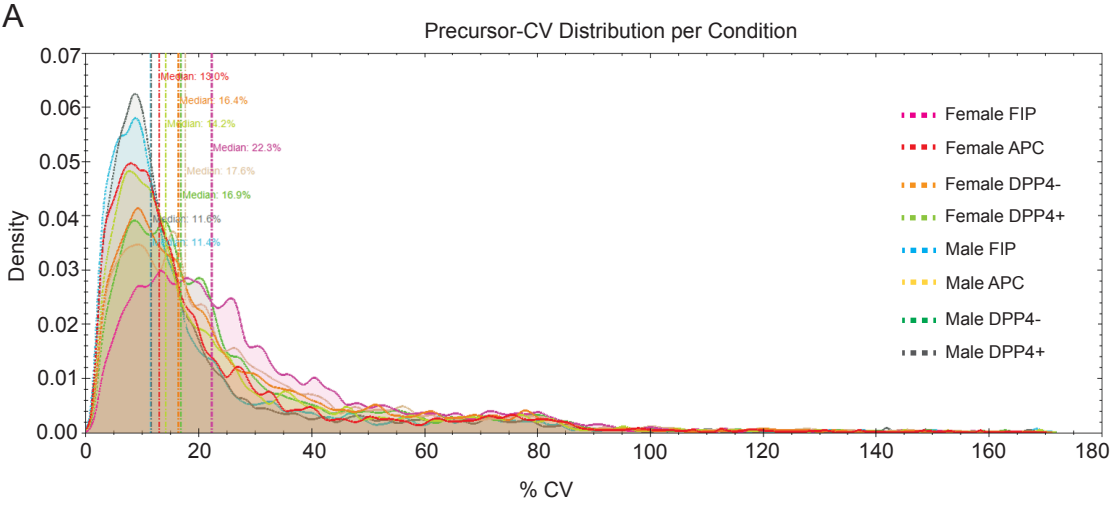
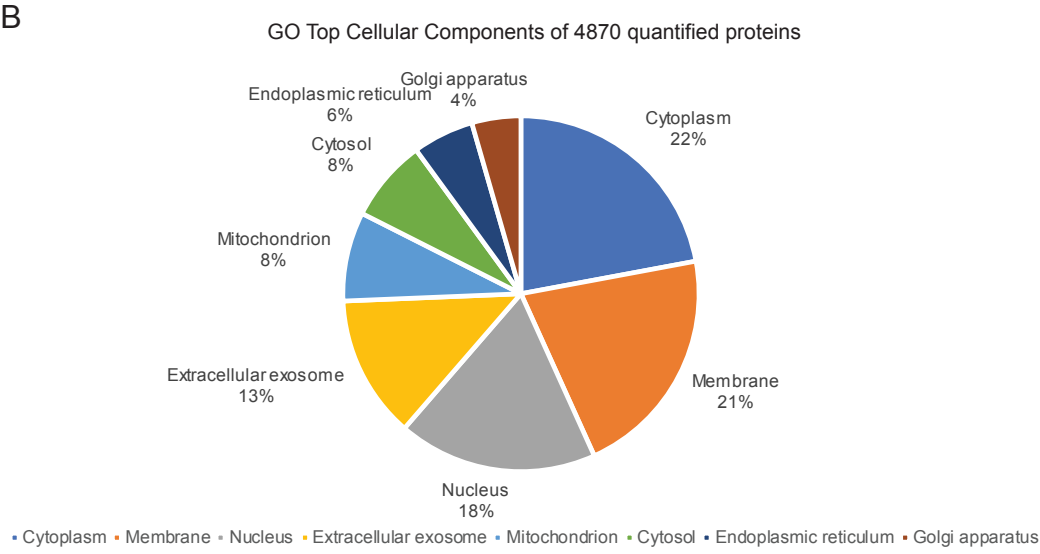
A



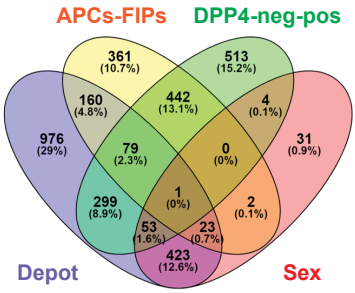
B



C

Group comparison	ANOVA significant proteins (adj. p < 0.05)
Among all 8 groups	3444
Among cell populations	2708
Between two depots	2014
Between sexes	537

D



E

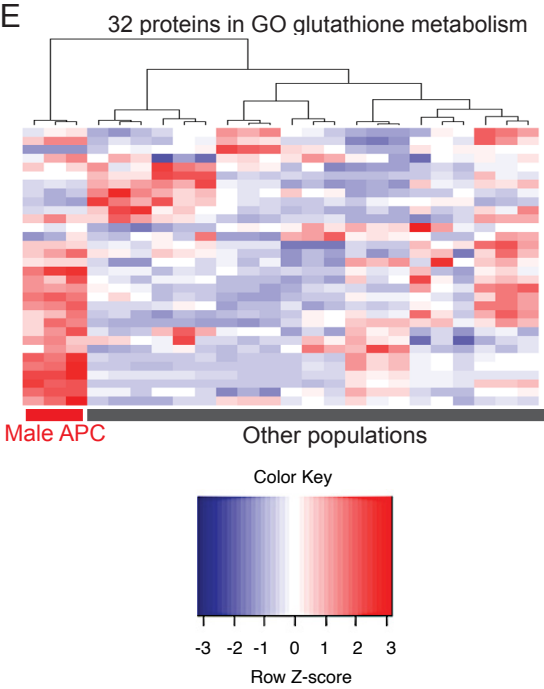


Figure S1: Related to Figure 1

Figure S1. Related to Figure 1: Proteomics data revealed protein signatures that distinguish adipose tissue stromal cells in dimensions of sex and depot.

(A) Coefficient of variation (CV) of protein quantification across three biological replicates.
(B) Gene Ontology (GO) annotation of cellular localization of quantified proteins.
(C) Numbers of significantly regulated proteins (ANOVA adjusted p value < 0.05) in three dimensions, including cell population, depot (gonadal vs. inguinal WAT), and sex.
(D) Venn diagram illustrating overlap of significant proteins among dimensions.
(E) Heat map depicting protein expression of genes involved in glutathione metabolism.

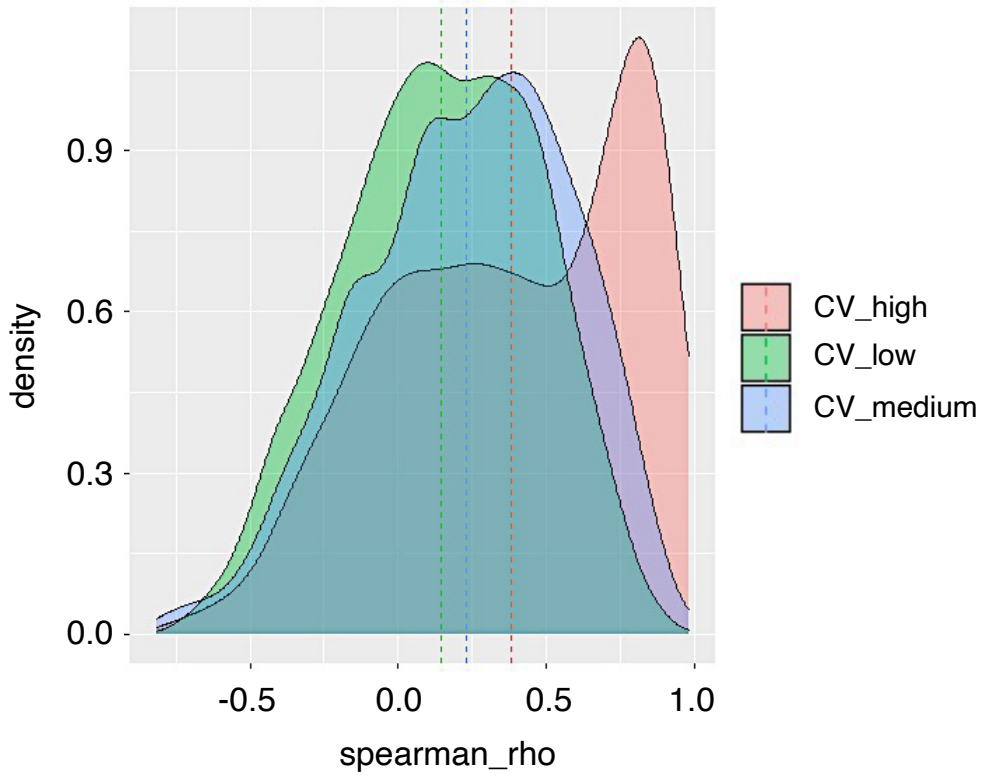


Figure S2: Related to Figure 2

Figure S2. Related to Figure 2: Dependence of protein-mRNA correlation on protein variation.

4540 protein-mRNA pairs were categorized into 10 bins based on their coefficient of variation (CV) at the protein level. Genes from bin 1 have the lowest CV, and genes from bin 10 have the highest CV of protein abundances across all samples. The Spearman's rho was plotted for bin 1 and 2 (low CV group), bin 5 and 6 (medium CV group) and bin 9 and 10 (high CV group), respectively. Dashed lines show the median of Spearman's rhos in each group.

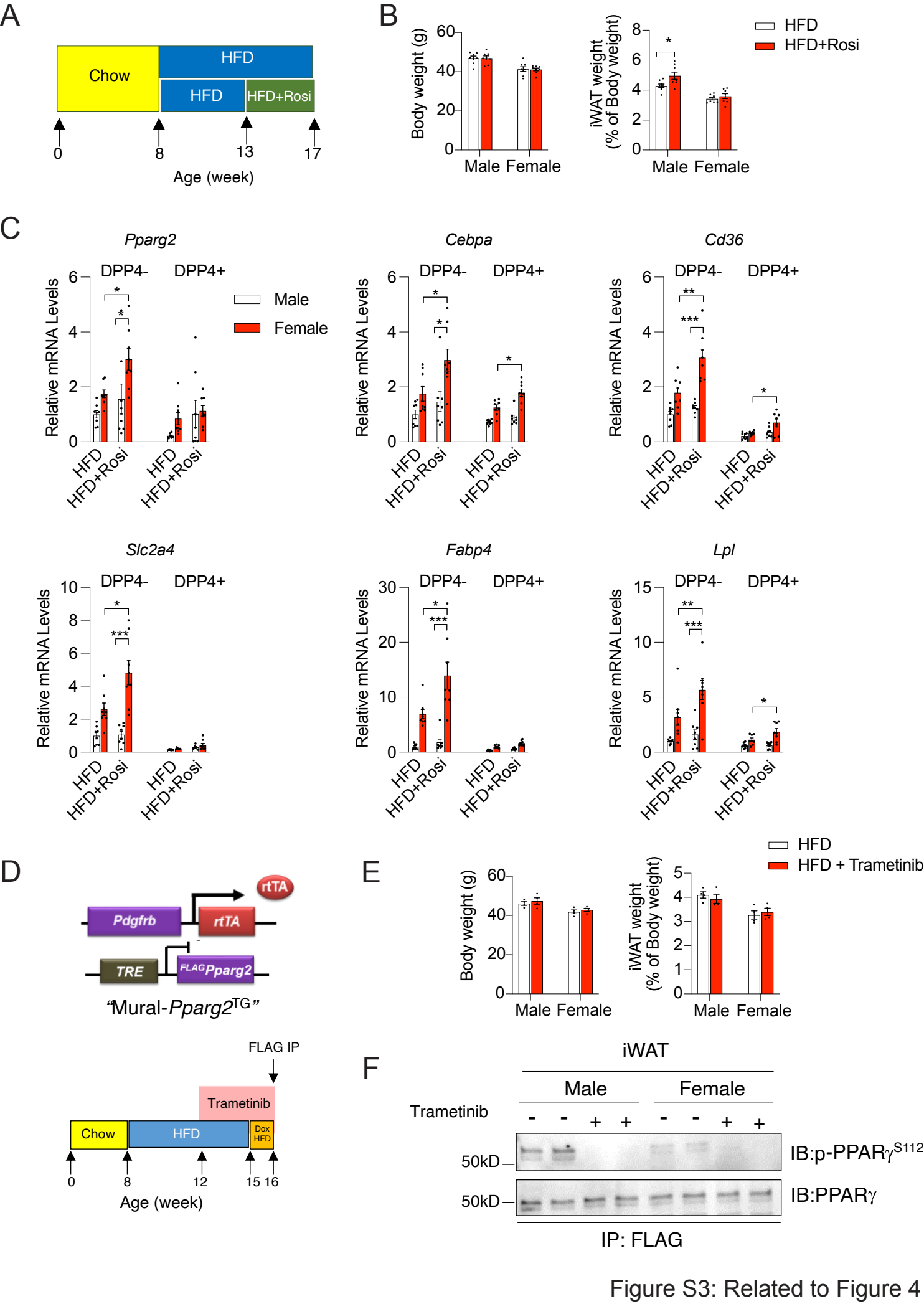


Figure S3: Related to Figure 4

Figure S3. Related to Figure 4: Sex-differences in the activity of PPARγ in iWAT APCs.

(A) Experimental approach: male and female mice were maintained on a standard chow diet until 8 weeks of age before being switched to high-fat diet (HFD) feeding for another 9 weeks. The animals were administered either Rosiglitazone-containing HFD or control HFD for the last 4 weeks.

(B) Body weight (left) and and inguinal WAT (iWAT) mass. n=8 mice for each group. Bars represent mean +/- s.em. * denotes $p < 0.05$ by unpaired two-tailed Student's t-test.

(C) mRNA levels of indicated *Pparg* regulated genes in freshly isolated DPP4- and DPP4+ APCs. n = 8 mice for each group. Bars represent mean +/- s.em. * denotes $p < 0.05$, ** denotes $p < 0.01$, *** denotes $p < 0.001$ by two-way ANOVA.

(D) Experimental approach to assay PPARγ S112 phosphorylation in iWAT of obese male and female mice: Doxycycline (Dox)-inducible Mural-*Pparg2*^{TG} mice were fed a standard chow diet until 8 weeks of age before being switched to HFD feeding for another 8 weeks. During the last 4 weeks of HFD, the animals were administered either Trametinib (3 mg/kg body weight) or vehicle via oral gavage every two days. Following HFD-feeding, male and female Mural-*Pparg2*^{TG} mice were fed with Dox-HFD for another 7 days to induce the expression of FLAG-tagged *Pparg2* transgene in PDGFRβ+ cells. FLAG-tagged PPARγ protein was then immunoprecipitated from whole depots using anti-FLAG antibodies.

(E) Body weight (left) and and inguinal WAT (iWAT) mass. n=4 mice for each group. Bars represent mean +/- s.em.

(F) Western blot analysis of PPARγ S112 phosphorylation in PDGFRβ+ cells of iWAT of male and female Mural-*Pparg2*^{TG} mice described in (D).

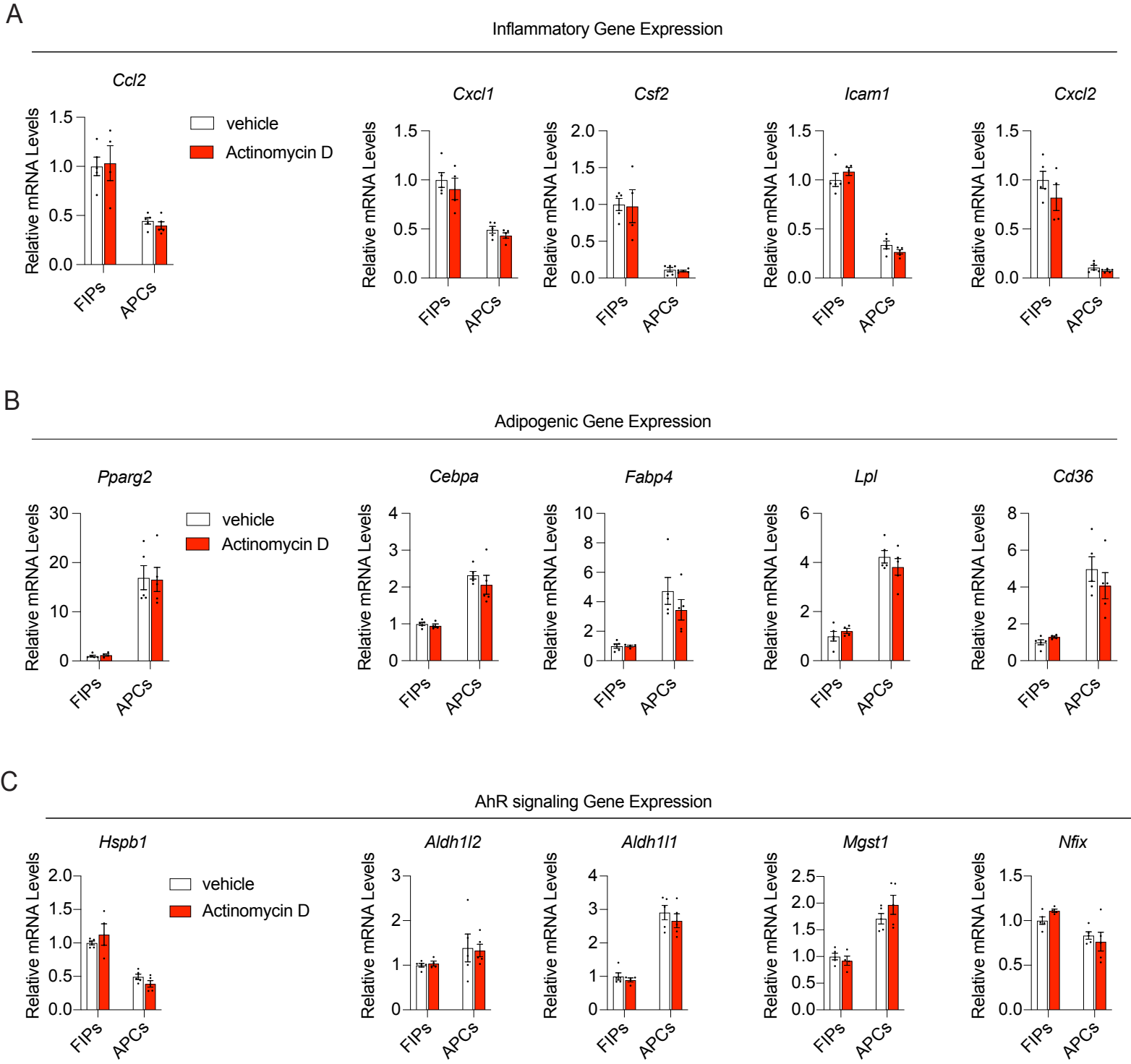


Figure S4: Related to Figure 5

Figure S4. Related to Figure 5: Gene expression analysis of gWAT APCs and FIPs isolated in the presence of actinomycin D.

FIPs and APCs were freshly sorted from gonadal WAT with or without the presence of actinomycin D (1 ug/ml) throughout the digestion and FACS procedure. n=5 for each group.
(A) mRNA levels of indicated pro-inflammatory genes in FIPs and APCs of each group.
(B) mRNA levels of indicated adipogenic genes in FIPs and APCs of each group.
(C) mRNA levels of indicated genes involved in AhR signaling pathway in FIPs and APCs of each group.
In all panels, bars represent mean $\pm$ s.e.m.

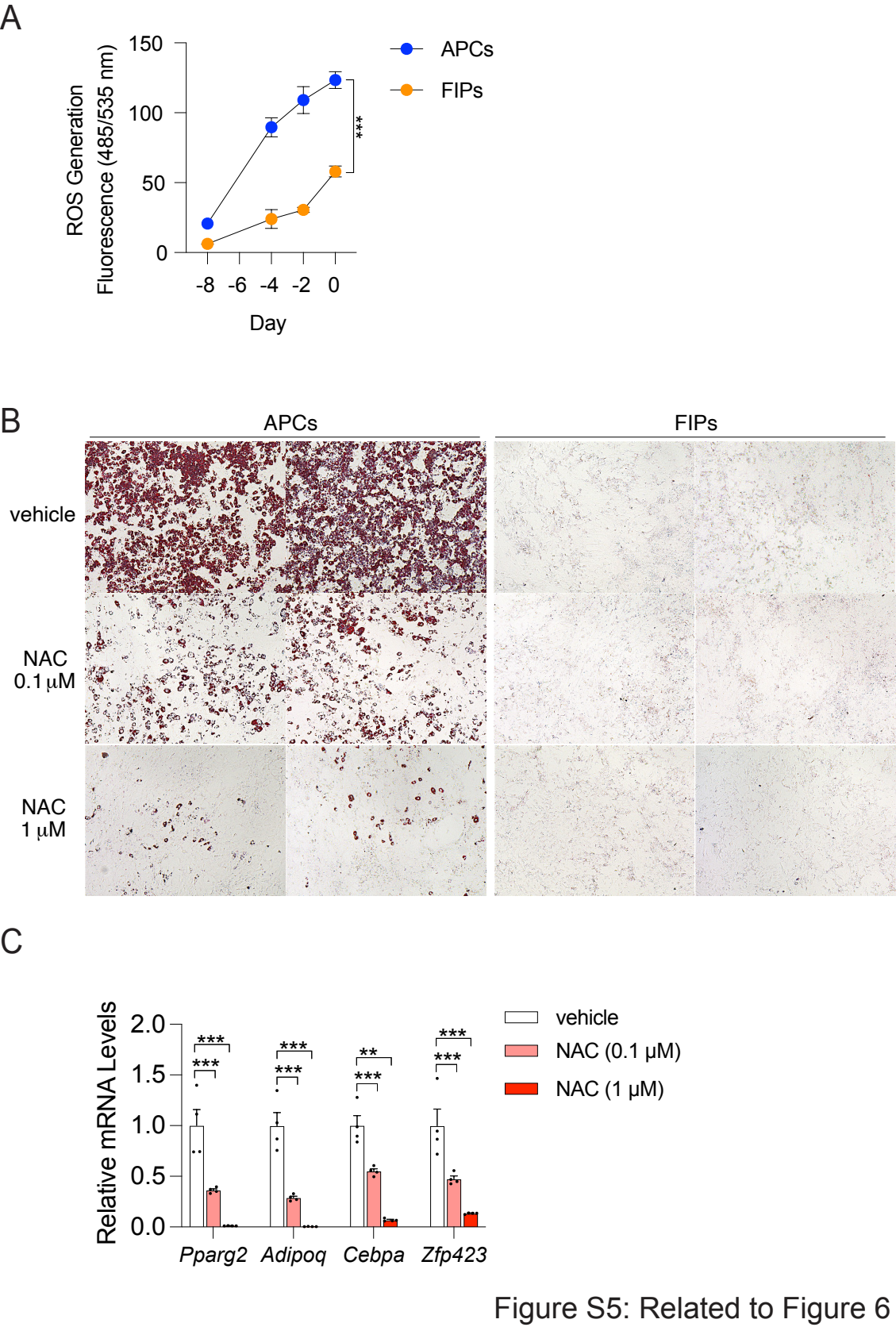


Figure S5: Related to Figure 6

Figure S5. Related to Figure 6: ROS production is required for gWAT APC differentiation in vitro.

(A) ROS contents were determined in primary FIPs and APCs maintained in ITS growth media for 8 days up until the time of confluence (Day 0). n=4 for each group. Data are shown as the mean ± s.e.m. *** denotes $p < 0.001$ compared to APCs at Day 0 by unpaired two-tailed Student's t-test.

(B) Representative bright-field images of Oil-red O-stained cultures of differentiated primary APCs and FIPs exposed to NAC of indicated concentration during differentiation. Differentiation was allowed to occur spontaneously while cells were maintained in ITS growth media. Scale bar = 200 μm.

(C) mRNA levels of adipocyte-selective genes (*Pparg2, Adipoq*, *Cebpa* and *Zfp423*) in cultures described in (B). Bars represent mean ± s.e.m. ** denotes $p < 0.01$, *** denotes $p < 0.001$ by one-way ANOVA.

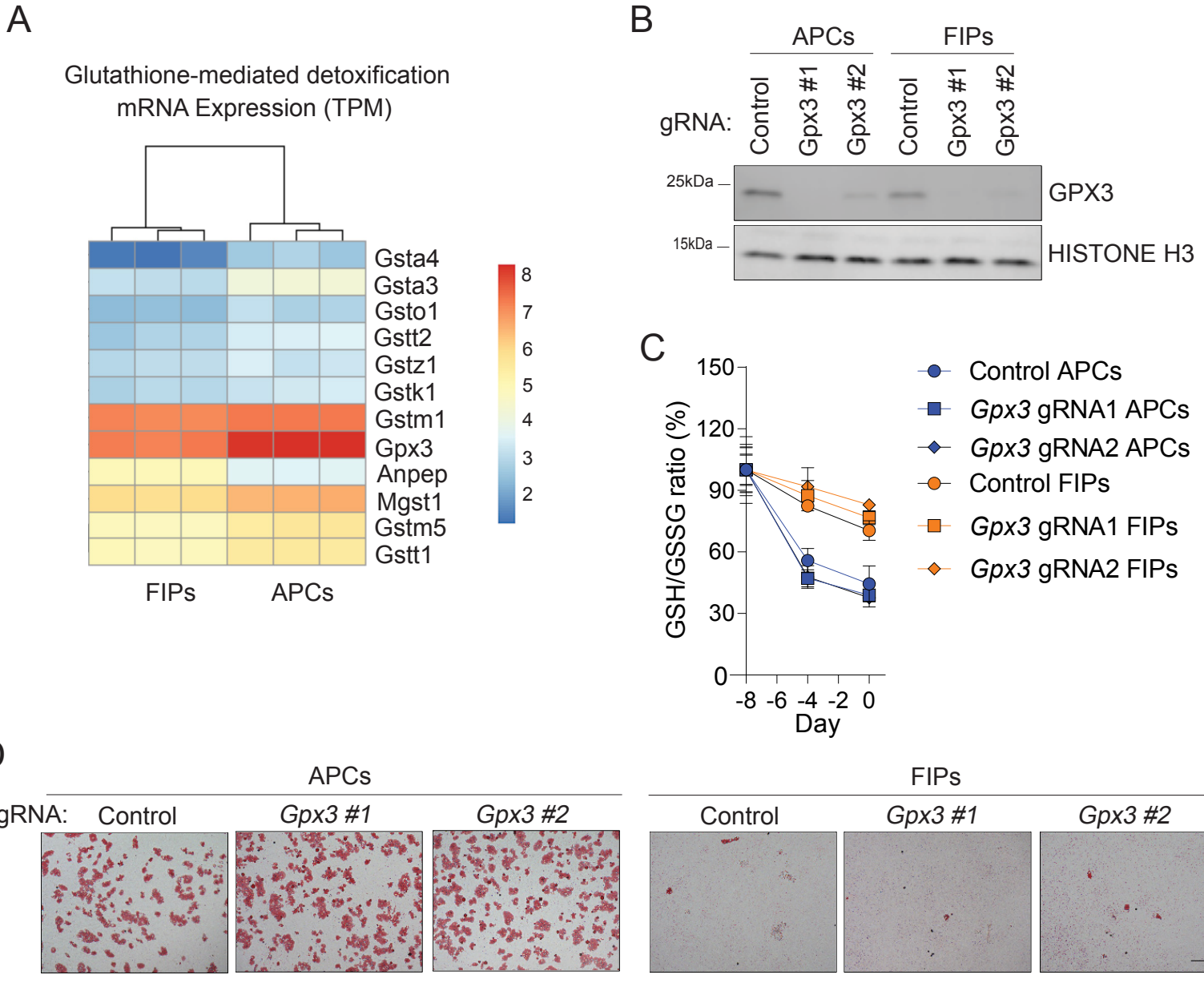


Figure S6: Related to Figure 6

Figure S6. Related to Figure 6: *Gpx3* is dispensable for redox control of APC differentiation

(A) Heat map of transcript levels (TPM) of genes involved in glutathione-mediated detoxification in male APCs and FIPs.
(B) Western blot analysis of GPX3 in primary FIPs and APCs transduced with CRISPR lentivirus expressing the indicated gRNAs.
(C) GSH:GSSG ratios in the cell lysates of primary FIPs and APCs transduced with the indicated CRISPR lentivirus and maintained in ITS growth media for 8 days up until the time of confluence (Day 0). n = 4. Data points represent the mean ± s.e.m. * denotes $p < 0.05$ between APCs and FIPs by two-way ANOVA.
(D) Representative bright field images of Oil-red O stained cultures of differentiated primary FIPs and APCs transduced with the indicated CRISPR lentivirus. Differentiation was allowed to occur spontaneously while cells were maintained in ITS growth media. Scale bar = 200 μm.

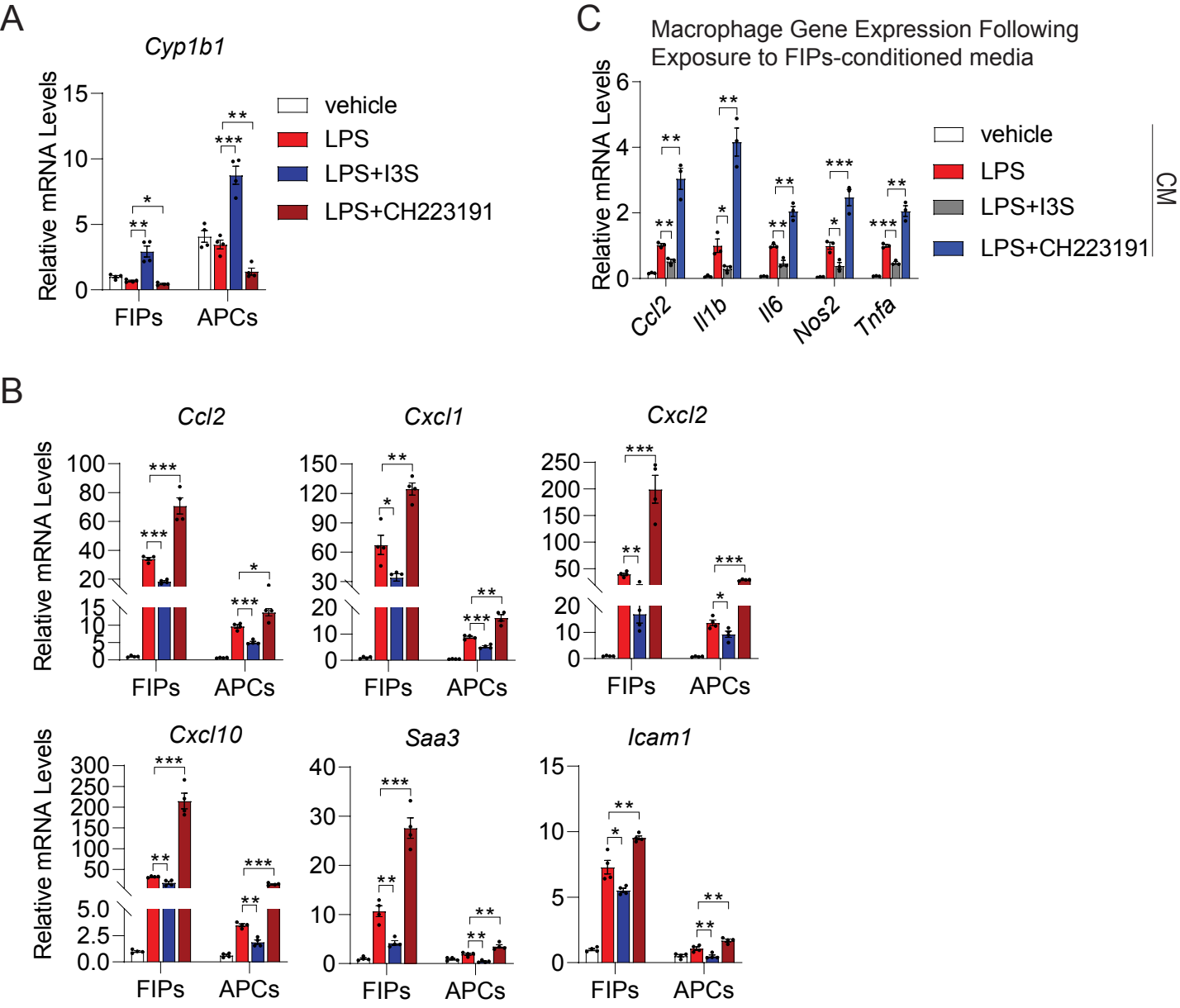


Figure S7: Related to Figure 7

Figure S7. Related to Figure 7. Pharmacological modulation of AhR activity impacts the inflammatory responses of gWAT FIPs and APCs.

(A) mRNA levels of *Cyp1b1* in primary cultures of FIPs and APCs incubated in the presence of vehicle, AhR agonist I3S (100 μg/ml), or inhibitor CH223191 (10 μM), for 12 hours prior to the treatment of LPS for 2 hours. N = 4 each group. Each sample represents cells from pooled depots of 6 mice. Bars represent mean ± s.e.m., * denotes $p < 0.05$, ** denotes $p < 0.01$, *** denotes $p < 0.001$ by one-way ANOVA.
(B) mRNA levels of the indicated pro-inflammatory genes in cultured FIPs and APCs described in (A). N = 4 each group. Bars represent mean ± s.e.m., * denotes $p < 0.05$, ** denotes $p < 0.01$, *** denotes $p < 0.001$ by one-way ANOVA.
(C) mRNA levels of genes associated with macrophage activation in cultured BMDMs following exposure to the indicated FIPs conditioned medium (CM) for 90 min. N = 3 each group. Bars represent mean ± s.e.m., * denotes $p < 0.05$, ** denotes $p < 0.01$, *** denotes $p < 0.001$ by one-way ANOVA.
FIPs (isolated from pooled depots of 8 mice) were treated with vehicle or LPS (100 ng/ml) for 2 hours following treatment with chemical compounds treatments. The cells were then incubated in serum-free medium for an additional 24 hour to produce conditioned medium.

Table S5. Related to STAR Methods: **Primer Sequences for quantitative PCR analysis**

Gene	Forward (5' -3')	Reverse (5' -3')
Ccl2	CCACAACCACCTCAAGCACTTC	AAGGCATCACAGTCCGAGTCAC
Cxcl1	CTGGGATTCACCTCAAGAACATC	CAGGGTCAAGGCAAGCCTC
Cxcl10	CTCAGGCTCGTCAGTTCTAAGT	CCCTTGGGAAGATGGTGGTTAA
Cxcl2	ACTAGCTACATCCCACCCACAC	GCACACTCCTTCCATGAAAGCC
Icam1	GTGATGCTCAGGTATCCATCCA	CACAGTTCTCAAAGCACAGCG
Il1b	GCAACTGTTCCTGAACTCAACT	ATCTTTTGGGGTCCGTCAACT
Il6	AAGCCAGAGTCCTTCAGAGAGA	ACTCCTTCTGTGACTCCAGCTT
Nos2	CCTCTGGTCTTGCAAGCTGAT	ACTCGTACTTGGGATGCTCCA
Rps18	CATGCAAACCCACGACAGTA	CCTCACGCAGCTTGTTGTCTA
Tnfa	GAAAGGGGATTATGGCTCAGG	TCACTGTCCCAGCATCTTGTG
Pparg2	GCATGGTGCCTTCGCTGA	TGGCATCTCTGTGTCAACCATG
Adipoq	AGATGGCACTCCTGGAGAGAA	TTCTCCAGGCTCTCCTTTCCT
Cebpa	TGGCCTGGAGACGCAATGA	CGCAGAGATTGTGCGTCTTT
Zfp423	CAGGCCCACAAGAAGAACAAG	GTATCCTCGCAGTAGTCGCACA
Gstm1	ATACTGGGATACTGGAACGTCC	AGTCAGGGTTGTAACAGAGCAT
Saa3	TGCCATCATTCTTTGCATCTTGA	CCGTGAACTTCTGAACAGCCT
Cyp1b1	CACCAGCCTTAGTGCAGACAG	GAGGACCACGGTTTCCGTTG
Fabp4	GATGAAATCACCGCAGACGAC	ATTCCACCACCAGCTTGTCAC
Lpl	GGGAGTTTGGCTCCAGAGTTT	TGTGTCTTCAGGGGTCCTTAG
Cd36	ATGGGCTGTGATCGGAACTG	GTCTTCCCAATAAGCATGTCTCC
Hspb1	ATCCCCTGAGGGCACACTTA	GGAATGGTGATCTCCGCTGAC
Aldh1l2	ACCAGCCGGGTTTATTTCAAA	ACTCCCACTACTCGGTGGC
Aldh1l1	CAGGAGGTTTACTGCCAGCTA	CACGTTGAGTTCTGCACCCA
Mgst1	CTCAGGCAGCTCATGGACAAT	GTTATCCTCTGGAATGCGGTC
Nfix	AGCCCCAGCTACTACAACATA	AGTCCAGCTTTCCTGACTTCT
Slc2a4	GTGACTGGAACACTGGTCCTA	CCAGCCACGTTGCATTGTAG