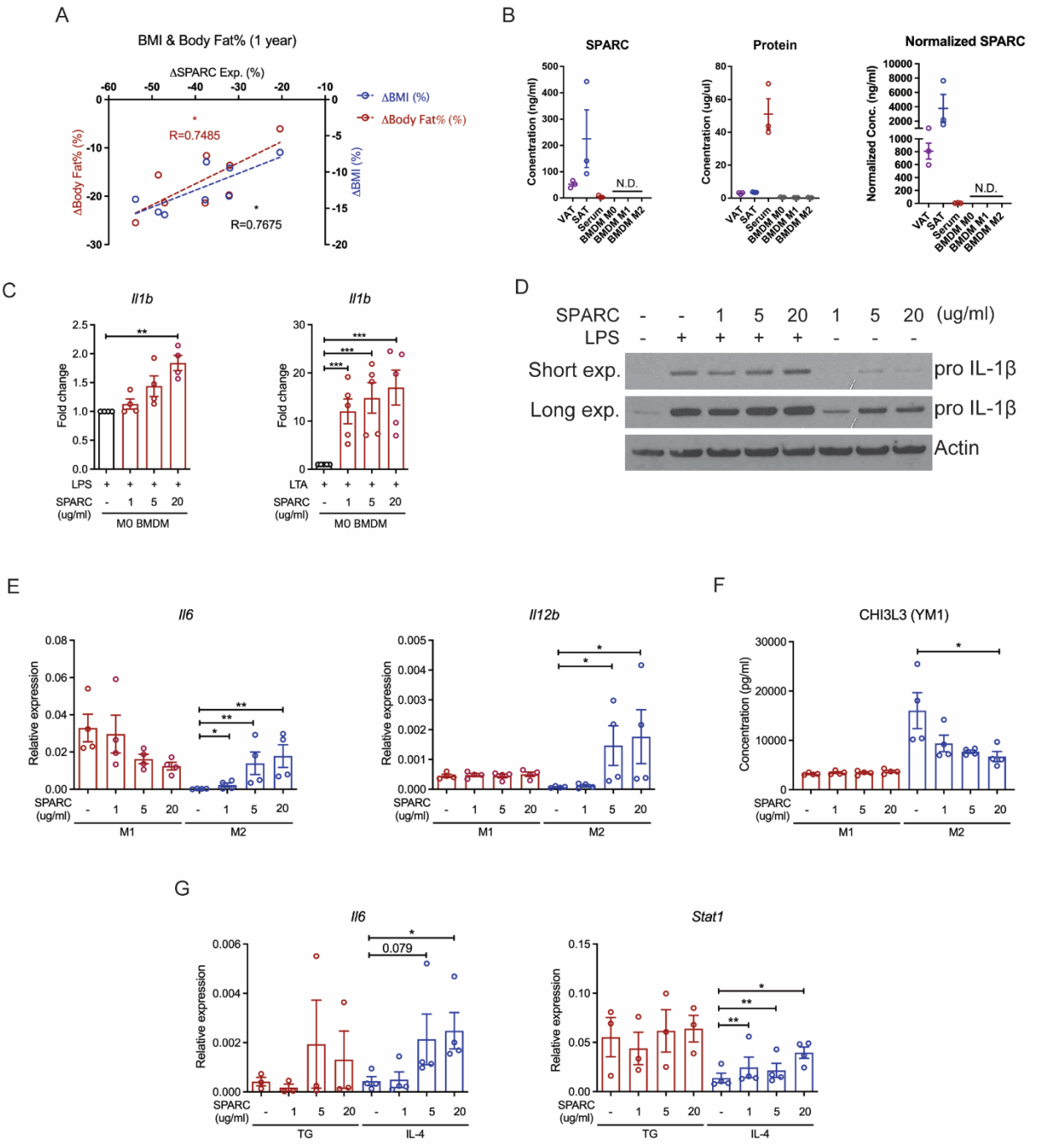

Figure S1. SPARC upregulates pro-inflammatory genes in macrophages, Related to Figure 1, 2. (A) Correlation analysis between the percentage of *SPARC* expression change and percentage of BMI, Body Fat% changes of participants after 1 year of CR. (B) Measurement of SPARC concentrations with or without normalization by total protein concentrations in serum,

VAT, SAT, BMDMs. N.D. indicates non-detected. (C) Q-PCR analysis for *Il1b* in M0 BMDMs after treatment of LPS (n=4) or LTA (n=5) with SPARC (1, 5, and 20 μg/ml) for 24 hours. (D) Immunoblot analysis for pro IL-1β in BMDMs after treatment of SPARC (1, 5, and 20 μg/ml) with or without LPS for 24 hours. (E) Gene expression analysis by Q-PCR for pro-inflammatory genes (*Il6*, *Il12b*) with the treatment of SPARC (1, 5, and 20 μg/ml) to M1 and M2 polarized BMDMs (n=4). (F) ELISA assay to detect M2 macrophage protein, YM1 and CHI3L3 in supernatants of SPARC treated M1 and M2 polarized BMDMs (n=4). (G) Gene expression analysis by Q-PCR for pro-inflammatory gene *Il6* and *Stat1* in controls and *ex vivo* SPARC treated peritoneal macrophages from thioglycollate (TG) or IL-4 complex injected (IL-4) mice (n=3, 4 each). All experiments were repeated independently at least twice. Error bars represent the mean ± S.E.M. Pearson correlation analysis, and two-tailed paired t-tests were performed for statistical analysis. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

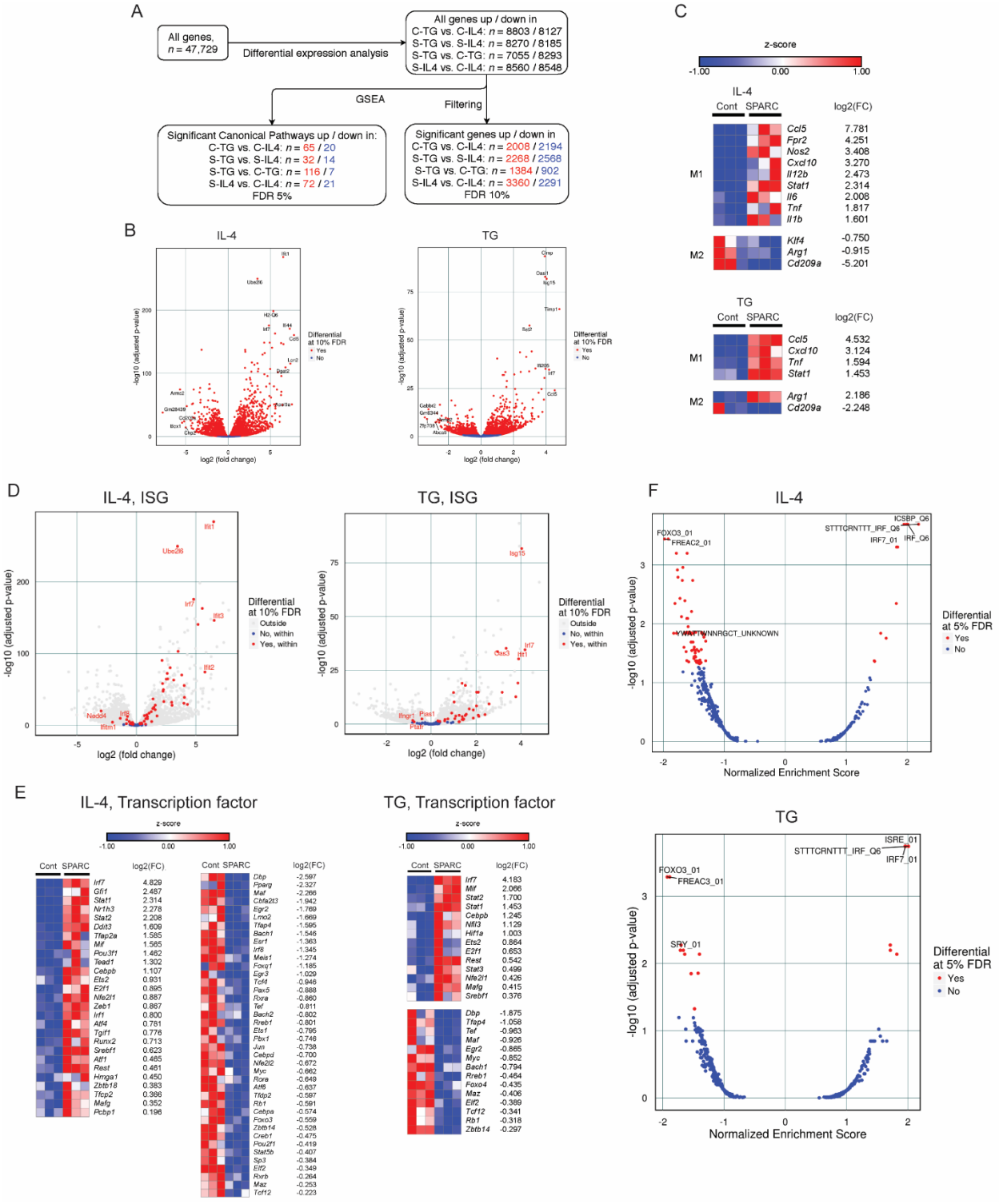

Figure S2. SPARC shifts transcriptomic profiles of macrophages with ISG induction, Related to Figure 3. (A) Workflow for differential gene expression and GSEA pathway analysis of RNA-sequencing results. (B) Volcano plots for significantly (red dots) and non-significantly

(blue dots) differentially expressed genes between controls and SPARC treated peritoneal macrophages from IL-4c injected (IL-4, left) and thioglycollate injected (TG, right) mice. (C) M1 and M2 marker gene expression patterns in controls and SPARC treated peritoneal macrophages from IL-4 complex injected (IL-4, upper) and thioglycollate injected (TG, lower) mice. (D) Volcano plots for significantly changed (red dots) and non-significantly changed (blue dots) interferon response genes (IGSs) with SPARC treatment to peritoneal macrophages from IL-4 complex injected (IL-4, left) and thioglycollate injected (TG, right) mice. (E) Significantly up or down-regulated transcription factors after treatment of SPARC to peritoneal macrophages from IL-4 complex injected (IL-4, left) and thioglycollate injected (TG, right) mice. (F) Transcription factor binding motifs significantly enriched around the transcription start sites of up-regulated (positive normalized enrichment score) or down-regulated (negative normalized enrichment score) genes by SPARC treatment in peritoneal macrophages from IL-4 complex injected (IL-4, upper) or thioglycollate injected (TG, lower) mice.

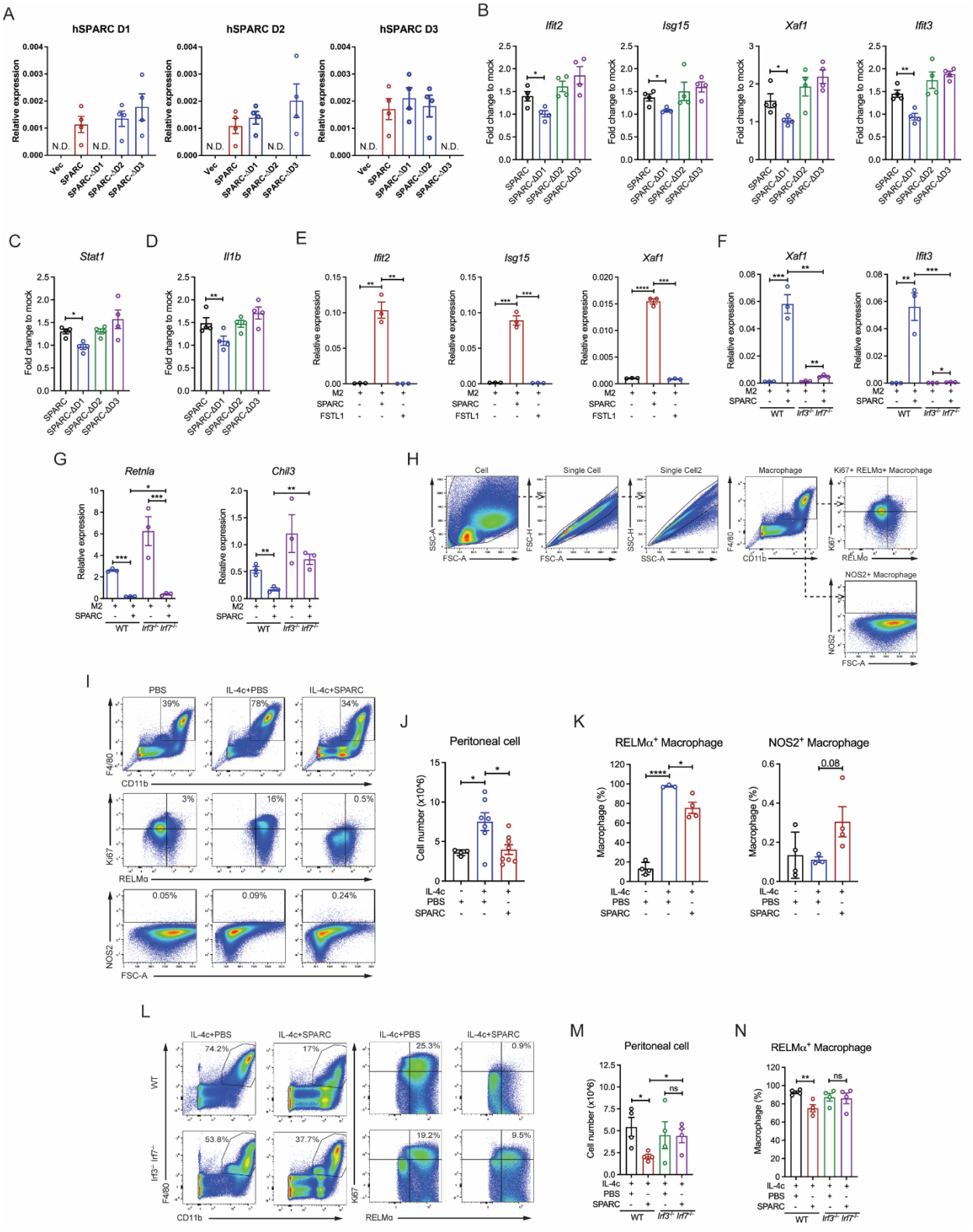

Figure S3. SPARC induces ISGs through IRF3 and IRF7 signaling, Related to Figure 4. (A) Q-PCR analysis for specific SPARC domain (D1, D2, D3) in mock vector, intact SPARC, and

domain deleted SPARC (ΔD1, ΔD2, ΔD3) transfected RAW 264.7 cell lines (n=4). (B-D) Q-PCR analysis for ISGs (B), *Stat1* (C), and *Il1b* (D) in SPARC and domain deleted SPARC (ΔD1, ΔD2, ΔD3) transfected RAW 264.7 cell lines (n=4). Fold changes were calculated based on mock vector-transfected RAW 264.7 cell lines. (E) Q-PCR analysis for ISGs in M2 polarized BMDMs with 20 μg/ml SPARC or FSTL1 treatment for 24 hours and non-treated controls (n=3) (F, G) Q-PCR analysis for ISGs (F) and M2 genes (G) in M2 polarized BMDMs from wide-type (WT) and *Irf3*$^{-/-}$ *Irf7*$^{-/-}$ mice with or without 20 μg/ml SPARC treatment for 24 hours (n=3). (H) Representative flow cytometry plots showing the gating strategy to detect macrophages, Ki67^{+} RELMα^{+} macrophages, and NOS2^{+} macrophages in peritoneal cells. (I) Representative flow cytometry plots of peritoneal cells from PBS, IL-4c with PBS, and IL-4c with SPARC injected mice. Percentages of macrophages (F4/80^{+} CD11b^{+}, top), proliferating M2 macrophages (Ki67^{+} RELMα^{+}, middle), and pro-inflammatory macrophages (NOS2^{+}, bottom) were indicated. (J, K) Peritoneal cell numbers (n=4, 8, 8) (J) and quantification of flow cytometry analysis for RELMα^{+} M2 and pro-inflammatory macrophages in peritoneal cells (n=4, 3, 4) (K) from PBS, IL-4c with PBS, or IL-4c with SPARC injected mice. (L) Representative flow cytometry plots for peritoneal cells from IL-4c with PBS or IL-4c with SPARC injected WT and *Irf3*$^{-/-}$ *Irf7*$^{-/-}$ mice. Percentages of macrophages and proliferating M2 macrophages were indicated. (M, N) Numbers of peritoneal cells (M) and quantification of flow cytometry analysis for RELMα^{+} M2 macrophages (N) from IL-4c with PBS or IL-4c with SPARC injected WT and *Irf3*$^{-/-}$ *Irf7*$^{-/-}$ mice (n=4 each). All experiments were repeated independently at least twice. Error bars represent the mean ± S.E.M. Two-tailed paired and unpaired t-tests were performed for statistical analysis. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

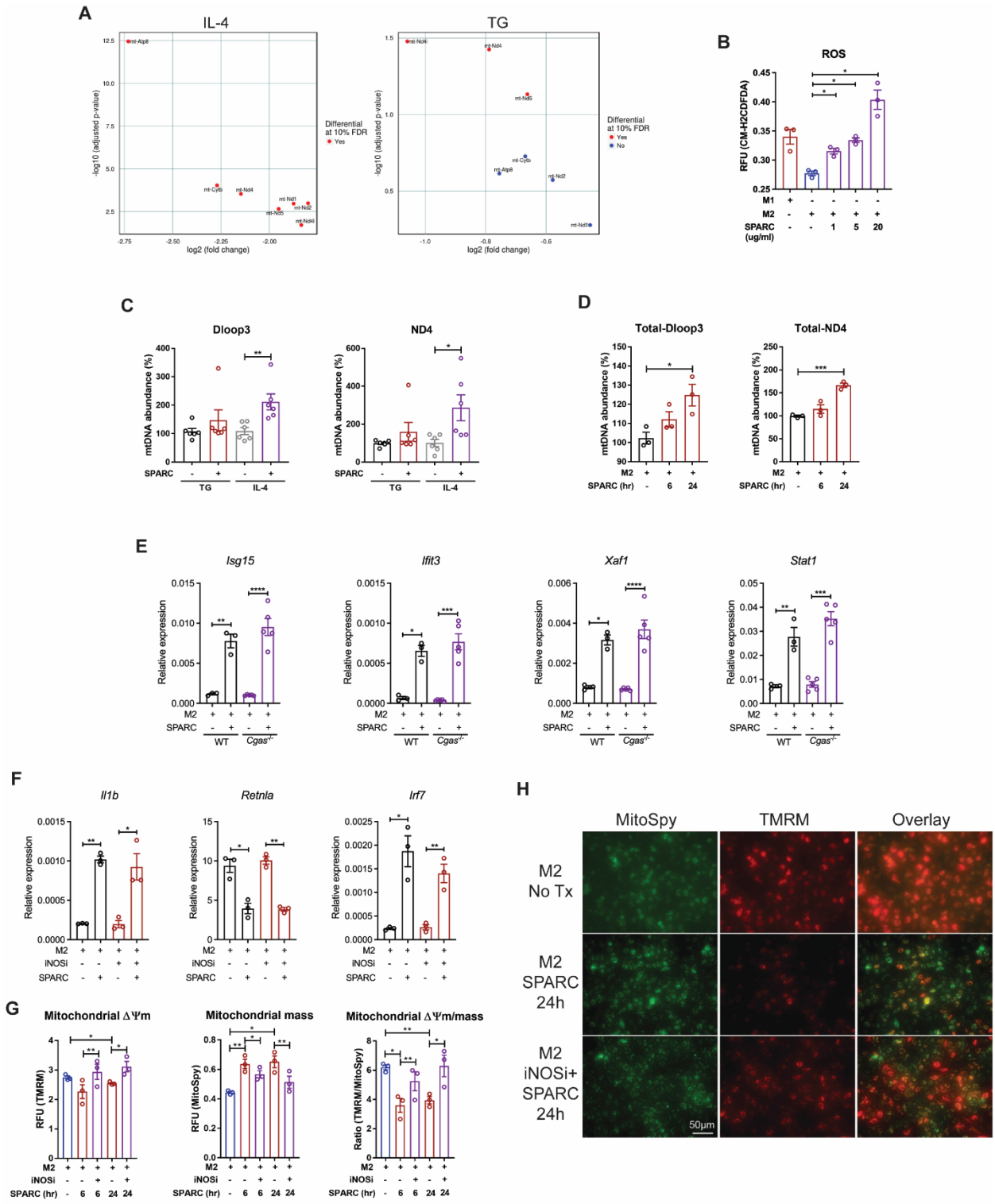

Figure S4. cGAS activation is not required for SPARC-inducted ISG induction, Related to Figure 4. (A) PCA plots for mitochondrial genes in RNA-sequencing analysis of peritoneal

macrophages from IL-4c injected (IL-4, left), and thioglycollate injected (TG, right) mice with SPARC treatment *ex vivo* (n=3). (B) ROS measurement by CM-H2CDFDA assay in non-treated or 1, 5, 20 μg/ml SPARC treated (24 hours) M2 polarized BMDMs, and M1 polarized BMDMs (n=3) (C) Mitochondrial DNA abundance measurement in peritoneal macrophages from IL-4c injected (IL-4), and thioglycollate injected (TG) mice with or without SPARC treatment *ex vivo* by Q-PCR for Dloop3 and ND4 (n=6). (D) Total mitochondrial DNA abundance measurement in M2 BMDMs with or without SPARC treatment for 6 and 24 hours by Q-PCR for Dloop3 and ND4 (n=3). (E) Gene expression analysis by Q-PCR for ISGs and *Stat1* in BMDMs from wide-type (WT) and *Cgas*$^{-/-}$ mice with or without SPARC treatment (20 μg/ml) for 24 hours (n=3, 5). (F) Q-PCR analysis for *Il1b*, *Retnla*, and *Irf7* in 20 μg/ml SPARC treated (24 hours) M2 polarized BMDMs with or without pre-treatment of iNOS inhibitor (L-NIL, 40 μM) and non-treated controls (n=3). (G, H) Quantification (G) and representative images (H) for mitochondrial functional assays in 20 μg/ml SPARC treated (24 hours) M2 polarized BMDMs with or without pre-treatment of iNOS inhibitor (L-NIL, 40 μM) and non-treated controls (n=3). MitoSpy, TMRM assay were used to measure each mitochondrial mass and membrane potential ($\Delta\psi$). Scale bar represents 50 μm. All experiments were repeated independently at least twice. Error bars represent the mean ± S.E.M. Two-tailed paired t-tests were performed for statistical analysis. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

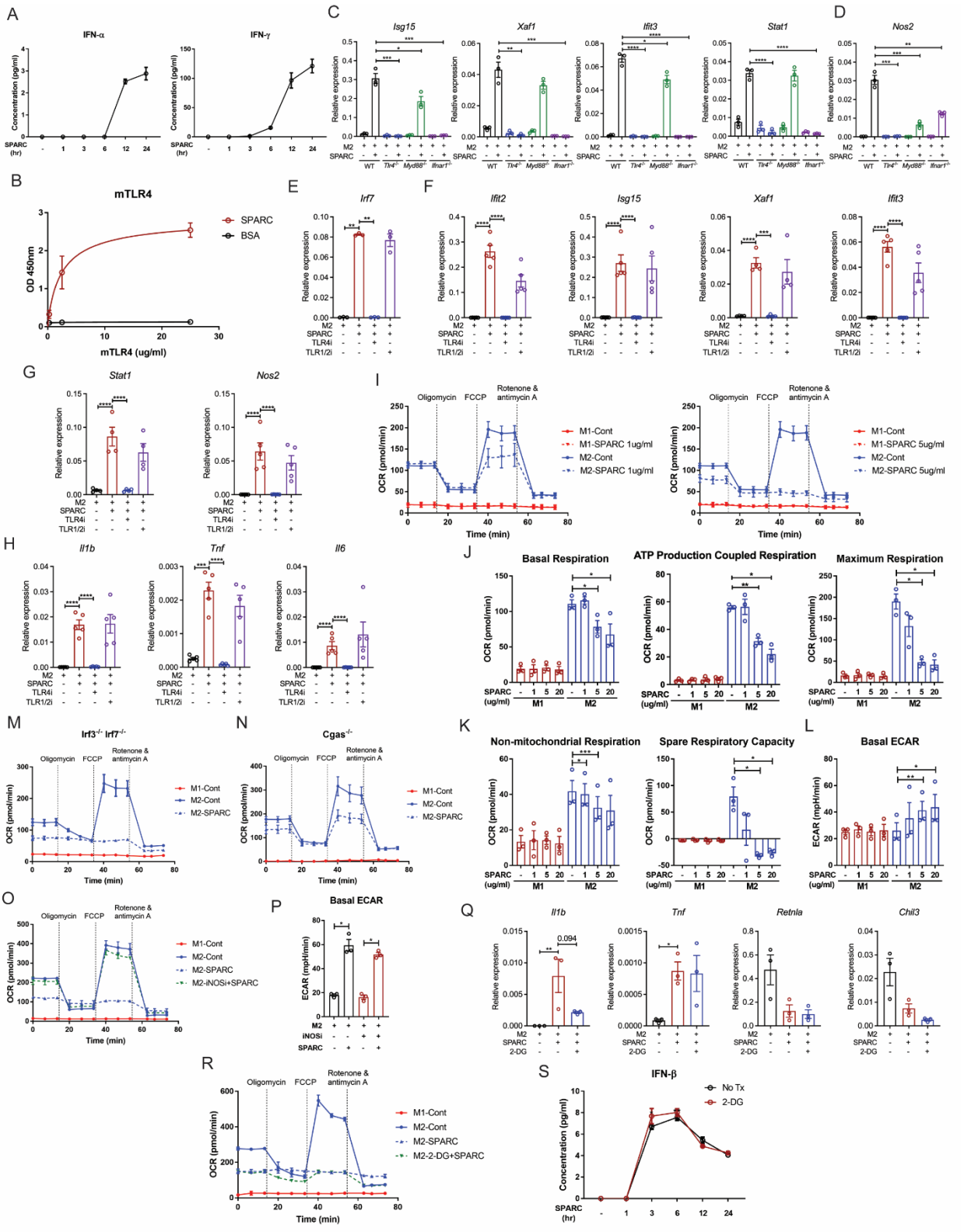

Figure S5. Induction of IGSs was mediated by TLR4 and interferon signaling, Related to Figure 5. (A) ELISA assays for IFN-α and IFN-γ detection in supernatants of M2 BMDMs non-

treated or treated with 20 μg/ml SPARC for 1, 3, 6, 12, and 24 hours (n=3). (B) Solid-phase binding assay to detect the interaction between SPARC and mouse TLR4 (mTLR). The indicated amount of TLR4s was coated on plates, and 20 μg/ml SPARC or BSA were added for interaction (n=3). Nonlinear regression analyses were performed for the values in the graph. (C, D) Gene expression analysis by Q-PCR for ISGs, *Stat1* (C), and *Nos2* (D) in M2 polarized BMDMs from wide-type (WT), *Tlr4*$^{-/-}$, *Myd88*$^{-/-}$, and *Ifnar1*$^{-/-}$ mice with or without SPARC (20 μg/ml) treatment (n=3). (E-H) Gene expression analysis by Q-PCR for *Irf7* (E), ISGs (F), *Stat1*, *Nos2* (G), and pro-inflammatory genes (H) in non-treated and SPARC (20 μg/ml) treated M2 polarized BMDMs with TLR4 inhibitor (TAK-242, 2.5 μM) or TLR1 and TLR2 inhibitor (CU-CPT22, 8 μM)-pre-treatment (n=3). (I) Oxygen consumption rate (OCR) for M1 and M2 BMDMs with or without SPARC (1, 5 μg/ml) treatment measured by seahorse mitostress assay (n=3). (J, K) Quantification of seahorse assay for basal respiration, ATP production coupled respiration, maximum respiration, non-mitochondrial respiration, and spare respiratory capacity (n=3). (L) Basal extracellular acidification rate (ECAR) of M1 and M2 BMDMs with or without SPARC (1, 5, 20 μg/ml) treatment measured by seahorse analyzer (n=3). (M, N) Seahorse assay to detect OCRs for M1, M2, and SPARC (20 μg/ml) treated M2 BMDMs from *Irf3*$^{-/-}$ *Irf7*$^{-/-}$ mice (M) and *Cgas*$^{-/-}$ mice (N) (n=3). (O, P) Seahorse assay to detect OCRs and basal ECAR for M1, M2, and SPARC (20 μg/ml) treated M2 BMDMs with or without iNOS inhibitor (L-NIL, 40 μM) (n=3). (Q) Gene expression analysis for pro-inflammatory and M2 genes in non-treated and SPARC (20 μg/ml, 24 hours) treated M2 BMDMs with or without pre-treatment of glycolysis inhibitor (2-DG, 10 mM) (n=3). (R) Seahorse assay to detect OCRs in M2 polarized BMDMs treated with SPARC (20 μg/ml) for 24 hours with or without pre-treatment of glycolysis inhibitor (2-DG, 10 mM) (n=3). (S) ELISA assay for IFN-β detection in supernatants of SPARC treated M2 BMDMs

with or without pre-treatment of glycolysis inhibitor (2-DG, 10 mM) (n=3). All experiments were repeated independently at least twice. Error bars represent the mean ± S.E.M. Two-tailed paired and unpaired t-tests were performed for statistical analysis. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

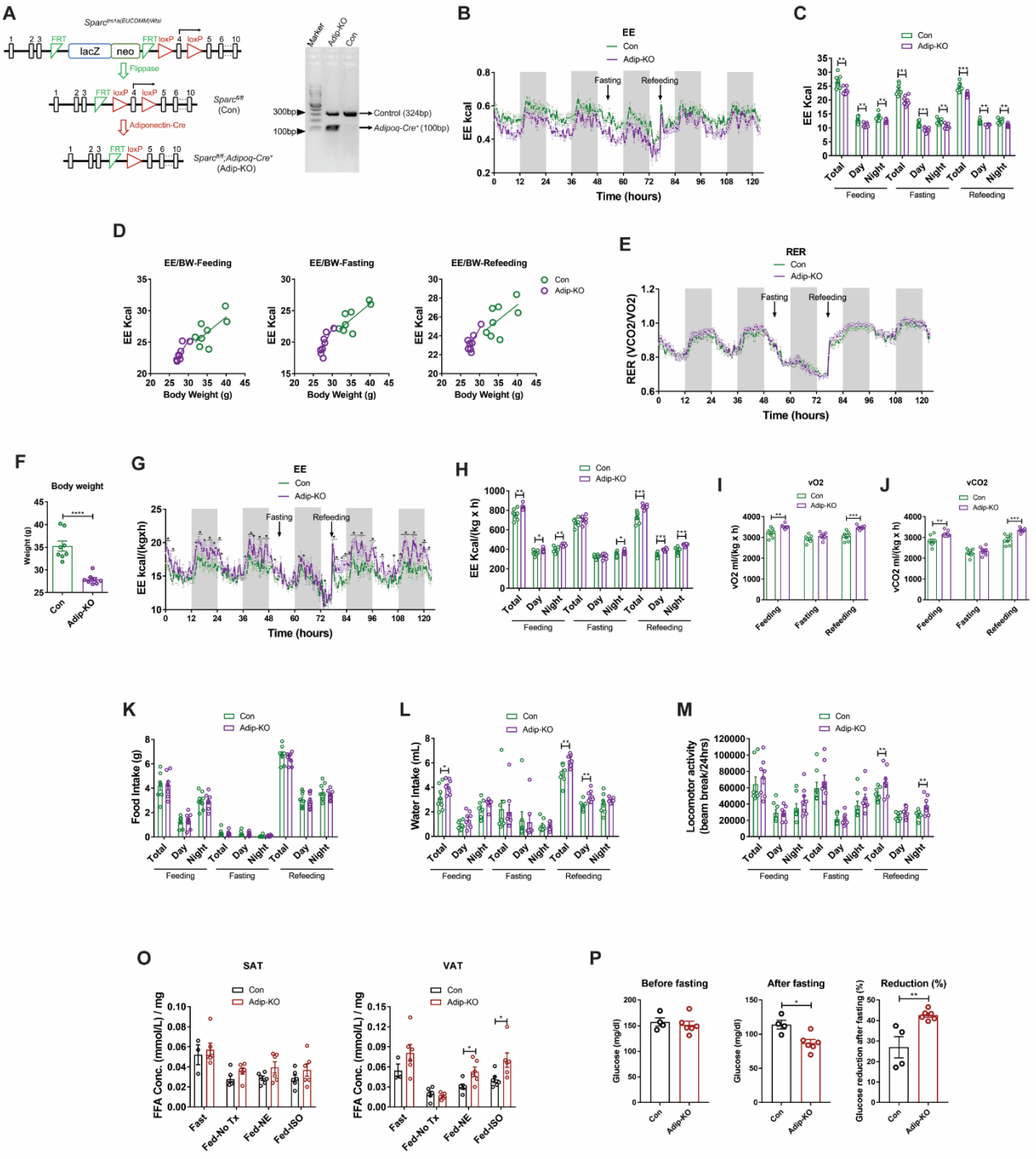

Figure S6. Enhancement of metabolic healthspan in aged adipocyte-specific SPARC KO, Related to Figure 6. (A) Schematic of adipocyte-specific SPARC KO mouse generation (left) and gel electrophoresis of genotyping PCR products with extracted genomic DNA from Con and Adip-KO mice (right). Control (324bp) is the product for positive control genotyping PCR, and

Adipoq-Cre^{+} (100bp) is the product for Adipoq-Cre construct genotyping PCR. (B-E) Analysis results from metabolic cage experiments. Unnormalized EE (B, C), comparison of linear regression lines (D), and RER (E) of 20-month-old control and Adip-KO mice with fasting (24 hr) and refeeding (48 hr) measured in metabolic cages (n=8, 8). (F-J) Body weight (F) normalized parameters detected in metabolic cages. EE (G, H), vO_2 (I), vCO_2 (J), and food intake (K), water intake (L), and locomotor activity (M) of 20-month-old control and Adip-KO mice. (O) FFA analysis with explant of SAT and VAT from 22-month-old control and Adip-KO mice with lipolysis. FFA concentrations released from adipose tissue was measured with 24 hr fasting (n=3, 6) and either norepinephrine (NE) or isoproterenol (ISO) incubation in fed condition (n=6, 6). (P) Glucose concentrations before and after 24 hr fasting of 22-month-old control and Adip-KO mice (n=4, 6). All *in vitro* or *ex vivo* experiments were repeated independently at least twice. Error bars represent the mean ± S.E.M. Two-tailed unpaired t-tests were performed for statistical analysis. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

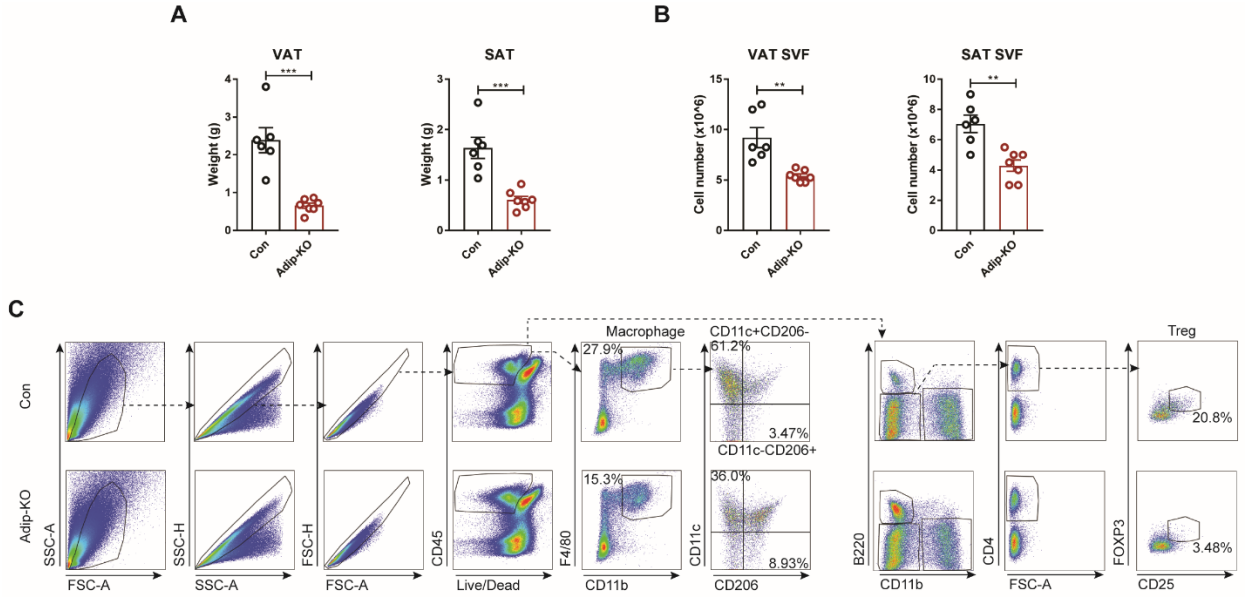

Figure S7. Aging-related adipose immune cell dysregulation is attenuated in adipocyte specific SPARC KO mice, Related to Figure 7. (A, B) Adipose tissue weight (A), and SVF cell number in adipose tissue (B) in 22-month-old control and Adip-KO mice (n=6, 7). (C) Gating plot of FACS analysis to detect CD11c+ CD206- and CD11c- CD206+ macropahges and Tregs in SVF of 22-month-old control and Adip-KO mice. All *in vitro* or *ex vivo* experiments were repeated independently at least twice. Error bars represent the mean ± S.E.M. Two-tailed unpaired t-tests were performed for statistical analysis. ** $P < 0.01$; *** $P < 0.001$.

Table S1. Primer information for qPCR, Related to STAR METHODS.

Gene	Direction	5'-3'
Il1b	Forward	GGTCAAAGGTTTGGAAGCAG
	Reverse	TGTGAAATGCCACCTTTTGA
Tnf	Forward	TCTCAGCCTCTTCTCATT
	Reverse	AGAACTGATGAGAGGGAG
Il6	Forward	AGACAAAGCCAGAGTCCTTCAGAG
	Reverse	TTGGTCCTTAGCCACTCCTTCTGT
Nos2	Forward	CCCTCCTGATCTTGTGTTGG
	Reverse	GGCAGTGCATACCACTTCAA
Stat1	Forward	TCACAGTGGTTCGAGCTTCAG
	Reverse	GCAAACGAGACATCATAGGCA
Retnla	Forward	ACTTCTTGCCAATCCAGCTAAC
	Reverse	CAAGCACACCCAGTAGCAGT
Chil3	Forward	CTGGAATTGGTGCCCCTACAA
	Reverse	AGACCTCAGTGGCTCCTTCAT
Socs2	Forward	CAAACAGGATGGTACTGGGGA
	Reverse	CCAGCTGACGTCTTAACGGAT
Gapdh	Forward	TCAACAGCAACTCCCACTCTTCCA
	Reverse	ACCCTGTTGCTGTAGCCGTATTCA
18S	Forward	AACCCGTTGAACCCCATT
	Reverse	CCATCCAATCGGTAGTAGCG
Ifit2	Forward	ACAGCAGACAGTTACACAGCA
	Reverse	TCAGGTTCCAGGTGAAATGGC
Isg15	Forward	GGGACCTAGAGCTAGAGCCTG
	Reverse	AGTTAGTCACGGACACCAGGA
Xaf1	Forward	GAGACGAGACGGCCTATGAC
	Reverse	GTGAGCTAACCTCTGGCACT
Ifit3	Forward	GTGGTGGATTCTTGGCAGTT
	Reverse	GACACACTTCCGGTTGTCCT
Tert	Forward	CTAGCTCATGTGTCAAGACCCTCTT
	Reverse	GCCAGCACGTTTCTCTCGTT
Dloop3	Forward	TCCTCCGTGAAACCAACAA
	Reverse	AGCGAGAAGAGGGGCATT
ND4	Forward	AACGGATCCACAGCCGTA
	Reverse	AGTCCTCGGGCCATGATT
hSPARC	Forward	GAACCACCACTGCAAACACG
	Reverse	TGTCATTGCTGCACACCTTC
hSPARC D1	Forward	CAAGAAGCCCTGCCTGATG
	Reverse	TCTTCGGTTTCCTCTGCACC
hSPARC D2	Forward	CCCCATTGGCGAGTTTGAGA
	Reverse	TTGCAAGGCCCGATGTAGTC
hSPARC D3	Forward	CCCTGTACACTGGCAGTTCG
	Reverse	GCAATGCTCCATGGGGATGA
Calcrl	Forward	AGGCGTGAACCAAACAGACT
	Reverse	TTCCAGCATAGCCATCCGTC
Pde3e	Forward	ACATGGGGCTCTTTGAAGCC
	Reverse	CGTGTAGAACATCGGTGGCA
Ppara	Forward	GACAAGGCCTCAGGGTACCA
	Reverse	GCCGAATAGTTCGCCGAAA
Gdf3	Forward	AGGTCCTACTATAACCTGCG
	Reverse	CATATGCATCAGAGCCTGCA
Gdf15	Forward	CATCACTAGGCCCCTGAAGC
	Reverse	AGAGTTGCCTGCACAGTCTC
Casp1	Forward	GGACCCTCAAGTTTTGCCCT
	Reverse	AGACGTGTACGAGTGGTTGT