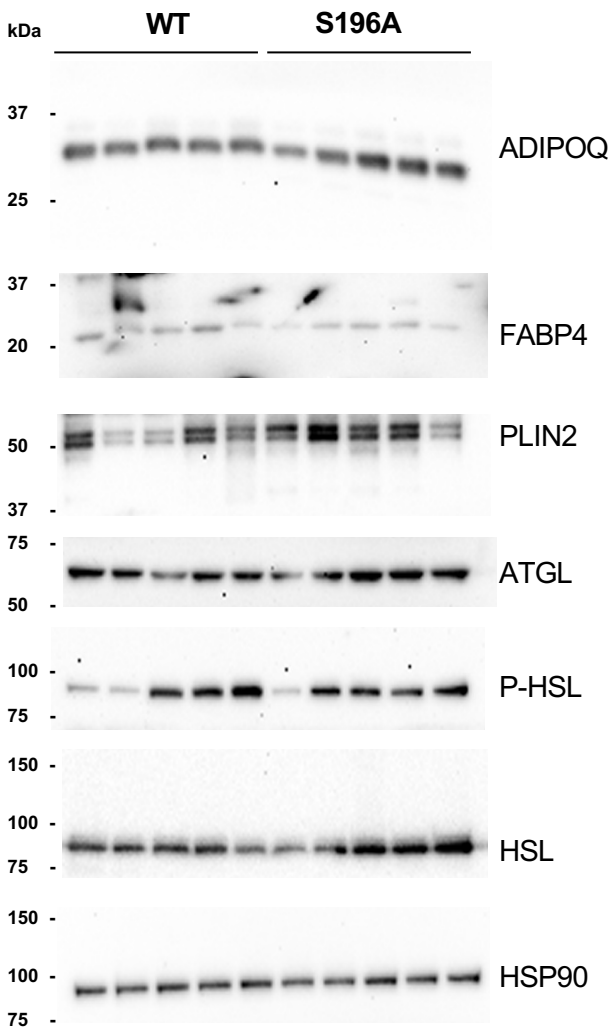
Supplementary Figure 15: Model for T cell-macrophage cross talk in the plaque of S196A mice



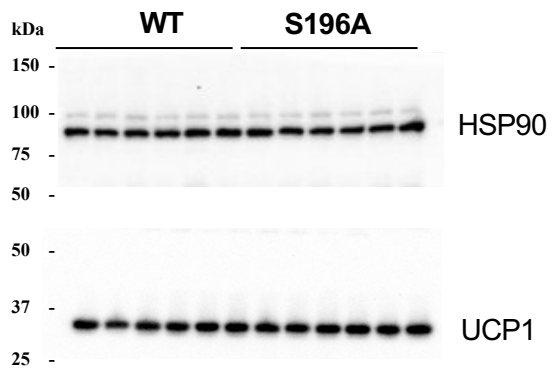
Mice expressing WT LXR α results in macrophage proliferation and atherosclerosis. In bone marrow transplant of S196A, where both innate and adaptive immune cells express S196A, we suggest that signals from T cells, such as IL4 from Th2 cells, are increased in S196A compared to WT, which can antagonize macrophage proliferation, promote a less inflammatory gene expression and metabolic phenotype in the plaque, thereby attenuating atherosclerosis. In the monocyte specific S196A mouse model in Gage *et al.*¹⁷, the increased expression of *Il4* from T cells would not occur because it expresses WT LXR α rather than LXR α S196A, and macrophage proliferation would not be restrained, therefore intensifying atherosclerosis. We have not included dendritic cells or B cells for simplicity. We posit similar effects could also be occurring in T cells in VAT that express LXR α S196A to restrain inflammatory macrophage accumulation.

Supplementary Figure 16: Complete western blots from Supplementary Figure 9

A Supplementary Figure 9C - western blot pWAT



B Supplementary Figure 9E - western blot BAT



Supplementary Table 1: Genes within IPA pathways in LXR α S196A versus WT from plaque CD68⁺ cells

| Mito. Function | |
|----------------|-------|
| Gene | LogFC |
| Cox7a1 | 8.54 |
| Cox8b | 6.80 |
| Cox6a2 | 6.78 |
| Cpt1b | 4.80 |
| Mapk10 | 4.09 |
| Ndufa5 | 1.84 |
| Atp5g1 | 1.50 |
| Atp5o | 1.42 |
| Ndufb9 | 1.41 |
| Ndufa4 | 1.41 |
| Aco2 | 1.38 |
| Cox7b | 1.29 |
| Pdha1 | 1.29 |
| Uqcrcf1 | 1.25 |
| Cycs | 1.20 |
| Ndufb11 | 1.18 |
| Cox6c | 1.17 |
| Atp5j | 1.11 |
| Atp5j2 | 1.09 |
| Atp5b | 1.08 |
| Cox7a2 | 1.07 |
| Atp5c1 | 1.07 |
| Ndufb4 | 1.04 |
| Ndufs3 | 1.04 |
| Atp5a1 | 0.95 |
| Atp5h | 0.90 |
| Ndufb4 | 1.04 |
| Ndufs3 | 1.04 |
| Atp5a1 | 0.95 |
| Pink1 | 0.92 |
| Prdx3 | 0.91 |
| Atp5h | 0.90 |
| Ndufs1 | 0.89 |
| Cox4i1 | 0.88 |
| Ndufa13 | 0.87 |
| Atp5g3 | 0.86 |
| Vdac1 | 0.85 |
| Ndufs2 | 0.83 |
| Atp5i | 0.62 |
| Ogdh | 0.62 |

| Oxphos | |
|---------|-------|
| Gene | LogFC |
| Cox7a1 | 8.54 |
| Cox8b | 6.80 |
| Cox6a2 | 6.78 |
| Ndufa5 | 1.84 |
| Atp5g1 | 1.50 |
| Atp5o | 1.42 |
| Ndufb9 | 1.41 |
| Ndufa4 | 1.41 |
| Cox7b | 1.29 |
| Uqcrcf1 | 1.25 |
| Cycs | 1.20 |
| Ndufb11 | 1.18 |
| Cox6c | 1.17 |
| Atp5j | 1.11 |
| Atp5j2 | 1.09 |
| Atp5b | 1.08 |
| Cox7a2 | 1.07 |
| Atp5c1 | 1.07 |
| Ndufb4 | 1.04 |
| Ndufs3 | 1.04 |
| Atp5a1 | 0.95 |
| Atp5h | 0.90 |
| Ndufs1 | 0.89 |
| Cox4i1 | 0.88 |
| Ndufa13 | 0.87 |
| Atp5g3 | 0.86 |
| Ndufs2 | 0.83 |
| Atp5i | 0.62 |

| Sirtuin Signaling | |
|-------------------|-------|
| Gene | LogFC |
| Pgam2 | 6.25 |
| Ppargc1a | 5.21 |
| Ppara | 4.82 |
| Cpt1b | 4.80 |
| Rarb | 4.37 |
| Slc25a4 | 2.45 |
| Ndufa5 | 1.84 |
| Idh2 | 1.65 |
| Pdk1 | 1.56 |
| Atp5g1 | 1.50 |
| Ndufb9 | 1.41 |
| Ndufa4 | 1.41 |
| Pdha1 | 1.29 |
| Uqcrcf1 | 1.25 |
| Ndufb11 | 1.18 |
| Atp5j | 1.11 |
| Atp5b | 1.08 |
| Atp5c1 | 1.07 |
| Ndufb4 | 1.04 |
| Ndufs3 | 1.04 |
| Acadl | 1.00 |
| Got2 | 0.97 |
| Atp5a1 | 0.95 |
| Ndufs1 | 0.89 |
| Ndufa13 | 0.87 |
| Atp5g3 | 0.85 |
| Ndufs2 | 0.83 |

| TCA Cycle | |
|-----------|-------|
| Gene | LogFC |
| Mdh1 | 1.69 |
| Aco2 | 1.38 |
| Idh3a | 1.30 |
| Fh1 | 1.16 |
| Mdh2 | 1.02 |
| Cs | 0.74 |
| Ogdh | 0.62 |

| β -adrenergic Signaling | |
|-------------------------------|-------|
| Gene | LogFC |
| Ppp1r3a | 6.19 |
| Ryr2 | 5.70 |
| Cacna1s | 5.47 |
| Ppp1r3c | 5.28 |
| Adcy1 | 4.56 |
| Ppp1r14c | 4.18 |
| Akap6 | 3.47 |
| Pde1c | 2.70 |
| Atp2a2 | 2.39 |
| Ppp2r3a | 1.70 |
| Prkag2 | 1.06 |
| Slc8a1 | 0.75 |

| PKA Signaling | |
|---------------|-------|
| Gene | LogFC |
| Myl7 | 13.56 |
| Myl1 | 11.60 |
| Myl4 | 10.06 |
| Mylk3 | 8.89 |
| Ttn | 7.53 |
| Tnni3 | 7.45 |
| Ppp1r3a | 6.19 |
| Ryr2 | 5.70 |
| Pygm | 5.34 |
| Ppp1r3c | 5.28 |
| Myl3 | 4.75 |
| Adcy1 | 4.56 |
| Ryr3 | 4.47 |
| Ppp1r14c | 4.18 |
| Akap6 | 3.47 |
| Pde1c | 2.70 |
| Pygb | 1.09 |
| Prkag2 | 1.06 |

| NFAT in Immune cells | |
|----------------------|-------|
| Gene | LogFC |
| Cd79b | -3.26 |
| Cd86 | -1.68 |
| Lcp2 | -0.99 |
| H2-Aa | -0.88 |
| Pik3cg | -0.84 |
| H2-Eb1 | -0.83 |
| Nfatc2 | -0.79 |
| Lyn | -0.77 |
| H2-Ab1 | -0.76 |

| Antigen Presentation | |
|----------------------|-------|
| Gene | LogFC |
| Gm11127 | -2.02 |
| H2-Aa | -0.88 |
| H2-Eb1 | -0.83 |
| Cd74 | -0.83 |
| H2-Ab1 | -0.76 |

| Leukocyte Extravasation | |
|-------------------------|-------|
| Gene | LogFC |
| Nox1 | -5.76 |
| Itgal | -1.98 |
| Prkcb | -1.93 |
| Rasgrp1 | -1.83 |
| Arhgap4 | -1.50 |
| Rac2 | -1.30 |
| Spn | -1.24 |
| Pik3cg | -0.84 |
| Ncf1 | -0.77 |
| Itgam | -0.72 |

| FC γ Recep-Med Phag | |
|----------------------------|-------|
| Gene | LogFC |
| Prkcb | -1.93 |
| Rac2 | -1.30 |
| Fyb | -1.28 |
| Pld4 | -1.14 |
| Lcp2 | -0.99 |
| Hck | -0.97 |
| Pik3cg | -0.84 |
| Lyn | -0.77 |
| Ncf1 | -0.77 |

| Neuro-Inflammation Sig | |
|------------------------|-------|
| Gene | LogFC |
| Nox1 | -5.76 |
| Cxcl10 | -4.52 |
| Il10 | -3.52 |
| Gm11127 | -2.02 |
| Grin1 | -1.91 |
| Cd86 | -1.68 |
| Tlr1 | -1.36 |
| Irak3 | -1.18 |
| Tlr9 | -1.04 |
| H2-Aa | -0.88 |
| Pik3cg | -0.84 |
| H2-Eb1 | -0.83 |
| Nfatc2 | -0.79 |
| Ncf1 | -0.77 |
| H2-Ab1 | -0.76 |
| Birc3 | -0.62 |

| Comm Btw Immune cells | |
|-----------------------|-------|
| Gene | LogFC |
| Cxcl10 | -4.52 |
| Il10 | -3.52 |
| Cd79b | -3.26 |
| Gm11127 | -2.02 |
| Ighm | -2.00 |
| Cd86 | -1.68 |
| Tlr1 | -1.36 |
| Ccl3 | -1.18 |
| Ccl9 | -1.11 |
| Tlr9 | -1.04 |
| Cd83 | -1.00 |
| H2-Eb1 | -0.83 |

Supplementary Table 2: Genes within IPA pathways in LXR α S196A versus WT from plaque T cells

| Cholesterol Bios. P. | |
|----------------------|-------|
| Gene | LogFC |
| Acat3 | 4.10 |
| Idi2 | 3.07 |
| Sqle | 1.73 |
| Tm7sf2 | 1.51 |
| Msmo1 | 1.19 |
| Ggps1 | 1.14 |
| Acat1 | 1.03 |

| Apelin Liver S. | |
|-----------------|-------|
| Gene | LogFC |
| Col18a1 | 4.39 |
| Pdgfrb | 4.29 |
| Col1a2 | 3.61 |
| Aplnr | 2.55 |
| Col3a1 | 2.13 |
| Col1a1 | 1.72 |

| GP6 Signaling | |
|---------------|-------|
| Gene | LogFC |
| Col5a2 | 5.76 |
| Lama2 | 4.87 |
| Col18a1 | 4.39 |
| Col6a1 | 3.94 |
| Col1a2 | 3.61 |
| Col4a1 | 3.60 |
| Lama4 | 2.85 |
| Col4a6 | 2.27 |
| Col15a1 | 2.16 |
| Col3a1 | 2.13 |
| Col1a1 | 1.72 |
| Lamb3 | 1.23 |
| Rasgrp2 | 1.11 |

| Wnt/ β -catenin Sign. | |
|-----------------------------|-------|
| Gene | LogFC |
| Wnt10b | 6.45 |
| Sox6 | 5.43 |
| Wnt3 | 5.23 |
| Hnf1a | 5.04 |
| Wnt16 | 4.86 |
| Sox17 | 3.74 |
| Sox9 | 3.46 |
| Tgfb3 | 2.71 |
| Tgfb2 | 2.54 |
| Sox1 | 2.30 |
| Cdh5 | 2.29 |
| Rarb | 2.03 |
| Fzd1 | 1.87 |
| Ppp2r3a | 1.83 |
| Lef1 | 1.80 |
| Ppp2r5b | 1.68 |
| Gja1 | 1.21 |

| ILK Signaling | |
|---------------|-------|
| Gene | LogFC |
| Myh11 | 4.67 |
| Myh14 | 3.82 |
| Vegfc | 3.41 |
| Lims2 | 3.33 |
| Myl9 | 2.96 |
| Fblim1 | 2.63 |
| Rac3 | 2.40 |
| Fermt2 | 2.08 |
| Rhoj | 2.07 |
| Snai2 | 1.99 |
| Ppp2r3a | 1.83 |
| Lef1 | 1.80 |
| Ppp2r5b | 1.68 |
| Rps6ka5 | 1.62 |
| Actn2 | 1.53 |
| Actn1 | 1.48 |
| Casp3 | 1.28 |
| Rnd1 | 1.03 |

| Reg. EMT Transition | |
|---------------------|-------|
| Gene | LogFC |
| Wnt10b | 6.45 |
| Wnt3 | 5.23 |
| Hnf1a | 5.04 |
| Wnt16 | 4.86 |
| Lox | 2.91 |
| Aph1a | 2.02 |
| Snai2 | 1.99 |
| Fzd1 | 1.87 |
| Lef1 | 1.80 |
| Brc1 | 1.67 |

| Gas Signaling | |
|---------------|-------|
| Gene | LogFC |
| Gng11 | -6.58 |
| Cngb3 | -6.21 |
| Prkar1b | -6.06 |
| Pth1r | -5.49 |
| Rapgef3 | -5.37 |
| Adcy5 | -5.37 |
| Creb3l4 | -5.20 |
| Creb3l3 | -5.13 |
| Chrm3 | -4.45 |
| Gnb3 | -4.00 |
| Adora2a | -2.77 |
| Ptgir | -2.54 |
| Gnb5 | -2.05 |
| Adcy9 | -2.00 |
| Ryr1 | -1.43 |
| Prkaca | -1.29 |
| Creb3 | -1.07 |
| Mapk3 | -1.04 |

| Axonal Guidance Sign. | |
|-----------------------|-------|
| Gene | LogFC |
| Efn2 | -8.24 |
| Pdgfrb | -7.79 |
| Adamts13 | -7.36 |
| Gng11 | -6.58 |
| Adam21 | -6.44 |
| Prkar1b | -6.06 |
| Wnt9a | -6.02 |
| Adamdec1 | -5.99 |
| Myl2 | -5.89 |
| Erb2 | -5.88 |
| Mmp2 | -5.82 |
| Plxn3 | -5.70 |
| Rhod | -5.63 |
| Opn1sw | -5.50 |
| Bmp10 | -5.44 |
| Myl7 | -5.35 |
| Pik3r3 | -5.28 |
| Myl6b | -5.11 |
| Adam30 | -4.93 |
| Gm4787 | -4.72 |
| Mmp27 | -4.41 |
| Mmp28 | -4.40 |
| Lrrc4c | -4.39 |
| Mmp23 | -4.27 |
| Mmp20 | -4.23 |
| Wnt8b | -4.07 |
| Gnb3 | -4.00 |
| Prkcz | -3.88 |
| Prkcg | -3.79 |
| Adam32 | -3.75 |
| Mmp8 | -3.68 |
| Ablim2 | -3.37 |
| Fzd4 | -3.15 |
| Kif7 | -2.76 |
| Pik3r2 | -2.71 |
| Unc5b | -2.67 |
| Ablim3 | -2.51 |
| Sema6b | -2.22 |
| Rgs3 | -2.18 |
| Pdgfa | -2.16 |
| Ptch1 | -2.15 |
| Glis2 | -2.13 |
| Gnb5 | -2.05 |
| Gna15 | -1.99 |
| Pik3c3 | -1.93 |
| Sema6d | -1.61 |
| Chmp1a | -1.61 |
| Ace | -1.50 |
| Rras | -1.40 |
| Crkl | -1.38 |
| Klc1 | -1.32 |
| Prkaca | -1.29 |
| Limk2 | -1.28 |
| Sufu | -1.09 |
| Itsn1 | -1.08 |
| Mapk3 | -1.04 |
| Mmp14 | -1.01 |

| Glutathione-Med. Detox | |
|------------------------|-------|
| Gene | LogFC |
| Gstm5 | -7.40 |
| Gstm4 | -6.59 |
| Gstp2 | -5.43 |
| Mgst1 | -3.05 |
| Lanc1 | -1.82 |
| Ggh | -1.18 |
| Gsto1 | -1.08 |
| Gstz1 | -1.03 |

| Xenobiotic Met. Sign. | |
|-----------------------|-------|
| Gene | LogFC |
| Gal3st2 | -8.74 |
| Gstm5 | -7.40 |
| Hs3st3a1 | -7.23 |
| Nos2 | -6.93 |
| Gstm4 | -6.59 |
| Gstp2 | -5.43 |
| Pik3r3 | -5.28 |
| Aldh5a1 | -5.19 |
| Hs6st2 | -4.79 |
| Prkcz | -3.88 |
| Prkcg | -3.79 |
| Cyp1b1 | -3.05 |
| Mgst1 | -3.05 |
| Map3k13 | -3.02 |
| Pik3r2 | -2.71 |
| Chst2 | -2.69 |
| Map3k10 | -2.69 |
| Aldh3b1 | -2.58 |
| Ugt1a7c | -2.38 |
| Mgmt | -2.23 |
| Camk2a | -1.97 |
| Map2k6 | -1.95 |
| Pik3c3 | -1.93 |
| Chst1 | -1.91 |
| Aldh6a1 | -1.68 |
| Aip | -1.44 |
| Ndst2 | -1.43 |
| Rras | -1.40 |
| Fmo5 | -1.37 |
| Aldh1a2 | -1.25 |
| Camk1 | -1.20 |
| Map3k11 | -1.14 |
| Gsto1 | -1.08 |
| Mapk3 | -1.04 |
| Gstz1 | -1.03 |
| Map2k4 | -1.02 |
| Aldh9a1 | -1.01 |

| Oleate Biosynthesis | |
|---------------------|-------|
| Gene | LogFC |
| Ufsp1 | -5.44 |
| Fads2 | -4.18 |
| Cyb5a | -2.28 |
| Fads1 | -1.86 |
| Aldh6a1 | -1.68 |
| Ptprt | -1.65 |

| Colorectal Cancer Met. | |
|------------------------|-------|
| Gene | LogFC |
| Nos2 | -6.93 |
| Gng11 | -6.58 |
| Prkar1b | -6.06 |
| Wnt9a | -6.02 |
| Mmp2 | -5.82 |
| Ptger3 | -5.74 |
| Rhod | -5.63 |
| Adcy5 | -5.37 |
| Pik3r3 | -5.28 |
| Rhov | -5.28 |
| Mmp27 | -4.41 |
| Mmp28 | -4.40 |
| Mmp23 | -4.27 |
| Mmp20 | -4.23 |
| Wnt8b | -4.07 |
| Gnb3 | -4.00 |
| Mapk10 | -3.82 |
| Mmp8 | -3.68 |
| Tlr12 | -3.52 |
| Fzd4 | -3.15 |
| Tlr6 | -2.93 |
| Pik3r2 | -2.71 |
| Gnb5 | -2.05 |
| Adcy9 | -2.00 |
| Tlr5 | -1.95 |
| Pik3c3 | -1.93 |
| Mmp19 | -1.59 |
| Rras | -1.40 |
| Tcf7l2 | -1.29 |
| Prkaca | -1.29 |
| Casp9 | -1.15 |
| Rhot2 | -1.11 |
| Tlr11 | -1.10 |
| Egfr | -1.08 |
| Smad2 | -1.08 |
| Trp53 | -1.05 |
| Mapk3 | -1.04 |
| Map2k4 | -1.02 |
| Mmp14 | -1.01 |

Supplementary Table 3: Genes within IPA pathways in LXR α S196A versus WT from pWAT FBC

| Glutamate Degradation | |
|-----------------------|-------|
| Gene | LogFC |
| Abat | 2.21 |
| Suclg2 | 1.61 |

| Glutathione Redox R. | |
|----------------------|-------|
| Gene | LogFC |
| Gpx5 | 7.24 |
| Gstp-ps | 5.88 |
| Gpx2 | 4.06 |

| Apelin Adipocyte Sign. | |
|------------------------|-------|
| Gene | LogFC |
| Gpx5 | 7.24 |
| Gstp-ps | 5.88 |
| Gpx2 | 4.06 |
| Mapk4 | 2.76 |
| Adcy6 | 2.14 |

| Matrix Metallop. Inh. | |
|-----------------------|-------|
| Gene | LogFC |
| Mmp1a | 5.96 |
| Mmp28 | 3.39 |
| Mmp15 | 1.34 |

| GABA Recept. Sign. | |
|--------------------|-------|
| Gene | LogFC |
| Abat | 2.21 |
| Adcy6 | 2.14 |
| Cacna1c | 1.78 |
| Kcnq3 | 1.16 |

| Lip./Lip. Rafts in Influ. | |
|---------------------------|-------|
| Gene | LogFC |
| Ifng | 4.38 |
| Ifnk | 3.90 |

| Endothelin-1 Sign. | |
|--------------------|-------|
| Gene | LogFC |
| Pla2g2e | -5.97 |
| Gucy2c | -3.90 |
| Gnai1 | -2.94 |
| Abhd3 | -2.75 |
| Casq1 | -2.67 |
| Pla2r1 | -1.01 |

| Myc-Med. Apoptosis | |
|--------------------|-------|
| Gene | LogFC |
| FasI | -4.96 |
| Cdkn2a | -4.58 |
| Prkag1 | -1.07 |

| Wnt/ β -catenin Sign. | |
|-----------------------------|-------|
| Gene | LogFC |
| Hnf1a | -5.86 |
| Cdkn2a | -4.58 |
| Wnt5a | -2.28 |
| Ppm1l | -1.67 |
| Lrp5 | -1.06 |
| Ppard | -1.02 |

| Fatty Acid Oxidation | |
|----------------------|-------|
| Gene | LogFC |
| Bco2 | -1.85 |
| Aldh3b3 | -1.74 |

| Atherosclerosis Sign. | |
|-----------------------|-------|
| Gene | LogFC |
| Pla2g2e | -5.97 |
| Clu | -4.18 |
| Alox15 | -3.86 |
| Abhd3 | -2.75 |
| Apom | -2.40 |
| Pla2r1 | -1.01 |

| Eicosanoid Signaling | |
|----------------------|-------|
| Gene | LogFC |
| Pla2g2e | -5.97 |
| Ptgis | -5.69 |
| Alox15 | -3.86 |
| Abhd3 | -2.75 |
| Pla2r1 | -1.01 |

Supplementary Table 4: Genes within IPA pathways in LXR α S196A versus WT from pWAT FB

| Hematopoiesis fr. PSC | |
|-----------------------|-------|
| Gene | LogFC |
| Il5 | 5.80 |
| Csf2 | 3.66 |
| Il12b | 3.15 |
| Cd3g | 1.77 |

| Hematopoiesis fr. MSC | |
|-----------------------|-------|
| Gene | LogFC |
| Il5 | 5.80 |
| Csf2 | 3.66 |

| Cytokine Prod. in Mac. | |
|------------------------|-------|
| Gene | LogFC |
| Csf2 | 3.66 |
| Il12b | 3.15 |

| Glycolysis | |
|------------|-------|
| Gene | LogFC |
| Aldob | 4.43 |
| Eno4 | 1.18 |

| Gluconeogenesis | |
|-----------------|-------|
| Gene | LogFC |
| Aldob | 4.43 |
| Eno4 | 1.18 |

| Pyruvate Fermentation | |
|-----------------------|-------|
| Gene | LogFC |
| Ldhc | 4.53 |

| PI3K/AKT | |
|----------|-------|
| Gene | LogFC |
| Itga3 | -2.94 |
| Il21r | -1.41 |
| Il2rg | -1.11 |
| Ikbke | -1.07 |

| IL7 Signaling | |
|---------------|-------|
| Gene | LogFC |
| Dntt | -5.87 |
| Ighg2c | -5.59 |
| Il2rg | -1.11 |

| Mol. Mech. of Cancer | |
|----------------------|-------|
| Gene | LogFC |
| Wnt8b | -3.65 |
| Prkar1b | -3.03 |
| Itga3 | -2.94 |
| Smad9 | -2.35 |
| Wnt5a | -2.02 |
| Bmp8b | -1.90 |
| E2f8 | -1.22 |

| Hepatic Fibrosis Sign. | |
|------------------------|-------|
| Gene | LogFC |
| Wnt8b | -3.65 |
| Prkar1b | -3.03 |
| Itga3 | -2.94 |
| Ednra | -2.52 |
| Spp1 | -2.39 |
| Wnt5a | -2.02 |
| Ikbke | -1.07 |

| NANOG in ESC Pluripot. | |
|------------------------|-------|
| Gene | LogFC |
| Wnt8b | -3.65 |
| Smad9 | -2.35 |
| Wnt5a | -2.02 |
| Bmp8b | -1.90 |

| Primary Immunodef. S. | |
|-----------------------|-------|
| Gene | LogFC |
| Cd19 | -6.10 |
| Ada | -2.18 |
| Il2rg | -1.11 |

Supplementary Table 5: Genes within IPA pathways in LXR α S196A versus WT from pWAT T cells

| Th1 and Th2 Activation | |
|------------------------|-------|
| Gene | LogFC |
| Il4 | 3.54 |
| Ccr3 | 3.08 |
| Acvr1c | 2.98 |
| Klrc1 | 2.16 |
| Cd40lg | 2.07 |
| Icos | 1.58 |
| Il2rb | 1.40 |
| Cd3g | 1.40 |
| Ifng | 1.38 |
| Cd28 | 1.30 |
| Cd3d | 1.28 |
| Il18r1 | 1.25 |

| Th1 | |
|--------|-------|
| Gene | LogFC |
| Il4 | 3.54 |
| Klrc1 | 2.16 |
| Cd40lg | 2.07 |
| Icos | 1.58 |
| Cd3g | 1.40 |
| Ifng | 1.38 |
| Cd28 | 1.30 |
| Cd3d | 1.28 |
| Il18r1 | 1.25 |

| Th2 | |
|--------|-------|
| Gene | LogFC |
| Il4 | 3.54 |
| Ccr3 | 3.08 |
| Acvr1c | 2.98 |
| Icos | 1.58 |
| Il2rb | 1.40 |
| Cd3g | 1.40 |
| Ifng | 1.38 |
| Cd28 | 1.30 |
| Cd3d | 1.28 |

| Crosstalk btw DC & NKC | |
|------------------------|-------|
| Gene | LogFC |
| Il4 | 3.54 |
| Csf2 | 2.79 |
| Cd40lg | 2.07 |
| Camk2b | 2.03 |
| Il2rb | 1.40 |
| Ifng | 1.38 |
| Cd28 | 1.30 |

| T Helper Cell Different. | |
|--------------------------|-------|
| Gene | LogFC |
| Il4 | 3.54 |
| Cd40lg | 2.07 |
| Icos | 1.58 |
| Ifng | 1.38 |
| Cd28 | 1.30 |
| Il18r1 | 1.25 |

| iCos iCosL Sign. In T H. | |
|--------------------------|-------|
| Gene | LogFC |
| Cd40lg | 2.07 |
| Camk2b | 2.03 |
| Icos | 1.58 |
| Il2rb | 1.40 |
| Cd3g | 1.40 |
| Cd28 | 1.30 |
| Cd3d | 1.28 |

| Antigen Presentation | |
|----------------------|-------|
| Gene | LogFC |
| Psm5 | -1.67 |
| Clita | -1.26 |
| H2-DMb1 | -1.08 |
| H2-Eb1 | -1.06 |

| Atherosclerosis Sign. | |
|-----------------------|-------|
| Gene | LogFC |
| Rbp4 | -6.40 |
| Mmp13 | -2.59 |
| Ccl12 | -2.28 |
| Lyz1 | -2.20 |
| Pdgfa | -2.18 |
| Lpl | -1.56 |
| Apoe | -1.15 |
| Pcyox1 | -1.13 |

| VDR/RXR Activation | |
|--------------------|-------|
| Gene | LogFC |
| Igf1bp6 | -3.17 |
| Pdgfa | -2.18 |
| Hr | -2.06 |
| Vdr | -1.51 |
| Cebpa | -1.36 |
| Ppard | -1.27 |
| Cd14 | -1.01 |

| FC γ Rec-Med. Phagocyt. | |
|--------------------------------|-------|
| Gene | LogFC |
| Src | -2.78 |
| Mapk3 | -1.63 |
| Fcgr3 | -1.22 |
| Ncf1 | -1.21 |
| Fgr | -1.20 |
| Dock1 | -1.17 |
| Syk | -1.09 |
| Hck | -1.07 |

| LXR/RXR Activation | |
|--------------------|-------|
| Gene | LogFC |
| Rbp4 | -6.40 |
| Ccl12 | -2.28 |
| Lyz1 | -2.20 |
| Lpl | -1.56 |
| Il1rl2 | -1.55 |
| Apoe | -1.15 |
| Pcyox1 | -1.13 |
| Pltp | -1.08 |
| Scd1 | -1.04 |
| Cd14 | -1.01 |

| Complement System | |
|-------------------|-------|
| Gene | LogFC |
| C6 | -3.01 |
| C1qc | -2.07 |
| C5ar1 | -1.93 |
| Cr2 | -1.75 |
| C1qb | -1.64 |
| C1qa | -1.49 |
| C3ar1 | -1.15 |

Supplementary Table 6: Cytokines differentially expressed in LXR α WT versus S196A macrophages and T cells from plaque and pWAT

| Cytokine gene symbols | |
|-----------------------|--------|
| Human | Mouse |
| IL1B | Il1b |
| IL27 | Il27 |
| IFNG | Ifng |
| IL1A | Il1a |
| TNF | Tnf |
| ICAM1 | Icam1 |
| IL6 | Il6 |
| CXCL1 | |
| CCL4 | Ccl4 |
| CXCL2 | Cxcl1 |
| CCL3 | Ccl3 |
| CXCL9 | Cxcl9 |
| CXCL10 | Cxcl10 |
| CCL2 | Ccl12 |
| CCL5 | Ccl5 |
| TIMP1 | Timp1 |
| IL4 | Il4 |
| IL13 | Il13 |
| IL10 | Il10 |
| CCL1 | Ccl1 |
| IL1RN | Il1rn |

| Plaque CD68+ cells S196A vs WT | | | | | |
|--------------------------------|------------|------------|------------|------------|------------------|
| Gene | logFC | logCPM | PValue | FDR | IN CYTOKINE LIST |
| Cxcl10 | -4.5181803 | 6.81757319 | 2.87E-06 | 0.00145392 | TRUE |
| Il10 | -3.5216461 | 5.94293414 | 0.00727541 | 0.58578367 | TRUE |
| Ccl3 | -1.1810085 | 6.74318444 | 0.03047074 | 1 | TRUE |

| Plaque T cells S196A vs WT | | | | | |
|----------------------------|------------|------------|------------|------------|------------------|
| Gene | logFC | logCPM | PValue | FDR | IN CYTOKINE LIST |
| Il27 | -5.0374382 | -0.1602636 | 1.91E-05 | 0.00034184 | TRUE |
| * Il4 | 5.33269845 | 0.96143339 | 2.40E-05 | 0.00040759 | TRUE |
| Ccl1 | -6.28282 | -1.3368069 | 0.00026277 | 0.00261577 | TRUE |
| Il10 | -1.2065791 | 5.94293414 | 0.00149055 | 0.00985684 | TRUE |
| Il13 | -3.5241425 | -0.8243496 | 0.03704799 | 0.10843988 | TRUE |

| pWAT FBC S196A vs WT | | | | | |
|----------------------|------------|------------|------------|------------|------------------|
| Gene | logFC | logCPM | PValue | FDR | IN CYTOKINE LIST |
| Ifng | 4.37547134 | 3.53356936 | 4.37E-05 | 0.00406814 | TRUE |
| Timp1 | 2.14935947 | 3.18141075 | 0.00517614 | 0.07674798 | TRUE |
| Il1a | 1.79310939 | 4.82842474 | 0.01678632 | 0.15108412 | TRUE |
| Ccl1 | 3.445453 | -1.3368069 | 0.02049116 | 0.16893682 | TRUE |
| Cxcl9 | 0.61220416 | 6.43347952 | 0.02863999 | 0.2031894 | TRUE |
| Cxcl10 | 0.60291901 | 6.81757319 | 0.04435914 | 0.25779763 | TRUE |

| pWAT FB S196A vs WT | | | | | |
|---------------------|------------|------------|------------|------------|------------------|
| Gene | logFC | logCPM | PValue | FDR | IN CYTOKINE LIST |
| Il1rn | -0.6892813 | 7.64877318 | 0.01738561 | 0.18644874 | TRUE |
| Il13 | 2.67056433 | -0.8243496 | 0.04863024 | 0.30770513 | TRUE |

| pWAT T cells S196A vs WT | | | | | |
|--------------------------|------------|------------|------------|------------|------------------|
| Gene | logFC | logCPM | PValue | FDR | IN CYTOKINE LIST |
| Ccl12 | -2.2827551 | 6.25617007 | 0.00018375 | 0.00548422 | TRUE |
| Timp1 | -2.839394 | 3.18141075 | 0.00179274 | 0.02606055 | TRUE |
| Ccl3 | -0.9298593 | 6.74318444 | 0.00206309 | 0.02866657 | TRUE |
| * Il4 | 3.54020535 | 0.96143339 | 0.0029395 | 0.03689565 | TRUE |
| Ifng | 1.38282339 | 3.53356936 | 0.00354547 | 0.04161017 | TRUE |
| Il1rn | -0.899455 | 7.64877318 | 0.00723997 | 0.06576119 | TRUE |
| Ccl4 | -0.6207519 | 6.34774006 | 0.04986694 | 0.2099485 | TRUE |

* Il4 is induced in plaque and pWAT T cells