SUPPLEMENTAL FIGURES

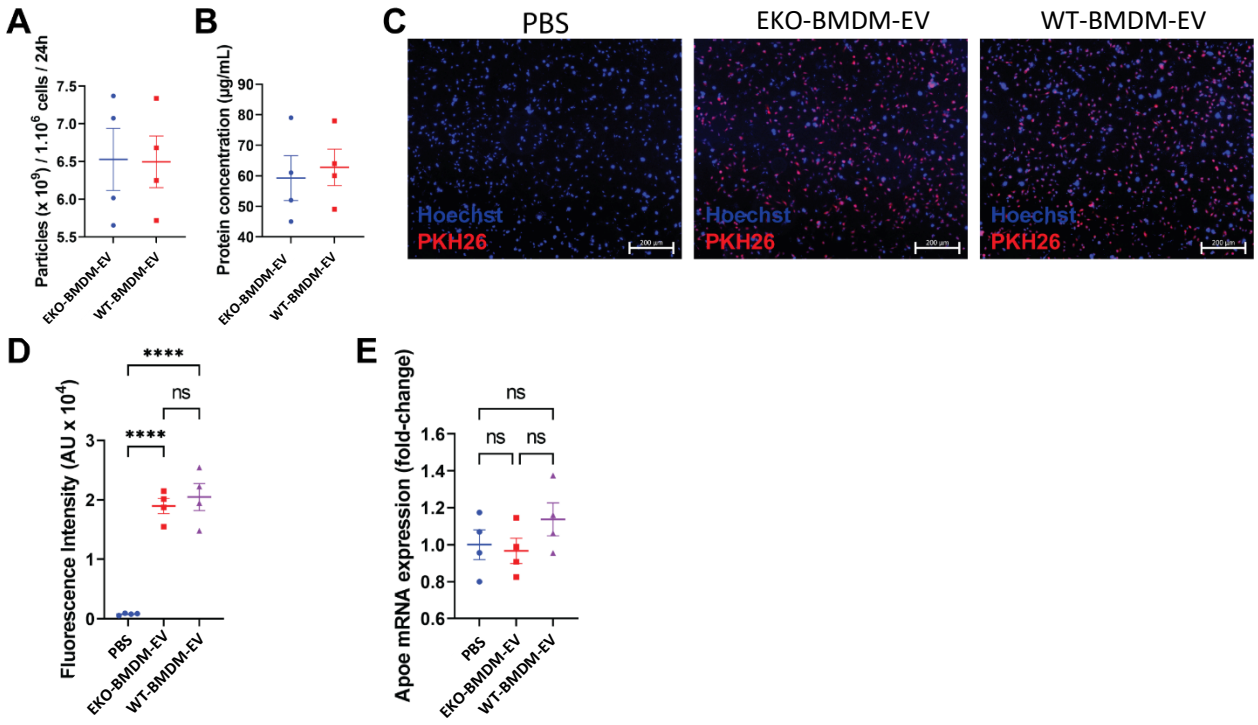

Figure S1. Characterization and *in vitro* uptake of BMDM EVs in recipient macrophages. **(A)** EVs secretion rate (x 10^9 particles) per million cells over a 24-hour incubation period as detected by NTA. **(B)** Protein measurements in EV-containing fractions isolated from conditioned media of BMDM macrophages. n = 4 per group. **(C-D)** Merged images (C) and quantification (D) of the internalization of PKH26-labeled BMDM-derived EVs by naive primary BMDM counterstained with Hoechst (blue). BMDM were co-incubated with 2 x 10^9 PKH26-labeled EVs for 2 h at 37°C and washed repeatedly to remove unbound EVs. All images were acquired using a Zeiss Axio microscope system with a 20x objective (n = 4 samples per group, representative of two independent experiments). Scale bar: 100 µm. **(E)** qRT-PCR analysis of *Apoe* mRNA expression in wildtype BMDM exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours. qRT-PCR results were normalized to *B2m* or *Gapdh.* One representative experiment out of three independent replicates is shown for all

experiments; n = 4 per group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$ as determined using one-way ANOVA followed by Holm-Sidak post-test. Data are presented as mean ± SEM.

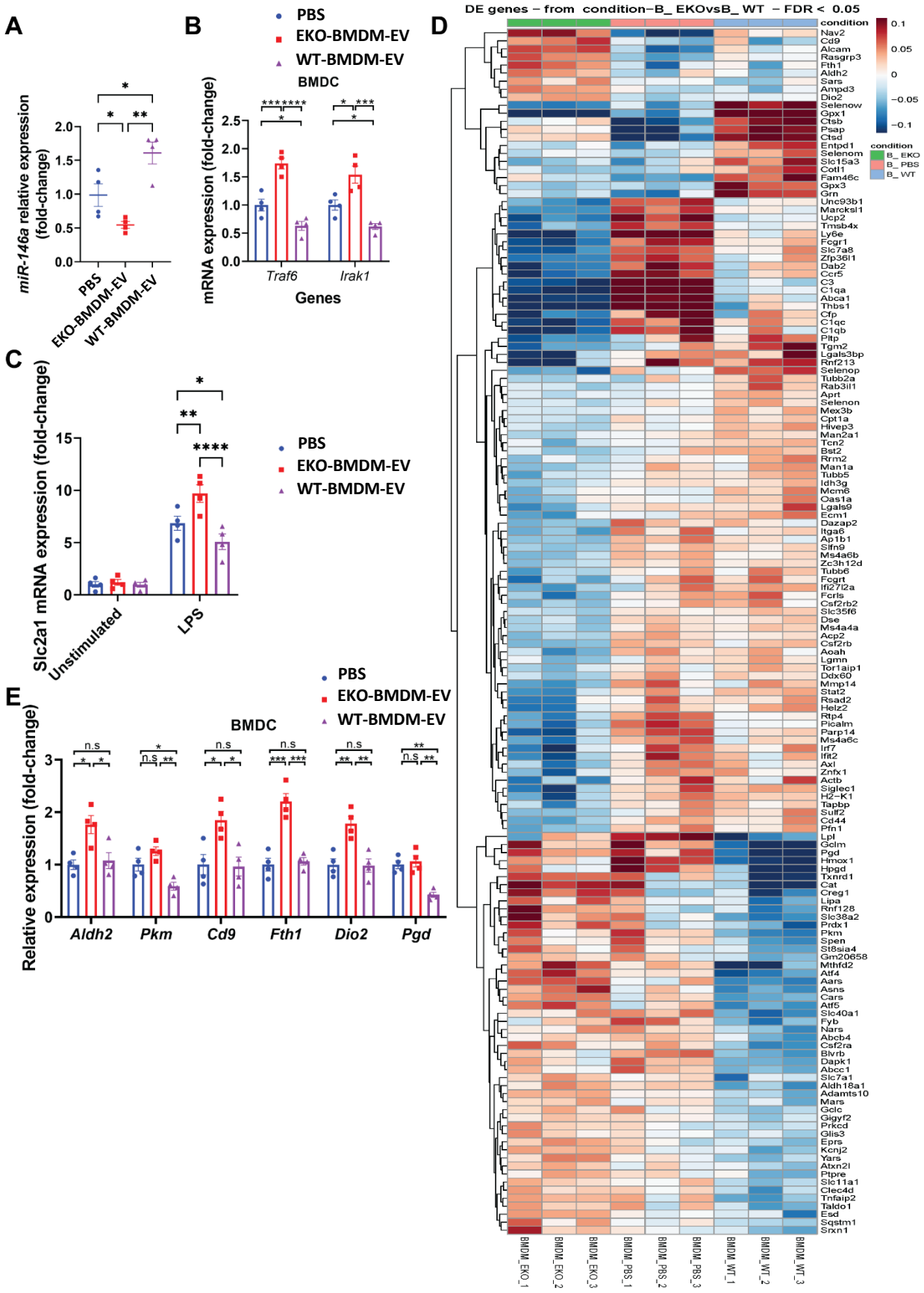
A
miR-146a relative expression (fold-change)
PBS
EKO-BMDM-EV
WT-BMDM-EV
B
PBS
EKO-BMDM-EV
WT-BMDM-EV
BMDC
mRNA expression (fold-change)
Traf6
Irak1
Genes
C
Slc2a1 mRNA expression (fold-change)
Unstimulated
LPS
PBS
EKO-BMDM-EV
WT-BMDM-EV
D
DE genes – from condition–B_ EKOvsB_ WT – FDR < 0.05
condition
B_ EKO
B_ PBS
B_ WT
BMDM_EKO_1
BMDM_EKO_2
BMDM_EKO_3
BMDM_PBS_1
BMDM_PBS_2
BMDM_PBS_3
BMDM_WT_1
BMDM_WT_2
BMDM_WT_3
E
BMDC
PBS
EKO-BMDM-EV
WT-BMDM-EV
Relative expression (fold-change)
Aldh2
Pkm
Cd9
Fth1
Dio2
Pgd

Figure S2. ApoE expression dictates the capacity for macrophage EVs to downregulate the expression of genes involved in glucose uptake and glycolytic activity in recipient BMDC. **(A)** qRT-PCR analysis of miR-146a-5p expression in wildtype BMDC exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours. **(B)** qRT-PCR analysis of *Irak1* and *Traf6* mRNA levels in wildtype BMDC exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours and subsequently stimulated with LPS (100 ng/mL) for 6 hours. **(C)** qRT-PCR analysis of *Slc2a1* mRNA expression in wildtype BMDC exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours and subsequently cultured in basal or LPS-stimulated condition (100 ng/mL) for 6 hours. **(D)** Annotated heatmap showing the distinct mRNA expression profiles between wildtype BMDM exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours (n = 3 per group, $p < 0.05$). **(E)** qRT-PCR analysis of *Aldh2*, *Pkm*, *Cd9*, *Fth1*, *Dio2*, and *Pgd* mRNA expression in wildtype BMDC exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours. qRT-PCR results were normalized to *B2m* or *Gapdh* for mRNA analysis and U6 snRNA or miR-16-5p for microRNA analysis. One representative experiment out of three independent replicates is shown for all experiments; n = 4 per group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$ as determined using one-way ANOVA followed by Holm-Sidak post-test. Data are presented as mean ± SEM.

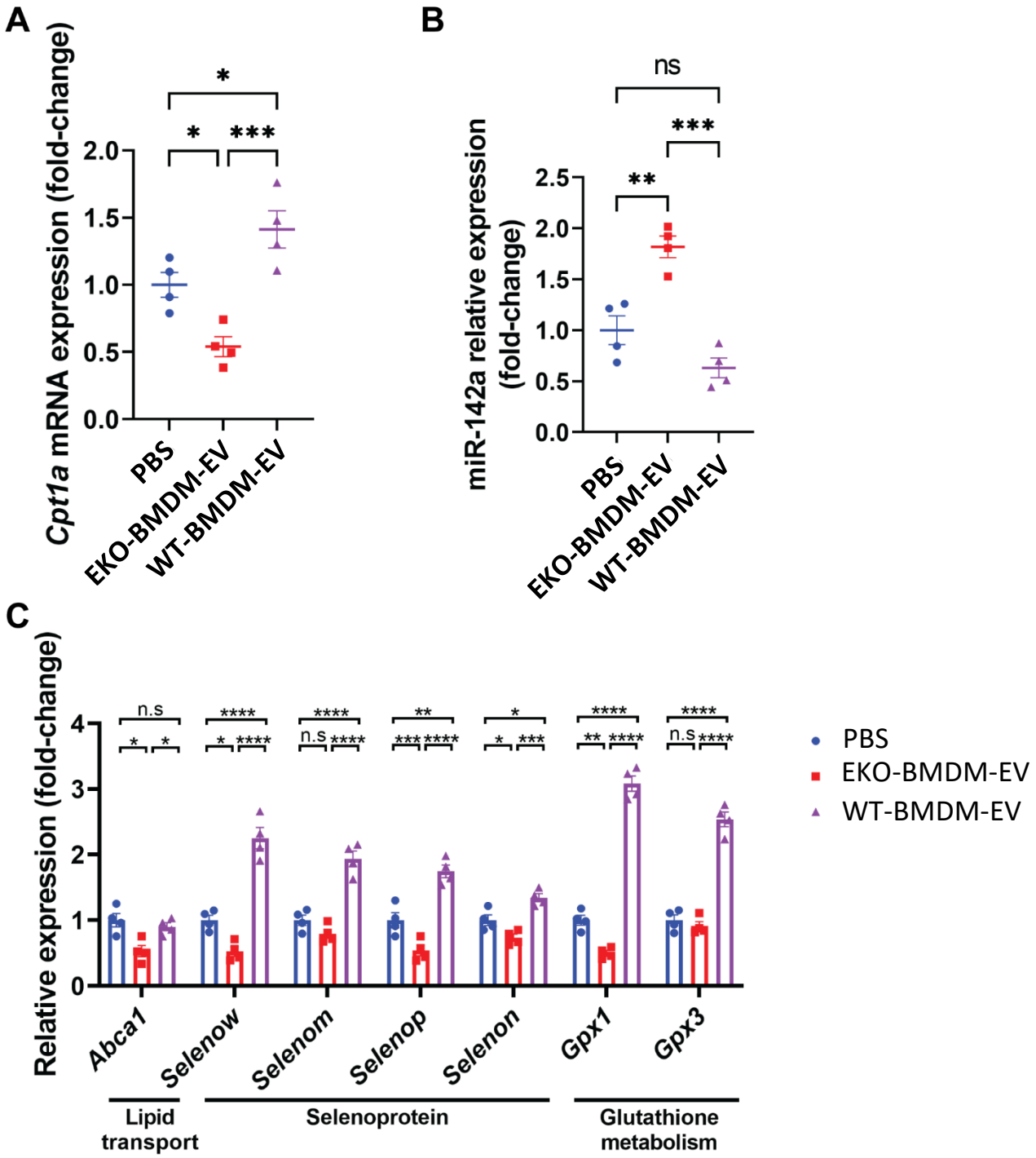

Figure S3. ApoE expression dictates the capacity for macrophage EVs to enhance the expression of genes involved in FAO, OxPHOS, lipid transport, and oxidative stress response in recipient BMDC. (A) qRT-PCR analysis of *Cpt1a* mRNA expression in wildtype

BMDC exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours. **(B)** qRT-PCR analysis of miR-142a-3p expression in wildtype BMDC exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours. **(C)** qRT-PCR analysis of *Abca1*, *Selenow*, *Selenom*, *Selenop*, *Selenon*, *Gpx1* and *Gpx3* mRNA expression in wildtype BMDC exposed to 2 x 10^9 particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS for 18 hours. qRT-PCR results were normalized to *B2m* or *Gapdh* for mRNA analysis and U6 snRNA or miR-16-5p for microRNA analysis. One representative experiment out of three independent replicates is shown for all experiments; n = 4 per group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$ as determined using one-way ANOVA followed by Holm-Sidak post-test. Data are presented as mean ± SEM.

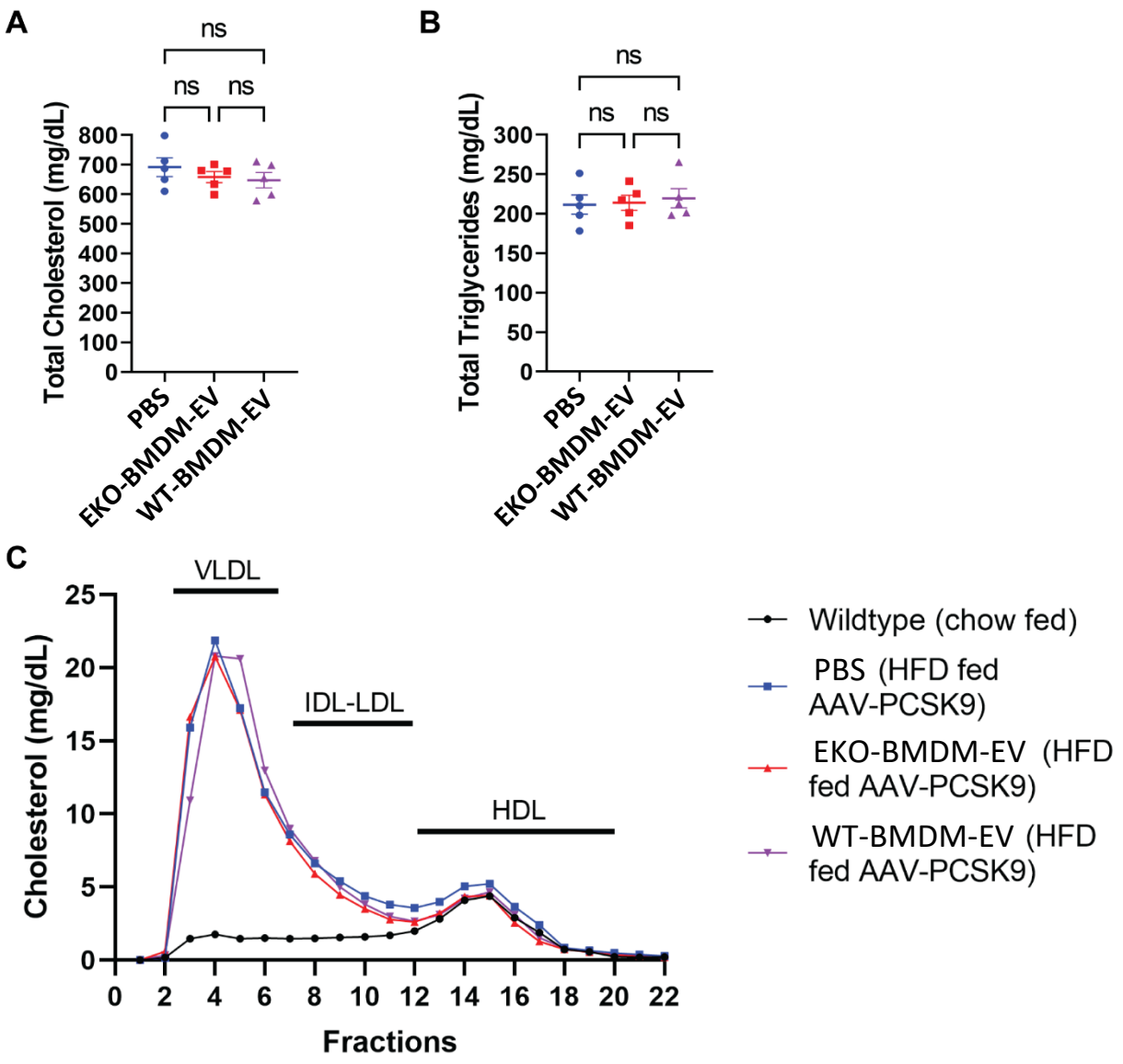

Figure S4. Lipid profiles of Western diet-fed AAV-PCSK9 mice infused with EKO-BMDM-EV, WT-BMDM-EV, or PBS. (A-B) Fasting plasma cholesterol (A) and triglycerides (B) in Western diet-fed AAV-PCSK9-injected mice repeatedly infused with 1 x 10^{10} particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS. **(C)** Cholesterol measurements in FPLC fractions from collected plasma of Western diet-fed AAV-PCSK9-injected mice repeatedly infused with 1 x 10^{10} particles of EKO-BMDM-EV, WT-BMDM-EV, or PBS. One representative experiment out of two independent replicates is shown for all experiments; n = 5 per group. *p < 0.05, **p <

0.01, ***$p < 0.001$, and ****$p < 0.0001$ as determined using one-way ANOVA followed by Holm-Sidak post-test. Data are presented as mean ± SEM.

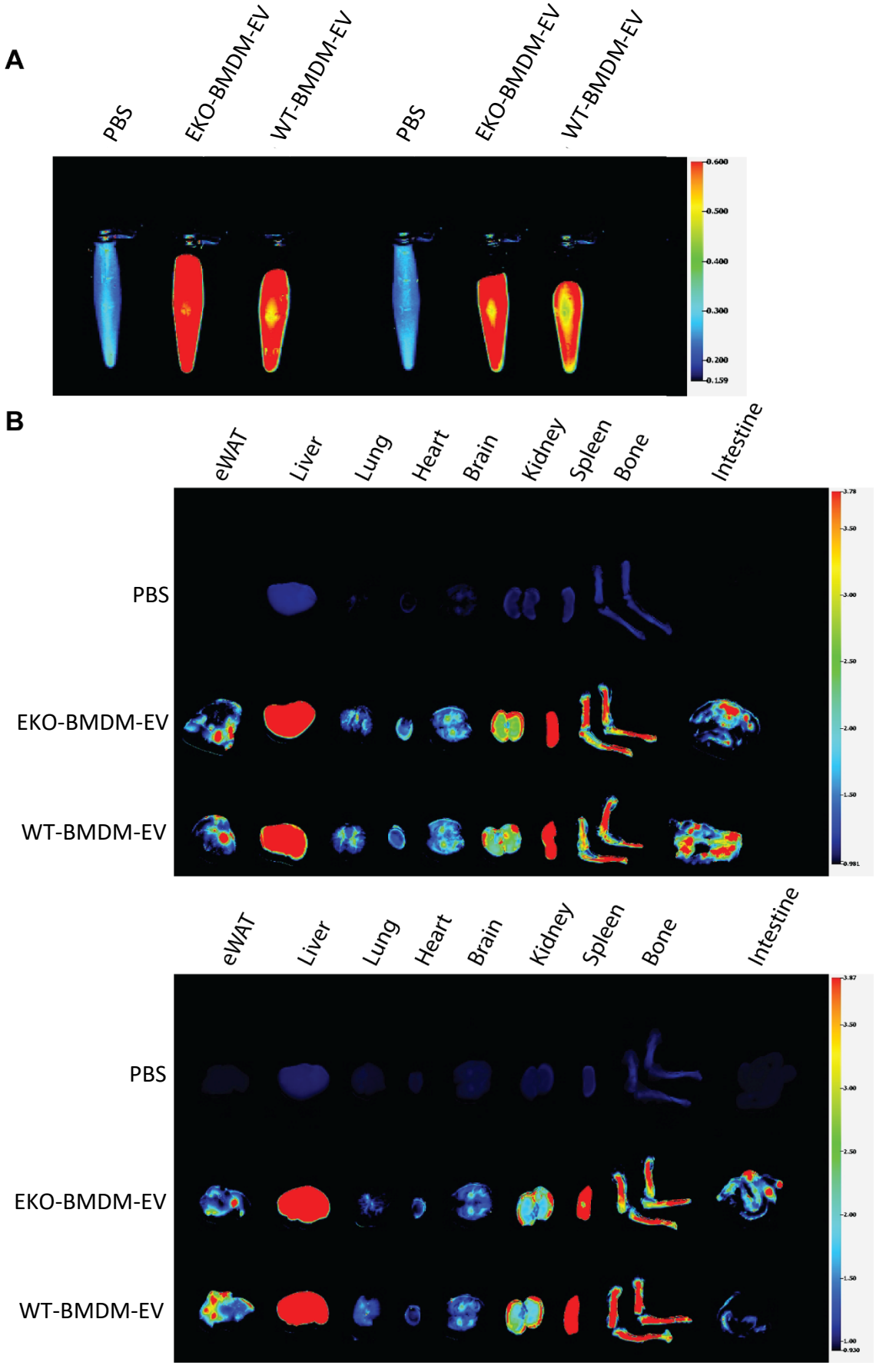
A
PBS
EKO-BMDM-EV
WT-BMDM-EV
PBS
EKO-BMDM-EV
WT-BMDM-EV
0.600
0.500
0.400
0.300
0.200
0.159
B
eWAT
Liver
Lung
Heart
Brain
Kidney
Spleen
Bone
Intestine
PBS
EKO-BMDM-EV
WT-BMDM-EV
3.78
3.50
3.00
2.50
2.00
1.50
0.981
eWAT
Liver
Lung
Heart
Brain
Kidney
Spleen
Bone
Intestine
PBS
EKO-BMDM-EV
WT-BMDM-EV
3.87
3.50
3.00
2.50
2.00
1.50
1.00
0.930

Figure S5. Biodistribution of DiR-labeled BMDM EVs upon infusion into Western diet-fed AAV-PCSK9 mice. (A-B) Images of DiR fluorescence in blood (A) and organs (B) 6 h post-injection from 8-week-old Western diet-fed AAV-PCSK9-injected mice infused i.p. with PBS as control or 1 x 10^{10} particles of EKO-BMDM-EV or WT-BMDM-EV.

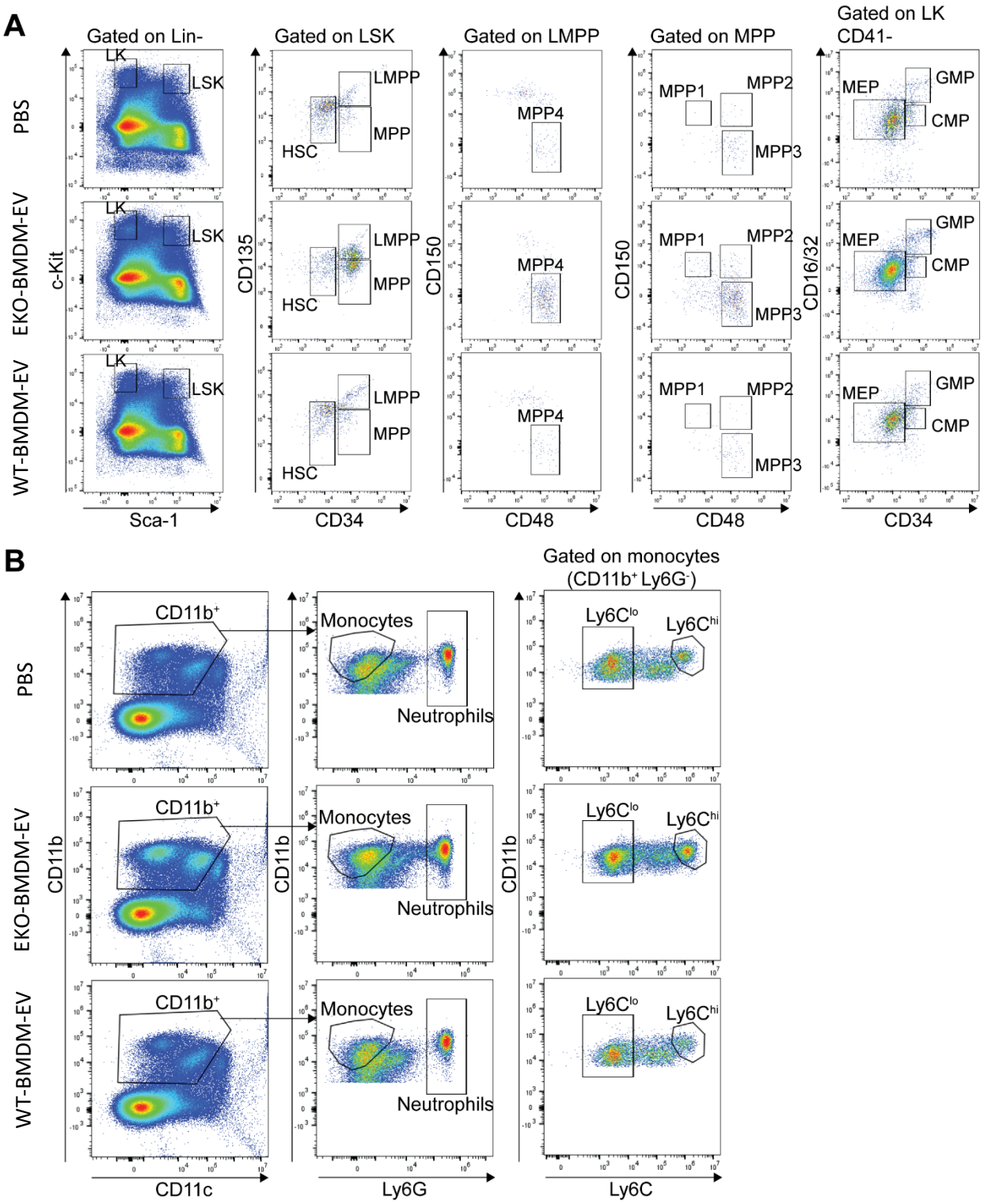
A
Gated on Lin-
Gated on LSK
Gated on LMPP
Gated on MPP
Gated on LK CD41-
PBS
EKO-BMDM-EV
WT-BMDM-EV
c-Kit
Sca-1
LK
LSK
CD135
CD34
HSC
LMPP
MPP
CD150
CD48
MPP4
MPP1
MPP2
MPP3
CD16/32
MEP
GMP
CMP
B
Gated on monocytes (CD11b+ Ly6G-)
CD11b+
CD11b
CD11c
Monocytes
Neutrophils
Ly6G
Ly6C
Ly6Clo
Ly6Chi

Figure S6. Gating strategy for flow cytometric analysis of splenic HSPC and myeloid cells.

(A-B). Representative flow cytometry plots of splenic hematopoietic stem/progenitor cell subsets (A) and myeloid cell subsets (B).

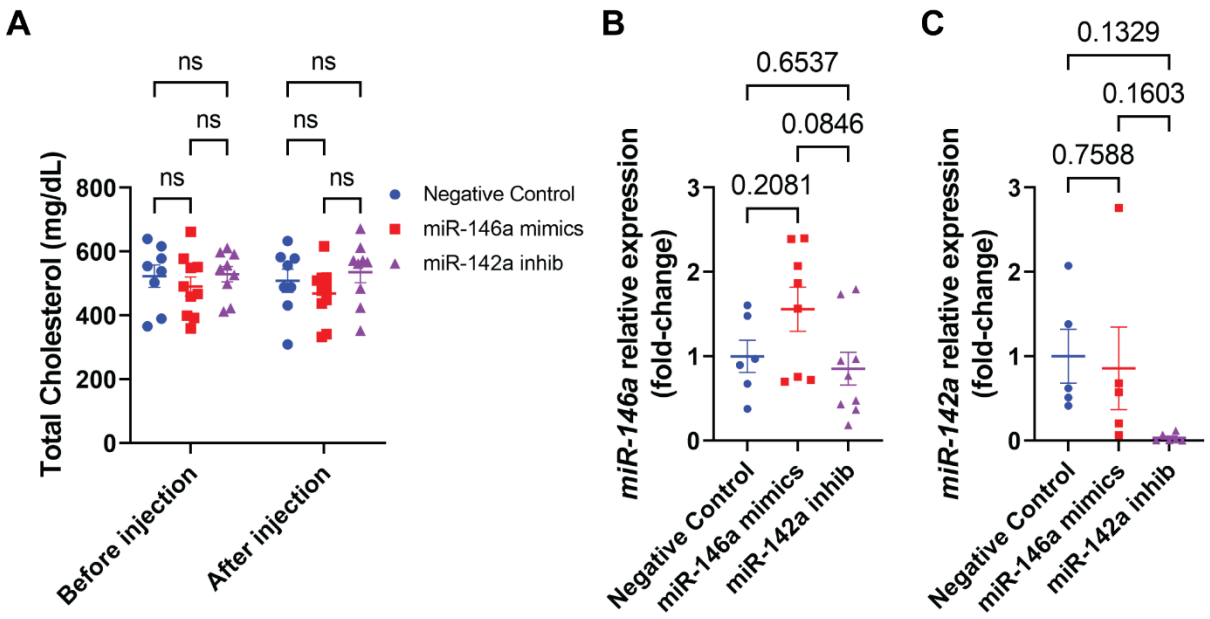

Figure S7. Infusions of RNA oligonucleotides regulated cellular miR-146a-5p and miR-142a-3p without altering plasma cholesterol levels. (A) Fasting plasma cholesterol in Western diet-fed *Apoe*$^{-/-}$ mice repeatedly infused with 1 nmol of miR-146a mimics, miR-142a inhibitors, or negative control. **(B-C)** qRT-PCR analysis of miR-146a-5p (B) and miR-142a-3p (C) expression in peritoneal macrophages of Western diet-fed *Apoe*$^{-/-}$ mice repeatedly infused with 1 nmol of miR-146a mimics, miR-142a inhibitors, or negative control. Pooled data from two independent replicates is shown for all experiments; n = 5-10 per group. *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 as determined using one-way ANOVA followed by Holm-Sidak post-test. Data are presented as mean ± SEM.