

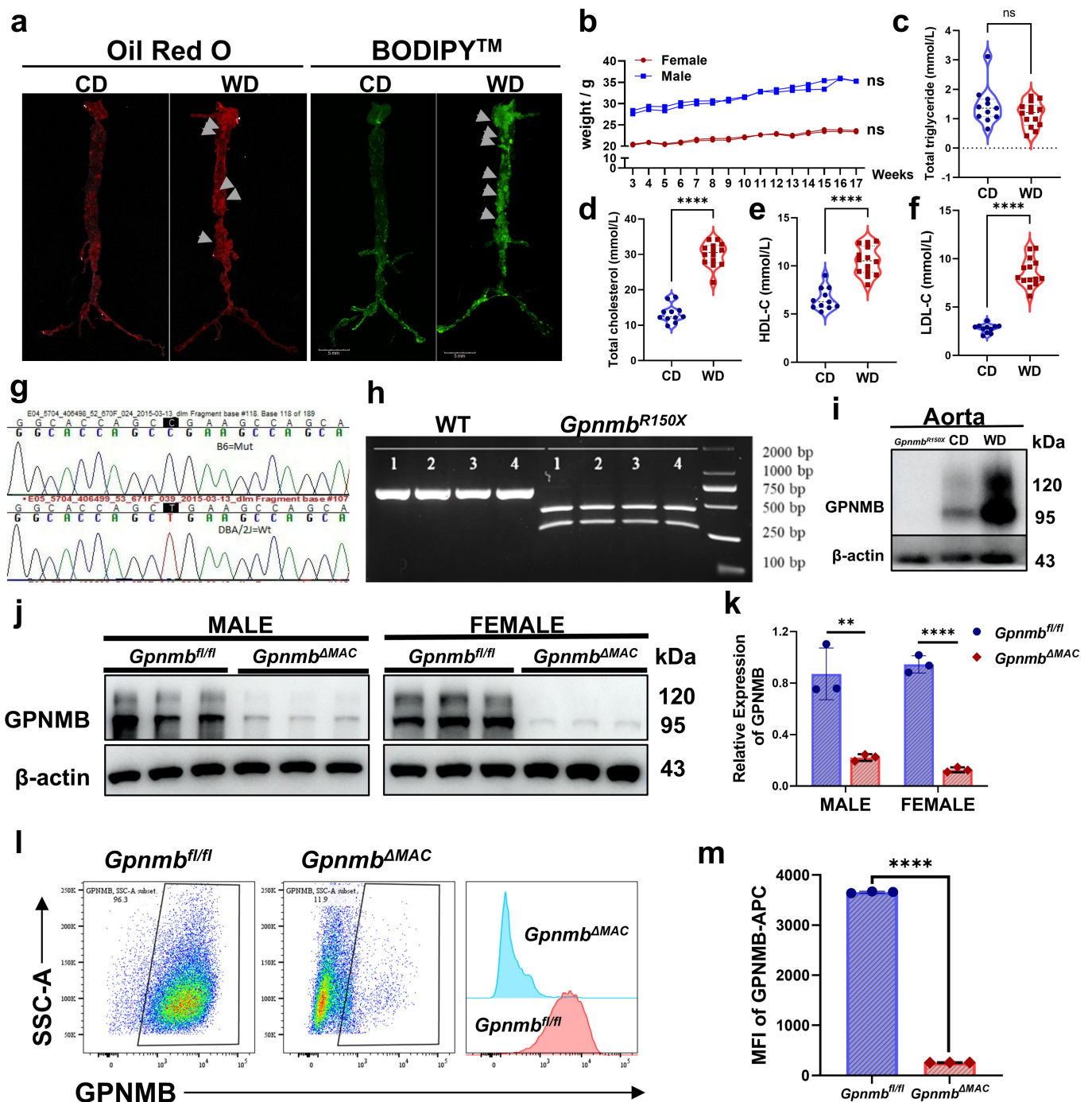


Figure S1. Identification of Mouse Models

(a-f) The features of *ApoE*^{-/-} mice fed with a CD (n=11) or WD (n=14) for 18 weeks, including Oil-Red-O staining and BODIPY staining of aorta en face (a), weight curves (b), and the quantitative analysis of total triglyceride (c), total cholesterol (d), HDL-C (e), and LDL-C (f).

(g-i) The mutation of *Gpnmb* is confirmed by sequencing (g), PCR (h), and western blot (i).

(j-k) The myeloid-specific knockout of *Gpnmb* is confirmed by western blot (n=3).

(l-m) The myeloid-specific knockout of *Gpnmb* is confirmed by flow cytometry (n=3).

Data are expressed as mean $\pm$ SEM. Data are expressed as mean $\pm$ SEM. *P*-values were calculated by an unpaired Student t-test (b-f, k, and m). Differences are significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

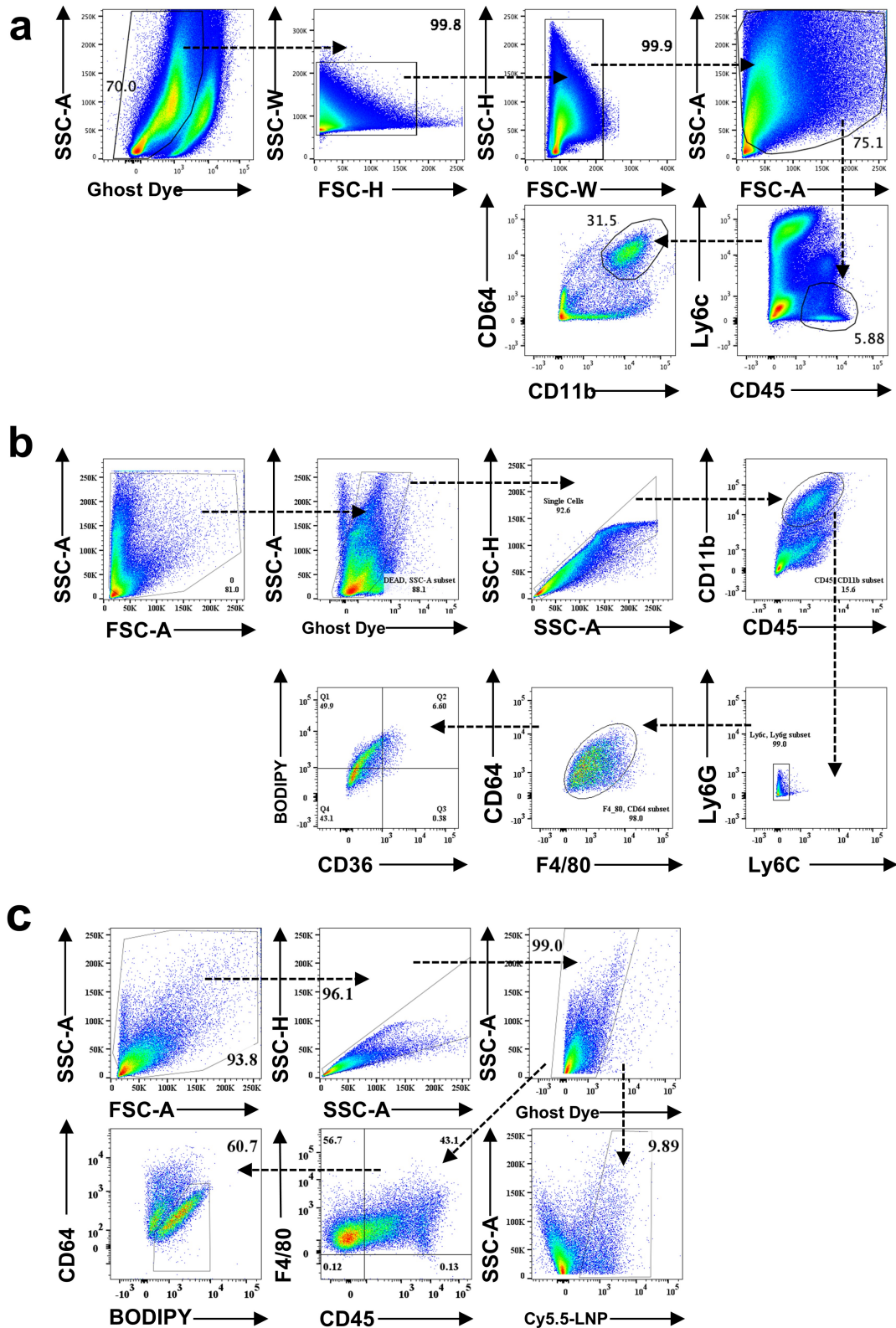


Figure S2. Gating strategy of flow cytometry

Gating strategy of flow cytometry for detecting aortic foam cells.

(a) *ApoE*^{-/-} mice fed with a CD or WD (corresponding to Figure 1N).

(b) WT *ApoE*^{-/-}, HET *ApoE*^{-/-}, and *Gpnmb*^{R150X} *ApoE*^{-/-} (all on hybrid DBA/2-C57BL/6J background) mice were fed a WD (corresponding to Figure 5J).

(c) *ApoE*^{-/-} mice were fed a WD and treated with siNC-LNPs or si*Gpnmb*-LNPs through tail vein injection (corresponding to Figure 7R).

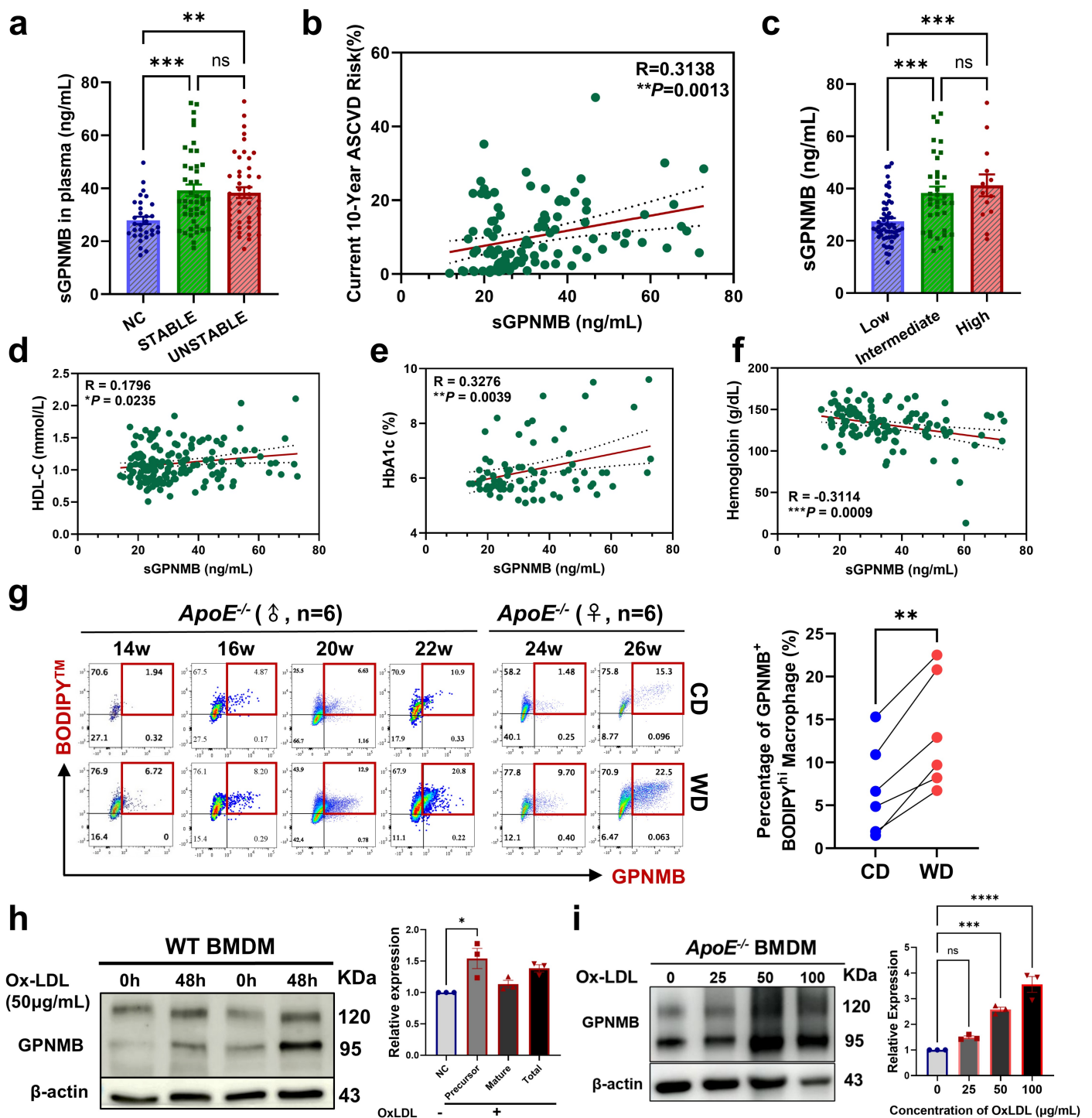


Figure S3. GPNMB Highly Expressed in Atherosclerotic Plaques and Colocalized with Macrophages

(a) Plasma sGNMB levels of patients with stable and unstable coronary atherosclerosis based on clinical diagnosis and the controls (n=31/44/45).

(b-c) The linear relationship of plasma levels of sGNMB with the current 10-year ASCVD Risk score (b, n=102) and comparison of plasma sGNMB levels among patients with varying severity based on the ASCVD Risk score (c, High, Intermediate, Low, n=56/35/13).

(d-f) The linear relationship of sGNMB with HDL-C (d, n=159), Hemoglobin A1C (HbA1c, e, n=76), and Hemoglobin (f, n=110) in the plasma of participants.

(g) Flow cytometry results of $GPNMB^{+} BODIPY^{hi}$ macrophages from $ApoE^{-/-}$ mice fed with a chow diet (CD) or western diet (WD) for different weeks (N=6 independent experiments, left) and the quantitative analysis (right).

(h) Representative western blot images showing the expression of GPNMB in BMDMs from C57/6J mice (WT BMDMs) treated with OxLDL (50 μ g/mL) for different hours and corresponding quantitative analysis of GPNMB expression in WT BMDMs (n=3).

(i) Representative western blot images showing the expression of GPNMB in BMDMs from $ApoE^{-/-}$ mice treated with different concentrations of OxLDL for 48 hours and corresponding quantitative analysis of GPNMB expression in $ApoE^{-/-}$ BMDMs (n=3).

Data are expressed as mean $\pm$ SEM. *P*-values were calculated by an unpaired Student t-test (g) or one-way ANOVA (a, c, and h-i). Spearman rank correlation test, $P < 0.05$ was regarded as the statistical criterion to set thresholds (b, and d-f).

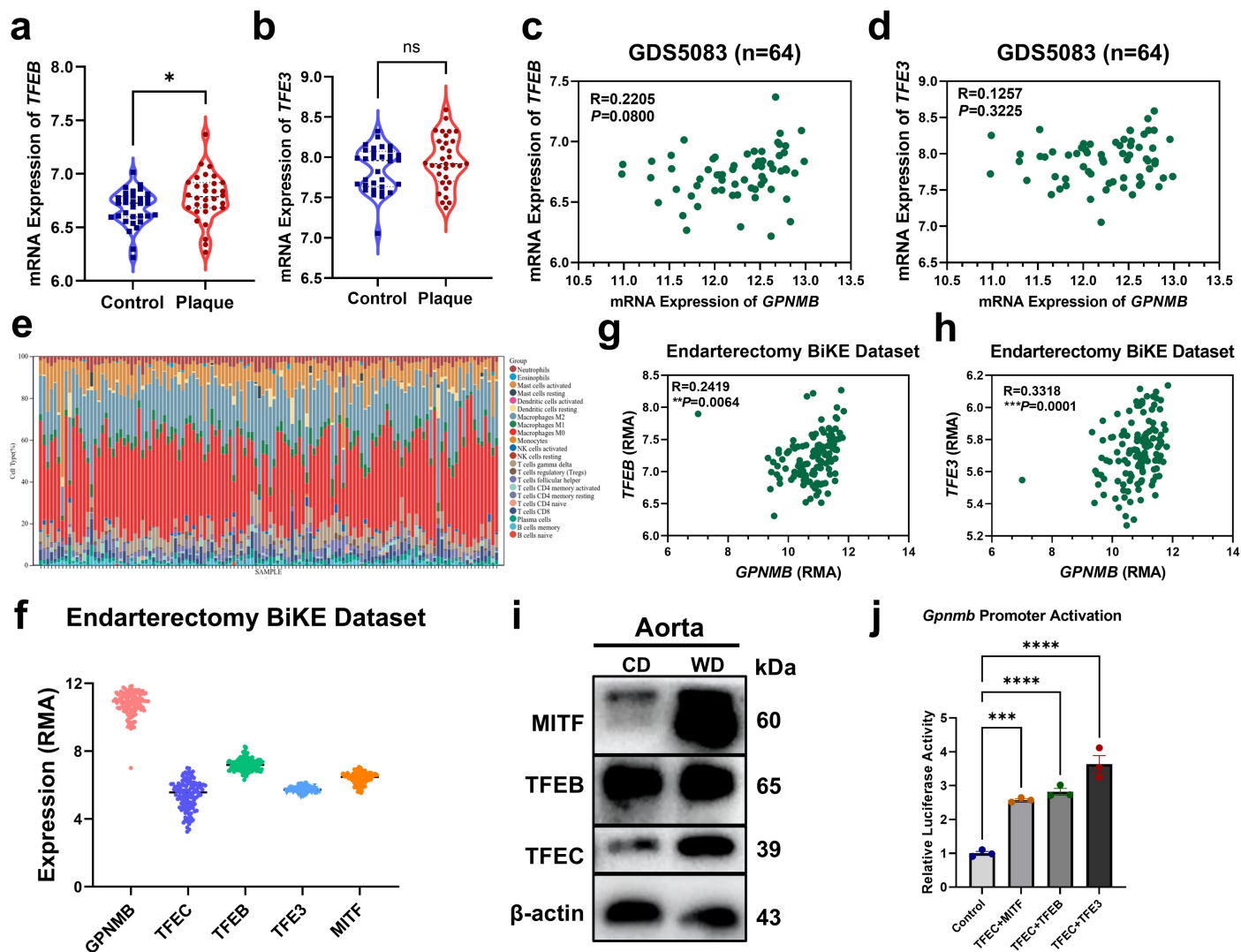


Figure S4. TFEC Induced *Gpnmb* Expression in Macrophages During Atherosclerosis Progression

(a-b) mRNA levels of *Tfeb* (a) and *Tfe3* (b) in human carotid artery atheromatous plaques and control intact tissue from hypertensive patients (n=32, based on dataset GDS5083).

(c-d) The relationships between *Gpnmb* expression with *Tfeb* expression (c) or *Tfe3* expression (d) in human carotid artery atheromatous plaques (d).

(e) Plaque composition extracted with Cibersort for representative *Gpnmb*^{high} (left) and *Gpnmb*^{low} (right) endarterectomy plaques (based on dataset GSE21545).

(f) mRNA levels of *Gpnmb* and MIT/TFE family of transcription factors measured by Affymetrix gene array (BiKE database, GSE21545) expressed as RMA (robust multi-array average; log scale).

(g-h) The relationships between *Gpnmb* expression with *Tfeb* expression (g) or *Tfe3* expression (h) in macrophages from human carotid plaque (n=126, based on dataset GSE21545).

(i) Representative western blot images showing the expression of MITF, TFEB, and TFEC in the aortas of *ApoE*^{-/-} mice fed with a CD or WD.

(j) *Gpnmb* promoter activity in HEK293T cells when co-transfected with pEGFP-TFEC plasmid and pEGFP-MITF plasmid, pEGFP-TFEB plasmid, or pEGFP-TFE3 plasmid by using a dual luciferase reporter assay (n=3).

Data are expressed as mean $\pm$ SEM. *P*-values were calculated by unpaired Student t-test (a-b) or one-way ANOVA (j). Differences are significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001. Spearman rank correlation test, *P* < 0.05 was regarded as the statistical criterion to set thresholds (c-d and g-h).

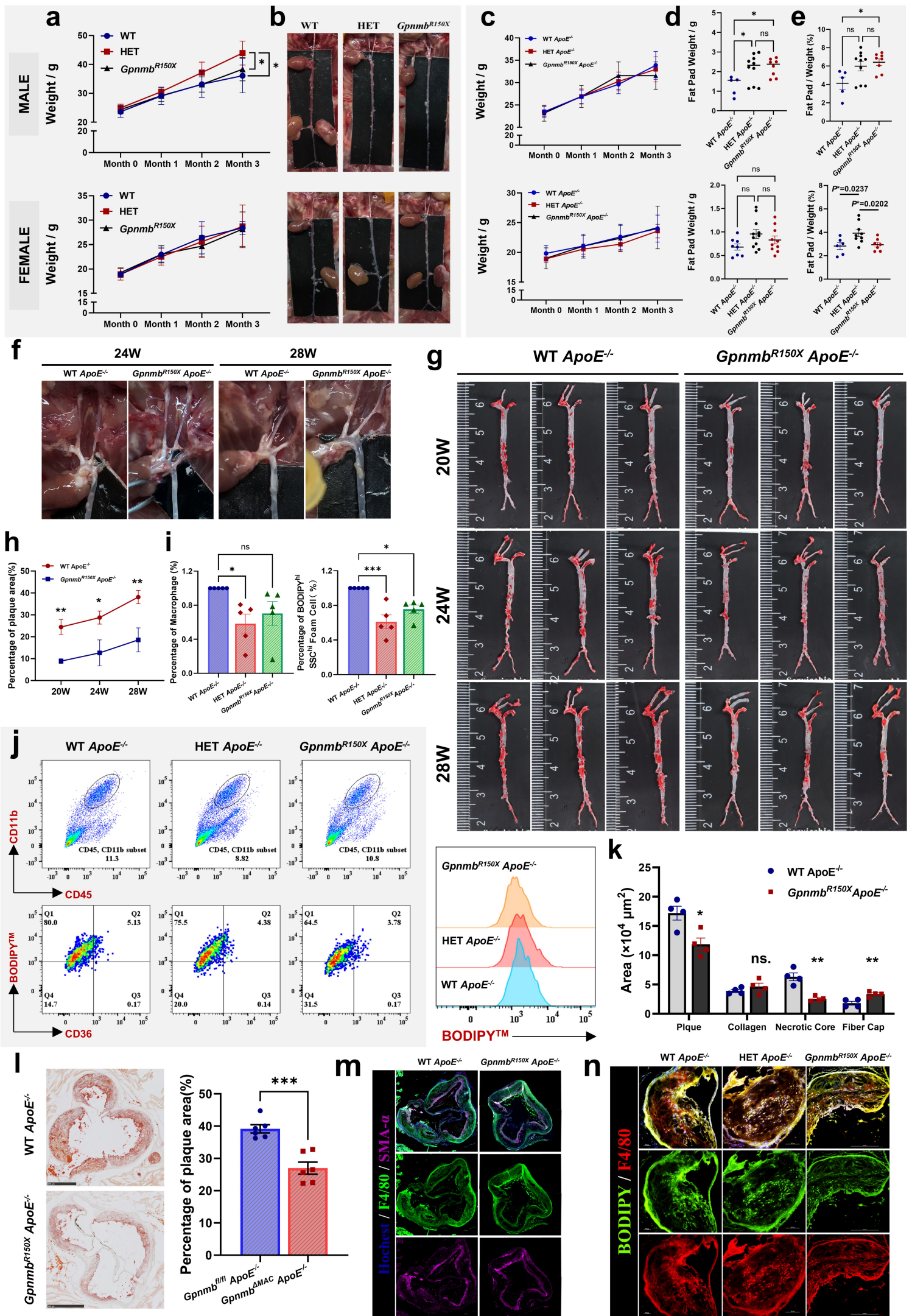


Figure S5. *Gpnmb*-mutation or Myeloid-specific *Gpnmb* knockout Alleviated Atherogenesis in *ApoE*^{-/-} Mice and Promotes a Favorable Plaque Phenotype

(a-b) The body weight curves (a) and representative aorta images (b) of WT, HET, and *Gpnmb*^{R150X} mice in the BXD-C background fed with a WD (male, upper, n=4/6/5; female, lower, n=4/6/6).

(c-e) The body weight curves (c, male, n=7/6/4; female, n=5) and the quantitative analysis of fat pad weight (d) and the proportion of fat pad weight to body weight (e) of WT *ApoE*^{-/-}, HET *ApoE*^{-/-}, and *Gpnmb*^{R150X} *ApoE*^{-/-} mice in the BXD-C background fed with a WD (male, upper, n=5/10/8; female, lower, n=8/11/10).

(f) The representative images of aortic arches of WT *ApoE*^{-/-} and *Gpnmb*^{R150X} *ApoE*^{-/-} mice in the BXD-C background fed with a WD.

(g-h) The representative photomicrographs and the quantification of en face lesion area in the whole aortas of WT *ApoE*^{-/-} and *Gpnmb*^{R150X} *ApoE*^{-/-} mice (female) fed a WD for 20, 24, and 28 weeks (n=3).

(i) The percentages of flow cytometric aortic macrophages (left) and BODIPY^{hi} SSC^{hi} foam cells in aortic macrophages (right) (male, N=5 independent experiments, n=3/group for each experiment).

(j) The representative flow cytometric expression of CD45 and CD11b in atherosclerotic aortas (upper dot plots) and CD36 and BODIPYTM levels in aortic macrophages (lower dot plots and histogram) (female, , N=3 independent experiments, n=3/group).

(k) The quantification of total plaque, collagen, necrotic core, and fiber cap area based on cross sections of the aortic sinus stained with Movat pentachrome (male, n=4).

(l) Representative Oil-Red-O-stained cross sections of aortic sinus from WT *ApoE*^{-/-} mice and *Gpnmb*^{R150X} *ApoE*^{-/-} mice and the quantification of plaque area percentages (male, n=6).

(m-n) Representative images of cross sections of the aortic sinus from immunofluorescence of F4/80⁺ macrophages (Red), BODIPY^{hi} foam cells (Green), and α -SMA⁺ fiber cap (Magenta) in atherosclerotic plaque from WT *ApoE*^{-/-}, HET *ApoE*^{-/-}, and *Gpnmb*^{R150X} *ApoE*^{-/-} mice in the BXD-C background fed with a WD for 22 weeks, N=3 independent experiments.

Data are expressed as mean $\pm$ SEM. *P*-values were calculated by unpaired Student t-test (a, c, h, k-l) or one-way ANOVA (d-e, and i). Differences are significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

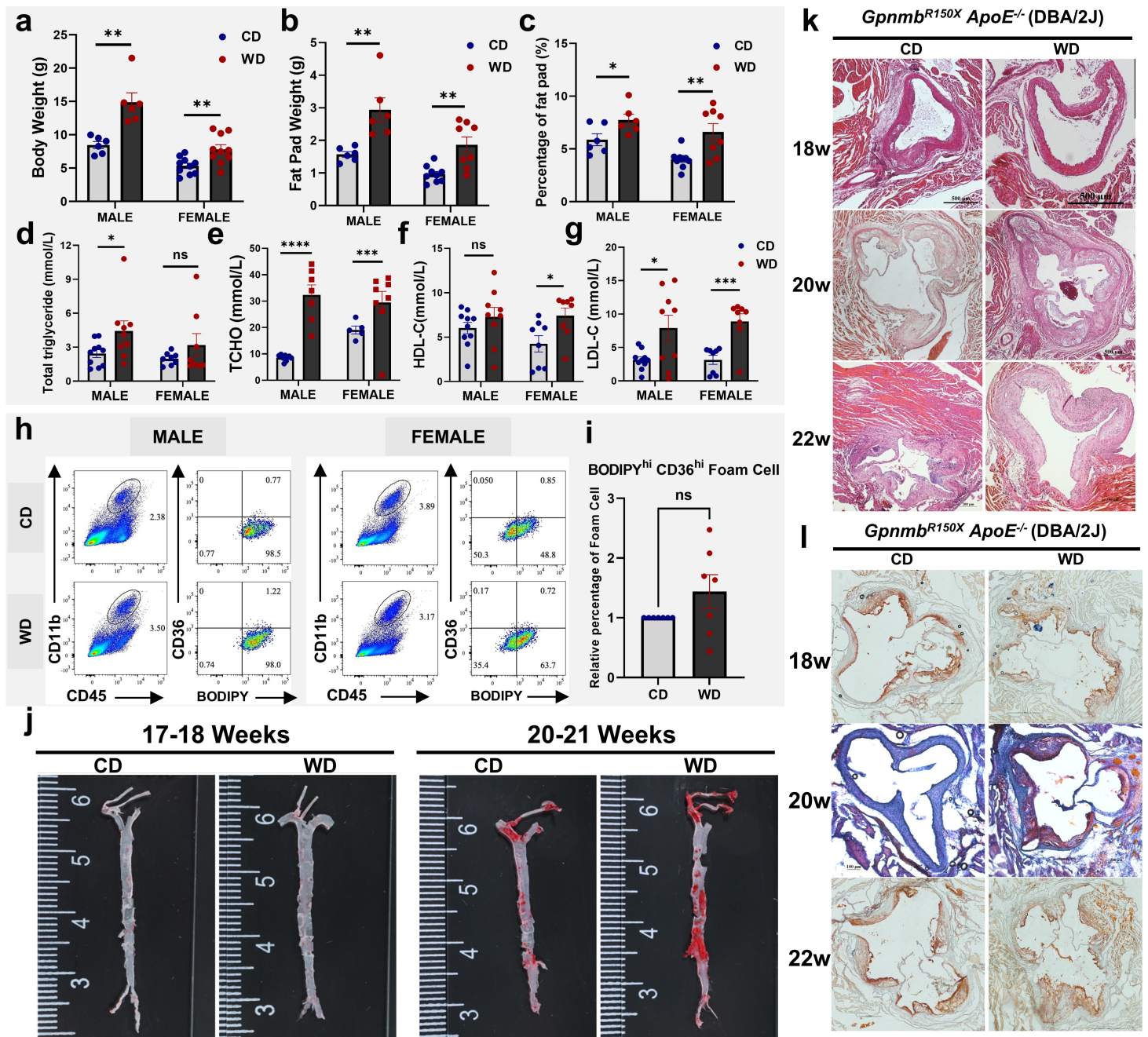


Figure S6. The characteristics of atherosclerosis in *Gpnmb*-mutation *ApoE*^{-/-} mice

The mice used in this figure were *Gpnmb*^{R150X} *ApoE*^{-/-} mice in the BXD-D background fed with a CD or WD for 18-22 weeks.

(a-c) The quantitative analysis of physiological characteristics, including body weight (a), fat pad weight (b), and the proportion of fat pad weight to body weight (c). Male, n=6; Female, n=9 in CD group, n=8 in WD group.

(d-g) The quantitative analysis of biochemical characteristics, including total triglyceride (d), total cholesterol (e), HDL-C (f), and LDL-C (g). Male, n=10 in CD group, n=9 in WD group; Female, n=8.

(h-i) The percentages of flow cytometric aortic macrophages and BODIPY^{hi} CD36^{hi} foam cells in aortic macrophages (h) (N=7 independent experiments on male mice).

(j) En-face Oil-Red-O staining of aortic lesions in the entire aorta.

(k-l) Representative images of cross sections of the aortic sinus stained with H&E staining and Oil-Red-O staining, N=3 independent experiments on male mice.

Data are expressed as mean $\pm$ SEM. *P*-values were calculated by unpaired Student t-test (a-g, and i). Differences are significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

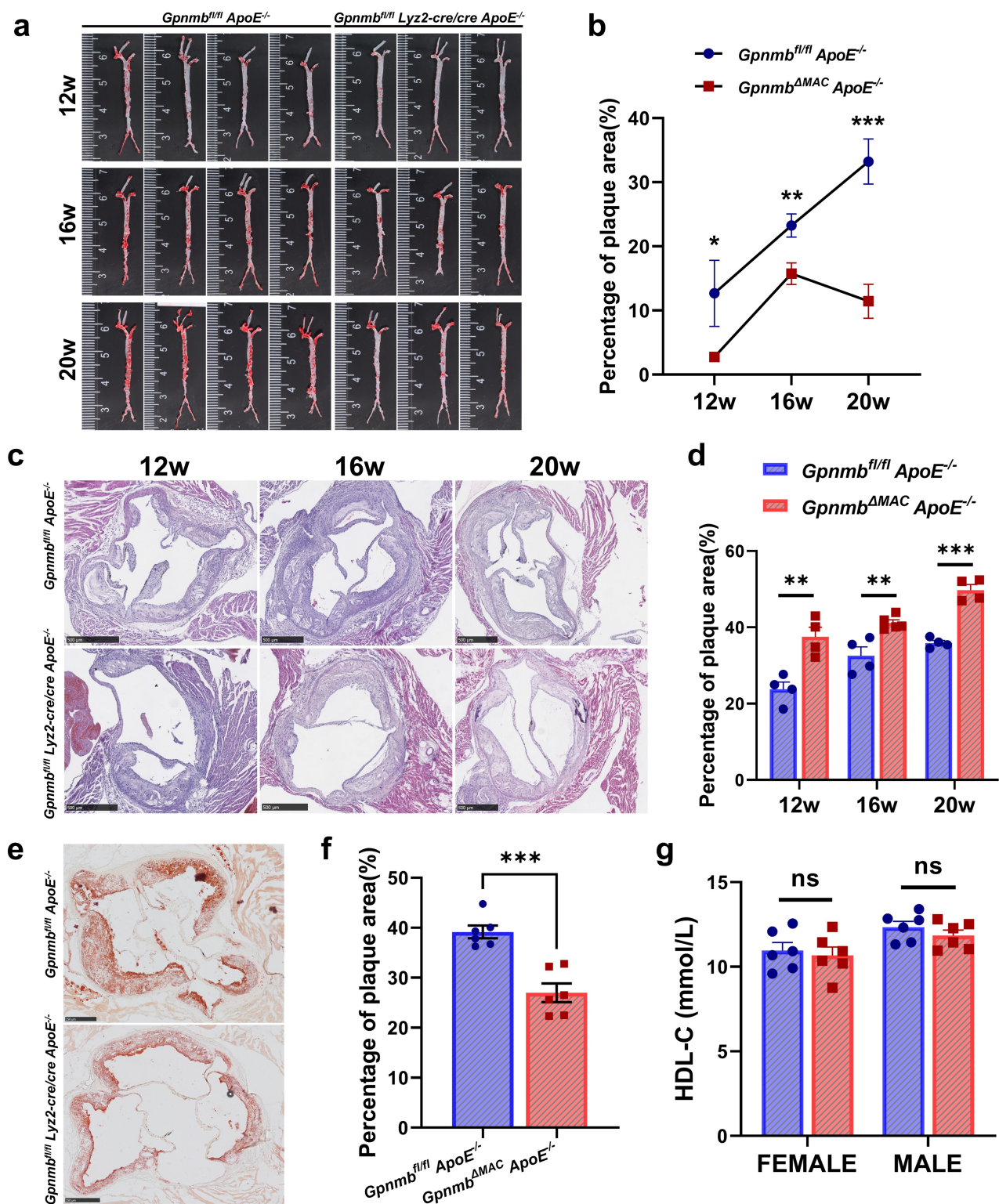


Figure S7. Myeloid-specific *Gpnmb* knockout suppressed atherosclerosis in *ApoE*^{-/-} mice

Gpnmb^{fl/fl} *ApoE*^{-/-} and *Gpnmb*^{fl/fl} *Lyz2*^{cre/cre} *ApoE*^{-/-} mice were fed a WD to induce lesion development. (a-b) Representative photomicrographs (J) and the quantification (K) of en face lesion area in the whole aortas of *Gpnmb*^{fl/fl} *ApoE*^{-/-} (male, n=4) and *Gpnmb*^{fl/fl} *Lyz2*^{cre/cre} *ApoE*^{-/-} mice (male, n=3) fed a WD for 12, 16, and 20 weeks. (c-d) Representative histological analysis of cross sections of the male aortic sinus stained with hematoxylin and eosin (H&E), and dashed lines delimited the plaque area. The quantification of plaque area percentages (male, n=4). (e-f) Representative Oil-Red-O-stained cross sections of aortic sinus from *Gpnmb*^{fl/fl} *ApoE*^{-/-} and *Gpnmb*^{fl/fl} *Lyz2*^{cre/cre} *ApoE*^{-/-} mice (e, female) and the quantification of plaque area percentages (f, n=6). (g) *Gpnmb*^{fl/fl} *ApoE*^{-/-} and *Gpnmb*^{fl/fl} *Lyz2*^{cre/cre} *ApoE*^{-/-} mice were fed a WD for 16 weeks. The quantification of HDL-C was shown in the graph (male, n=6).

Data are expressed as mean $\pm$ SEM. *P*-values were calculated by unpaired Student t-test (b, d, f-g). Differences are significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

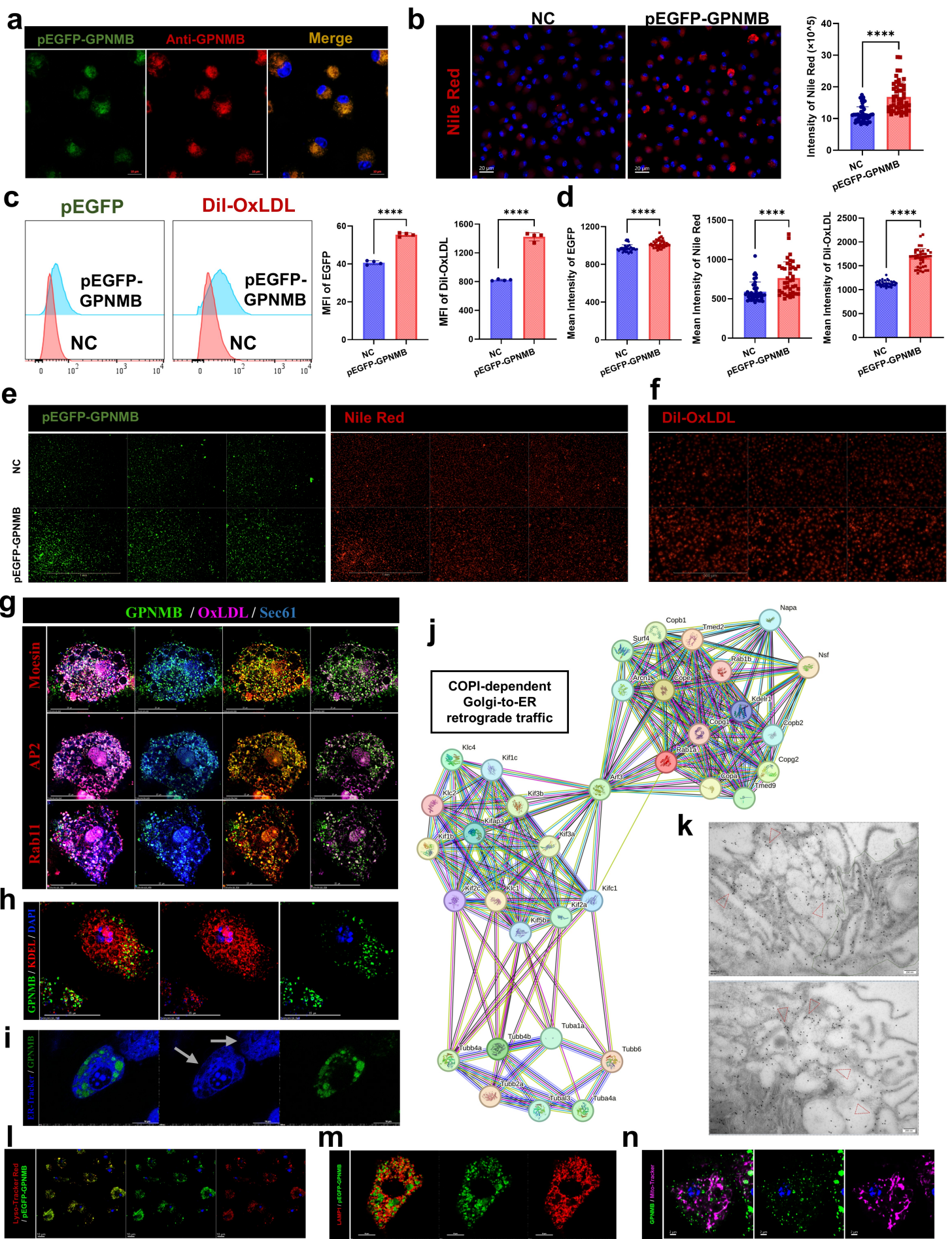


Figure S8. GPNMB Mediates the Internalization, Trafficking, and Metabolism of Lipoprotein in Macrophages

- (a) The expression of GPNMB in BMDM after transfection with the pEGFP-GPNMB plasmid and stained with anti-GPNMB antibody, followed by conjugated secondary antibody, N=3 independent experiments. Scale bar, 10 μ m.
- (b) Representative images of Nile Red staining (Red) in BMDMs transfected with pEGFP-GPNMB plasmid or empty vector (left, Scale bar, 7 μ m) and the quantitative analysis of Nile Red intensity (right, N=3 independent experiments, n=50 images each group).
- (c) The fluorescence peak diagram of pEGFP and Dil-OxLDL in BMDMs transfected with pEGFP-GPNMB plasmid or empty vector (left) and the quantitative analysis of intensity (right, N=4 independent experiments).
- (d-f) Representative images of BMDMs transfected with pEGFP-GPNMB plasmid or empty vector and treated with OxLDL for 24h, followed by Nile Red staining (e) or Dil-OxLDL for 12h (f) (captured with a high-content microscope, N=4 independent experiments) and corresponding quantitative analysis of fluorescence intensity (d , n=43 images each group).
- (g) Representative living cell images of Moesin, AP-2, or RAB11A expression (Red) in THP-1 derived macrophages transfected with pEGFP-GPNMB plasmid and treated with CF647-OxLDL (Magenta) for 36h, N=3 independent experiments. Scale bar, 15 μ m.
- (h) Representative living cell images of KDEL expression (Red) in THP-1 derived macrophages transfected with pEGFP-GPNMB plasmid (upper, Scale bar, 15 μ m), N=3 independent experiments.
- (i) Representative images of BMDMs transfected with pEGFP-GPNMB plasmid and stained with ER-Tracker (Blue), N=3 independent experiments. Scale bar, 15 μ m.
- (j) Force-directed network visualization of the STRING links between enriched proteins related to the Golgi-to-ER retrograde traffic from BMDM lysates using anti-GPNMB antibody, N=3 independent experiments.
- (k) Representative electron micrograph images of GPNMB expression (immuno-gold staining, indicated with red triangles) in WT BMDMs, N=3 independent experiments. Scale bars, 500 nm.
- (l) Representative images of WT BMDMs transfected with pEGFP-GPNMB plasmid and stained with Lyso-Tracker Red (LTR, Red), N=3 independent experiments. Scale bar, 15 μ m.
- (m) Representative images of LAMP1 expression (Red) in WT BMDMs transfected with pEGFP-GPNMB plasmid, N=3 independent experiments. Scale bar, 10 μ m.
- (n) Representative images of WT BMDMs transfected with pEGFP-GPNMB plasmid and stained with Mito-Tracker (Purple), N=3 independent experiments. Scale bar, 2 μ m.

Data are expressed as mean $\pm$ SEM. *P-values* were calculated by unpaired Student t-test (b-d). Differences are significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

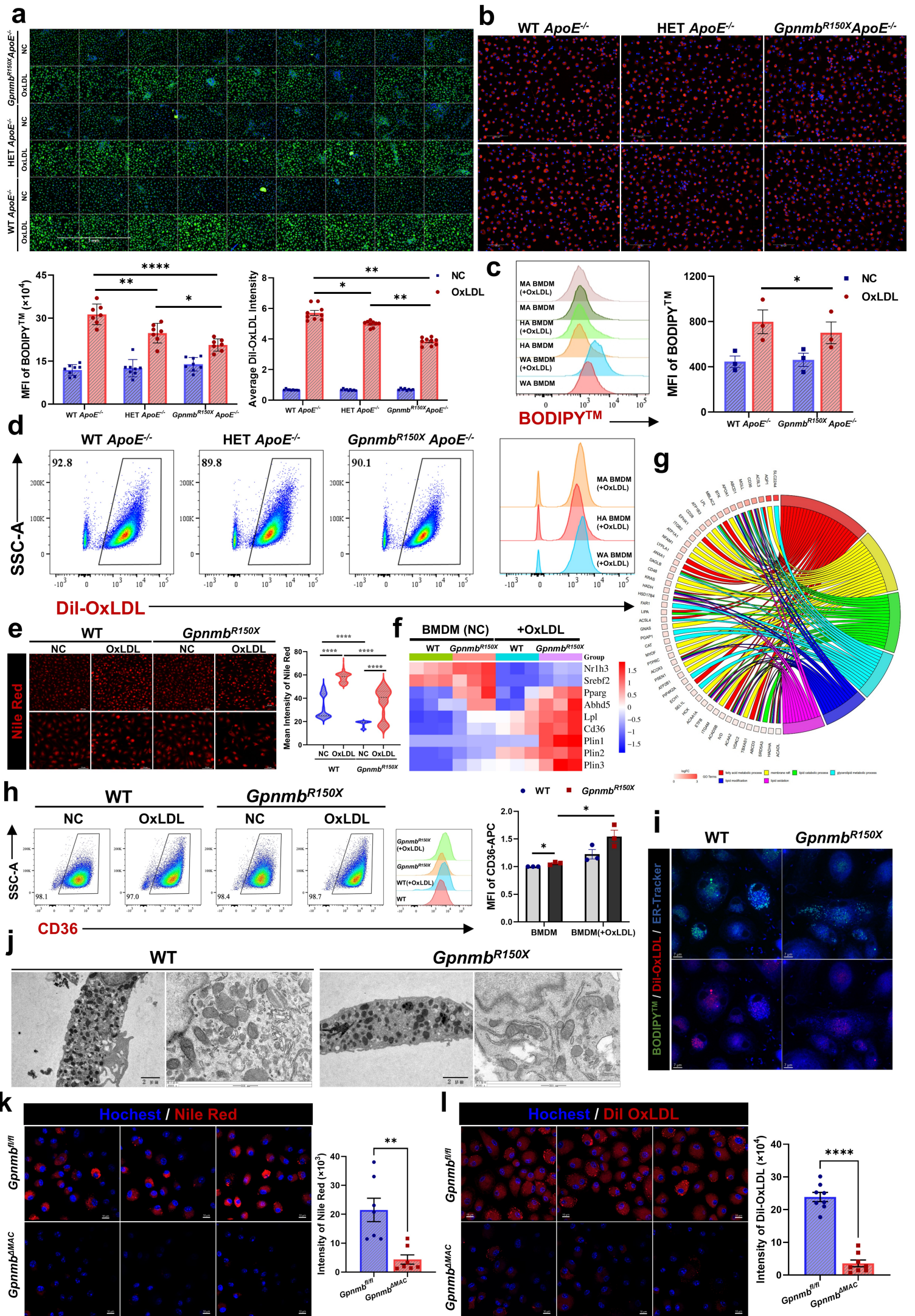


Figure S9. GPNMB-Mutation Inhibited Macrophage Foaming

- (a-b) Representative images of BMDMs from WT *ApoE*^{-/-}, HET *ApoE*^{-/-}, and *Gpnmb*^{R150X} *ApoE*^{-/-} mice treated with OxLDL for 24h, followed by BODIPYTM staining (a, n=8 in NC group, n=7 in OxLDL group) or Dil-OxLDL for 12h (b, n=9) (captured with a high-content microscope, N=3 independent experiments) and corresponding quantitative analysis of total fluorescence intensity.
- (c) Representative FACS histogram of MFI of BODIPYTM in BMDMs from WT *ApoE*^{-/-}(WA), HET *ApoE*^{-/-}(HA), and *Gpnmb*^{R150X} *ApoE*^{-/-}(MA) mice treated with OxLDL for 24 h, followed by BODIPY staining and corresponding quantitative analysis, N=3 independent experiments.
- (d) Representative dot plots and FACS histogram of MFI of Dil-OxLDL in BMDMs from WT *ApoE*^{-/-}(WA), HET *ApoE*^{-/-}(HA), and *Gpnmb*^{R150X} *ApoE*^{-/-}(MA) mice, N=3 independent experiments.
- (e) Representative images of BMDMs from WT and *Gpnmb*^{R150X} mice were treated with OxLDL for 24 h, followed by Nile Red staining and corresponding quantitative analysis of total fluorescence intensity. N=3 independent experiments, n=253 images in each group.
- (f) Heatmap of the expression of lipid metabolism-related genes from RNA-seq data of WT BMDMs and *Gpnmb*^{R150X} BMDMs treated with or without OxLDL.
- (g) The chord diagram shows the shared proteins between main enriched pathways based on up-regulated proteins in *Gpnmb*^{R150X} BMDMs compared to WT BMDM, identified by mass spectrometry analysis.
- (h) Representative dot plots and FACS histogram of MFI of APC-labeled CD36 in WT BMDMs and *Gpnmb*^{R150X} BMDMs treated with or without OxLDL for 48h and corresponding quantitative analysis of MFI of APC-labeled CD36, N=3 independent experiments.
- (i) Representative images of WT BMDMs and *Gpnmb*^{R150X} BMDMs treated with Dil-OxLDL for 12h (Red) and stained with ER-Tracker (Blue), followed by BODIPY staining (Green), N=3 independent experiments. Scale bar, 7μm.
- (j) Electron microscopy on BMDMs from WT and *Gpnmb*^{R150X} mice, N=3 independent experiments. Scale bar, 2μm or 500nm.
- (k) Representative images of BMDMs from *Gpnmb*^{flox/flox} mice or *Gpnmb*^{flox/flox} *Lyz2*^{cre/cre} mice treated with OxLDL for 24 h, followed by Nile Red staining and corresponding quantitative analysis of total fluorescence intensity, N=3 independent experiments, n=7 images in each group.
- (l) Representative images of BMDMs from *Gpnmb*^{flox/flox} mice or *Gpnmb*^{flox/flox} *Lyz2*^{cre/cre} mice treated with Dil-OxLDL for 12 h (r) and corresponding quantitative analysis of total fluorescence intensity (s), N=3 independent experiments, n=8 images in each group.

Data are expressed as mean $\pm$ SEM. *P*-values were calculated by unpaired Student t-test (a-c, e, h, and k-l). Differences are significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

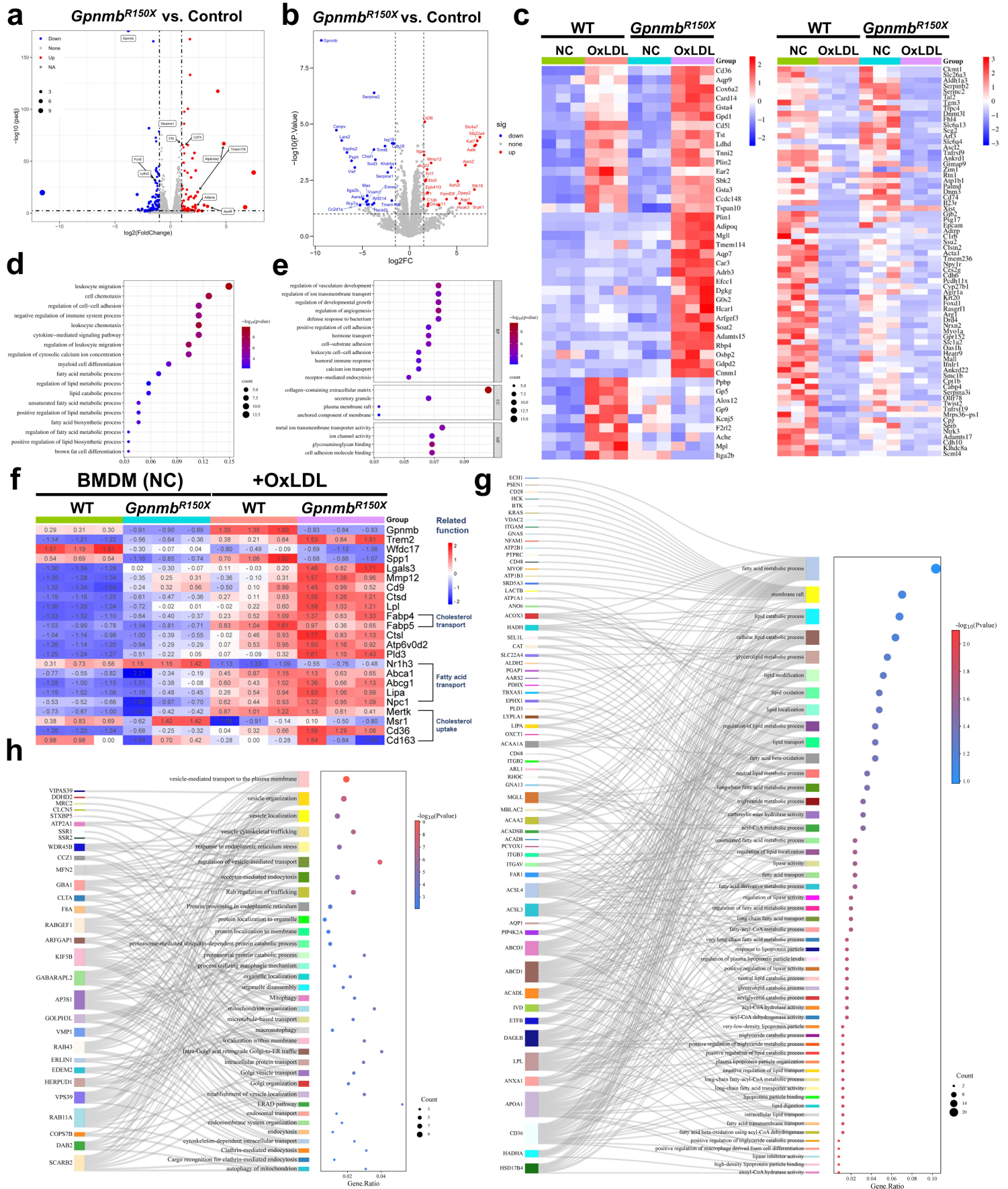


Figure S10. RNA-seq and Mass Spectrometry Analysis on BMDMs

(a-b) Volcano plot of differential genes (a) and proteins (b) expression analysis of *Gpnmb*^{R150X} BMDMs compared to WT BMDM.

(c) Heatmap of the expression of selected genes from RNA-seq data of WT BMDMs and *Gpnmb*^{R150X} BMDMs treated with or without OxLDL.

(d-e) Pathway enrichment analysis assessing GO terms for biological processes based on up-regulated genes (d) and down-regulated genes (e) from RNA-seq data of *Gpnmb*^{R150X} BMDMs compared to WT BMDM. Selected pathways are shown, ranked by Counts.

(f) Pathway enrichment analysis assessing GO terms for biological processes based on down-regulated proteins in *Gpnmb*^{R150X} BMDMs compared to WT BMDM, identified by mass spectrometry analysis. Selected pathways are shown, ranked by Counts.

(g) Sankey diagram of pathway enrichment analysis assessing GO terms for biological processes based on up-regulated proteins in *Gpnmb*^{R150X} BMDMs compared to WT BMDM, identified by mass spectrometry analysis. Selected pathways are shown, ranked by Counts.

(h) Sankey diagram of pathway enrichment analysis assessing GO terms for biological processes based on down-regulated proteins related to vesicle-trafficking in *Gpnmb*^{R150X} BMDMs compared to WT BMDM, identified by mass spectrometry analysis. Selected pathways are shown, ranked by Counts.

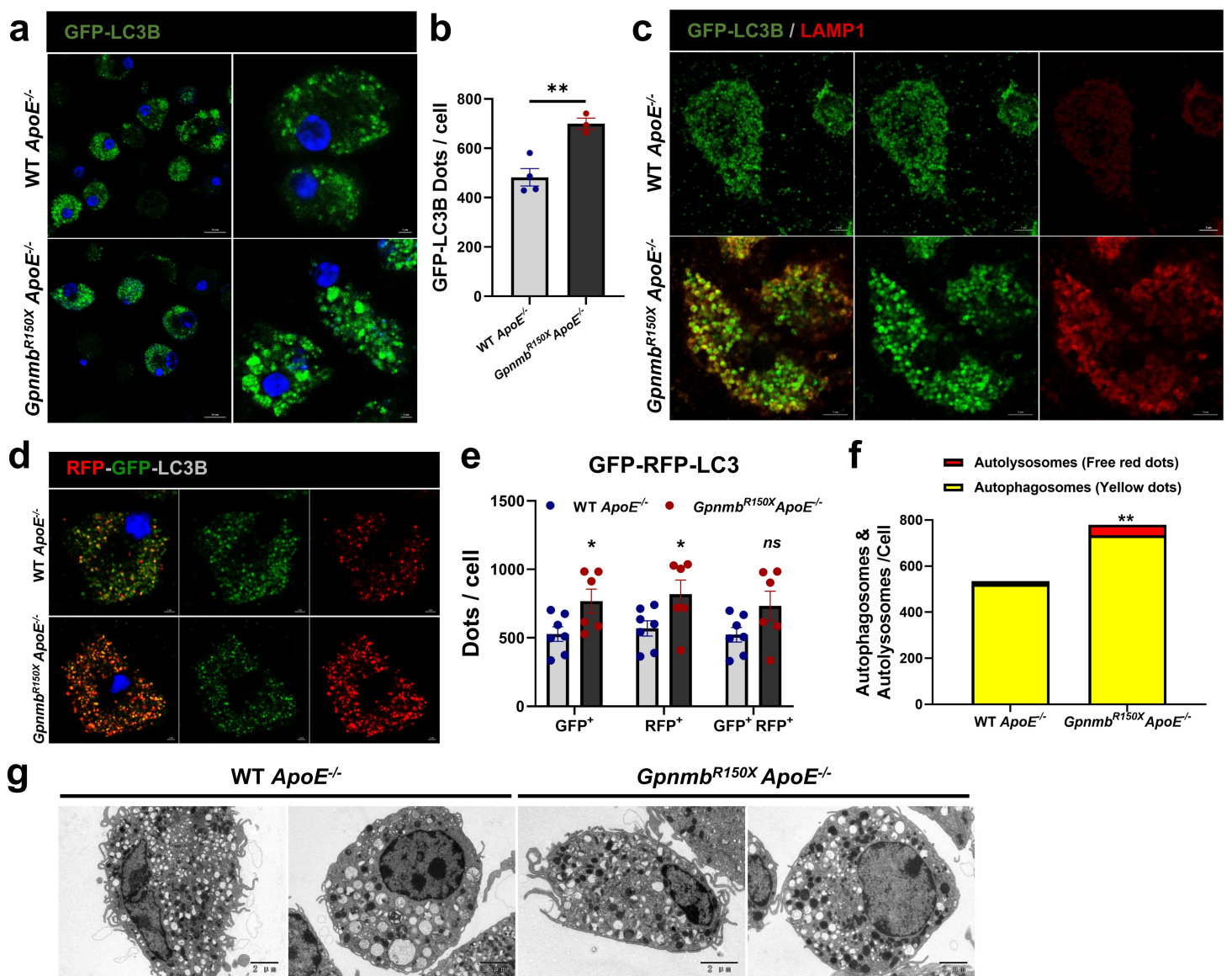


Figure S11. Mutation or knock-down of *Gpnmb* increased accumulation of autophagosomes and autolysosomes.

(a-b) Representative images of BMDMs transfected with GFP-LC3B plasmid from WT *ApoE*^{-/-} and *Gpnmb*^{R150X} *ApoE*^{-/-} mice (a, Scale bar, 10μm or 2μm) and the quantitative analysis of autophagosomes per cell (b, N=3 independent experiments, n=4 or 3 images).

(c) Representative images of LAMP1 expression in BMDMs transfected with GFP-LC3B plasmid from WT *ApoE*^{-/-} and *Gpnmb*^{R150X} *ApoE*^{-/-} mice (Scale bar, 5μm), N=3 independent experiments.

(d-f) Representative images of WT BMDMs and *Gpnmb*^{R150X} BMDMs transfected with RFP-GFP-LC3B plasmid (d, Scale bar, 2μm) and the quantitative analysis of autophagosome or autolysosomes per cell (e, N=3 independent experiments, n=7 or 6 images).

(g) Electron microscopy on BMDMs from WT *ApoE*^{-/-} and *Gpnmb*^{R150X} *ApoE*^{-/-} mice, N=3 independent experiments. Scale bar, 2 μm.

Data are expressed as mean $\pm$ SEM. Data were expressed as mean $\pm$ SEM. *P*-values were calculated by an unpaired Student t-test (b, e, and f). Differences were significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

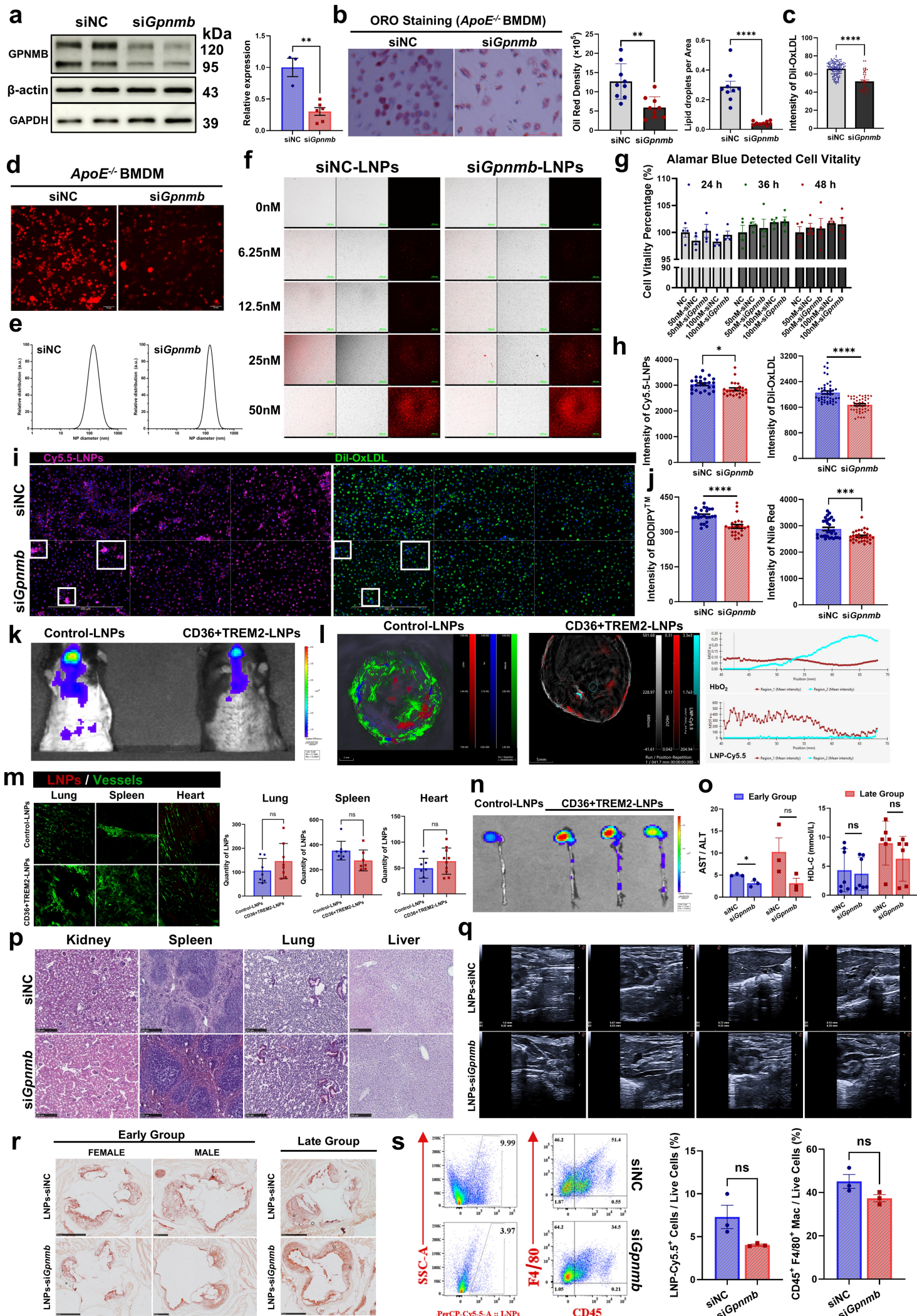


Figure S12. siRNA lipid nanoparticles targeting *Gpnmb* in lesional macrophages alleviated atherosclerosis in mice

- (a) Western blot confirming the knockdown efficiency of GPNMB after transfection with siRNA against *Gpnmb* (si*Gpnmb*) and siNC (n=3 or 6).
- (b) Representative Oil-Red-O (ORO) staining images of *ApoE*^{-/-} BMDMs transfected with si*Gpnmb* and siNC (Scale bar, 100 μ m) and corresponding quantitative statistics, N=3 independent experiments, n=9 images.
- (c-d) Representative images of *ApoE*^{-/-} BMDMs transfected with si*Gpnmb* and siNC, followed by treatment with Dil-OxLDL (d, Scale bar, 50 μ m) and corresponding quantitative statistics (c), N=5 independent experiments, n=134 or 40 cells.
- (e) The relative distribution of Cy5.5-siNC-LNPs (upper) or Cy5.5-si*Gpnmb*-LNPs (lower).
- (f) *ApoE*^{-/-} BMDMs were incubated for 24 hours without (0nM) or with Cy5.5-siRNA-LNPs of the indicated siRNA concentration. After changing the culture medium and following a 24-hour incubation, the cells were rinsed, and fluorescence images were captured. Representative merged bright-field fluorescence images are shown, N=3 independent experiments. Scale bar, 200 μ m.
- (g) Alamar blue viability assays of *ApoE*^{-/-} BMDMs incubated without (NC) or with Cy5.5-siRNA-LNPs of the indicated siRNA concentration for 24 hours, 36 hours, or 48 hours (mean $\pm$ SEM, n=4).
- (h-i) Representative images of *ApoE*^{-/-} BMDMs were incubated with Cy5.5-siRNA-LNPs with a siRNA concentration of 50nM for 24 hours and treated with Dil-OxLDL for 12 hours (i, Scale bar, 500 μ m). The quantitative analysis of Dil-OxLDL intensity per cell (h, N=3 independent experiments, n=44 cells each group).
- (j) *ApoE*^{-/-} BMDMs were incubated with Cy5.5-siRNA-LNPs with a siRNA concentration of 50nM for 24 hours and treated with OxLDL for 48 hours, followed by staining. The quantitative analysis of BODIPYTM staining intensity (left, N=3 independent experiments, n=24 images each group) or Nile Red staining intensity per cell (right, N=3 independent experiments, n=30 images each group).
- (k) *In vivo* fluorescence imaging of LNPs conjugated with anti-CD36 antibody and anti-TREM2 antibody (CD36+TREM2-LNPs) or LNPs conjugated with isotype control antibodies of anti-CD36 antibody and anti-TREM2 antibody (Control-LNPs) in mice at 24 hours after the second injection.
- (l) At 24 hours after whole eight injections of Control-LNPs or CD36+TREM2-LNPs, *in vivo* MSOT imaging of Cy5.5-LNPs in 16-week WD-fed *ApoE*^{-/-} mice (male). Aortic arch: red circle. Abdominal aorta: blue circle.
- (m) At 12 hours after whole eight injections of Control-LNPs or CD36+TREM2-LNPs, *In Vivo* Animal Live-Cell Imaging of Cy5.5-LNPs in 16-week WD-fed *ApoE*^{-/-} mice (male), N=3 independent experiments, n=7 or 8 images for lung, n=8 or 7 images for spleen, n=7 or 10 images for heart.
- (n) At the seventh day after whole eight injections of Control-LNPs or CD36+TREM2-LNPs, *ex vivo* fluorescence imaging of isolated aortas from 12-week WD-fed *ApoE*^{-/-} mice (Early Group, male).
- (o) The AST level-to-ALT level ratio (AST/ALT) (male, n=3) and the levels of HDL-C in serum from 12-week WD-fed *ApoE*^{-/-} mice (male, n=7) and 16-week WD-fed *ApoE*^{-/-} mice (male, n=6).
- (p) The major organs were sectioned, followed by H&E staining. Scale bars, 250 μ m.
- (q) On the sixth day after eight whole injections of Cy5.5-siRNA-LNPs, the representative images of ultrasound examinations on the aortic arch and abdominal aorta from 12-week WD-fed *ApoE*^{-/-} mice (female, n=3).
- (r) Representative Oil-Red-O (ORO) staining images of cross sections of aortic sinus from 12-week WD-fed male or female *ApoE*^{-/-} mice (Early Group) and 16-week WD-fed male *ApoE*^{-/-} mice (Late Group).
- (s) Representative flow cytometric expression of CD45 and F4/80 or Cy5.5-LNPs levels in aortic macrophages and the quantitative percentages of flow cytometric Cy5.5-LNPs⁺ cells or CD45⁺ F4/80⁺ aortic macrophages in live cells (male, n=3).

Data are expressed as mean $\pm$ SEM. *P*-values were calculated by unpaired Student t-test (a-c, h, j, m, o, and s) or one-way ANOVA (g). Differences are significant for **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

uncropped scans of all blots and gels in Supplementary Figures

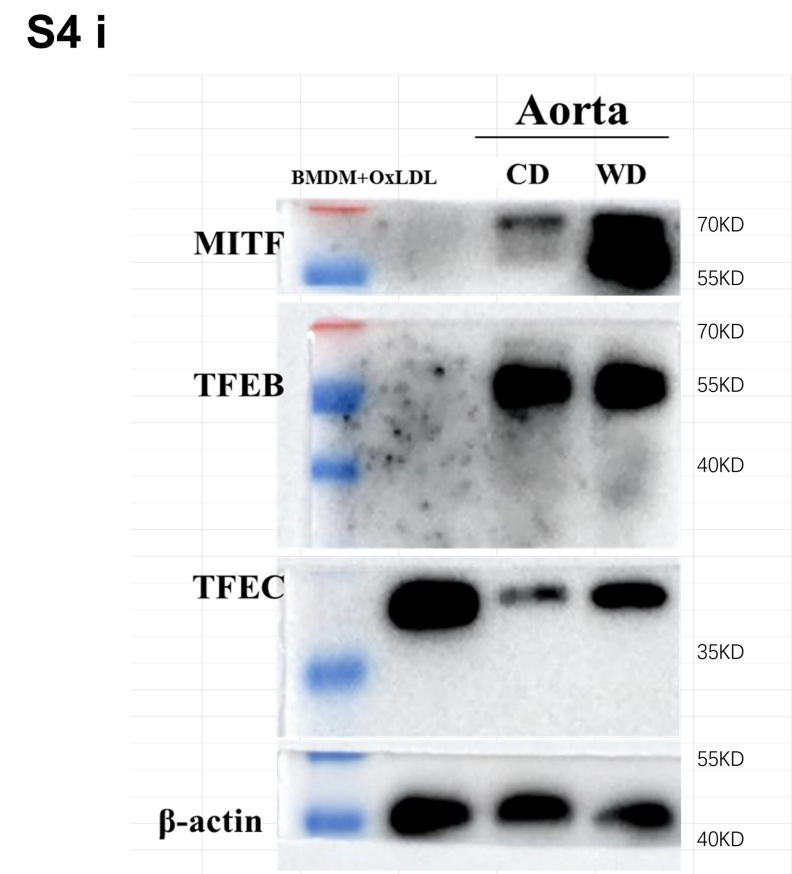
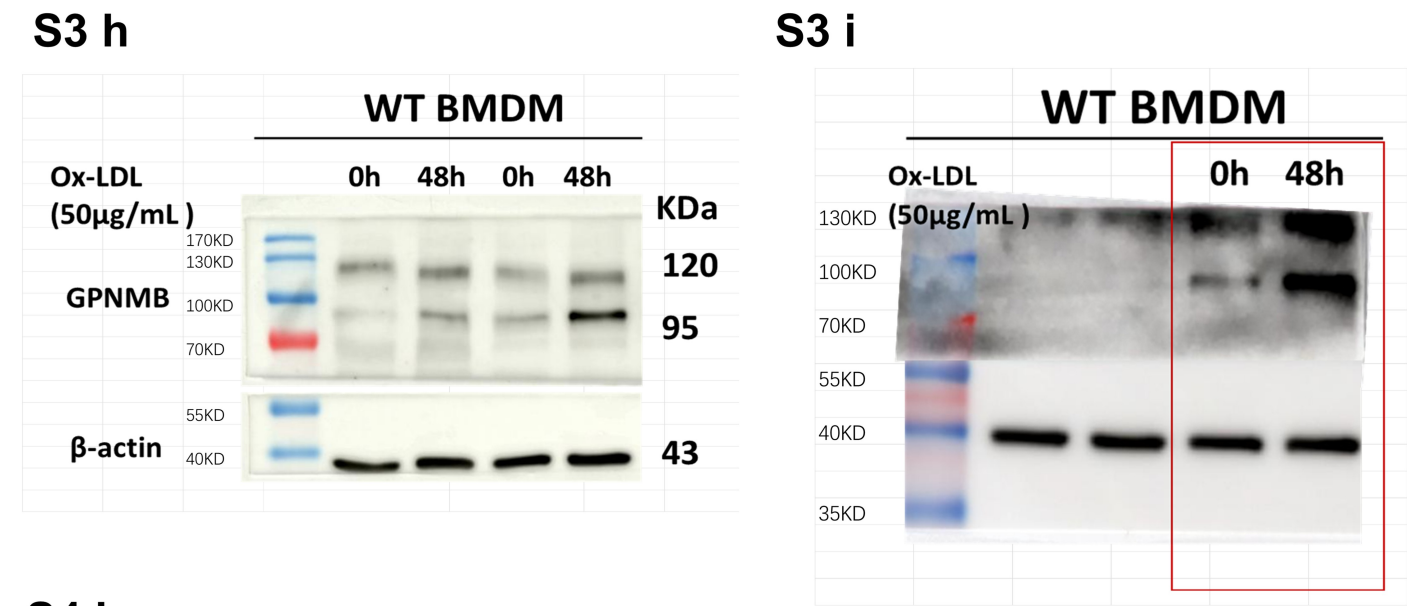
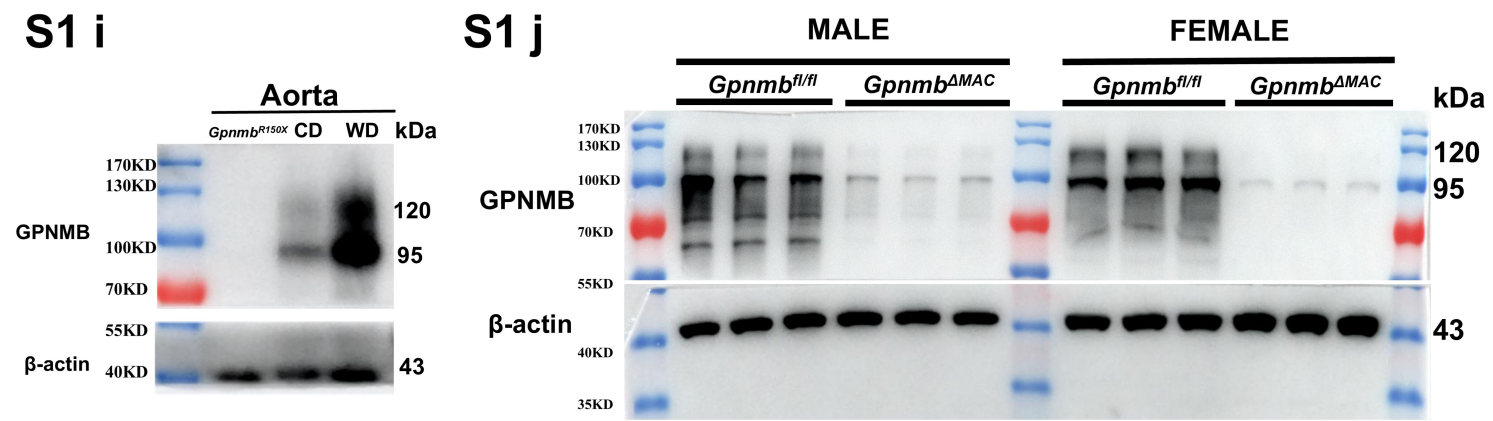


Table S1. Baseline Characteristics of the Study Participants

Characteristics	Total	Control	Stable Patients	Unstable Patients	P-value
Sample Size (n)	128	29	48	51	
sGPNMB	35.53 (14.34)	29.62 (10.44)	38.64 (15.43)	35.96 (14.41)	0.026
Age	62.12 (9.71)	58.90 (8.77)	63.85 (10.72)	62.33 (8.89)	0.092
Sex	1.44 (0.50)	1.76 (0.44)	1.38 (0.49)	1.31 (0.47)	<0.001
Height	162.12 (8.24)	157.41 (8.53)	163.79 (7.45)	163.24 (7.91)	0.002
Weight	64.43 (11.60)	58.45 (11.37)	66.54 (10.02)	65.85 (12.16)	0.006
BMI	24.52 (4.52)	23.86 (6.37)	24.70 (2.55)	24.72 (4.77)	0.681
SBP	126.70 (18.50)	119.97 (18.79)	128.10 (18.27)	129.20 (17.99)	0.079
DBP	77.95 (12.22)	75.45 (11.48)	79.60 (12.52)	77.82 (12.32)	0.353
Past medical history					
CAD = 1 (%)	29 (22.7)	0 (0.0)	17 (35.4)	12 (23.5)	0.002
Hypertension = 1 (%)	56 (43.8)	3 (10.3)	27 (56.2)	26 (51.0)	<0.001
Heart failure = 1 (%)	4 (3.1)	0 (0.0)	2 (4.2)	2 (4.0)	0.542
Dyslipidemia = 1 (%)	11 (8.6)	0 (0.0)	5 (10.4)	6 (11.8)	0.167
Stroke = 1 (%)	7 (5.5)	1 (3.4)	3 (6.2)	3 (5.9)	0.86
Diabetes = 1 (%)	22 (17.2)	0 (0.0)	11 (22.9)	11 (21.6)	0.02
Atrial fibrillation = 1 (%)	2 (1.6)	0 (0.0)	1 (2.1)	1 (2.0)	0.742
COPD = 1 (%)	1 (0.8)	0 (0.0)	0 (0.0)	1 (2.0)	0.467
Smoking (%)					0.004
Never	90 (70.3)	28 (96.6)	30 (62.5)	32 (62.7)	
Current	21 (16.4)	0 (0.0)	8 (16.7)	13 (25.5)	
Past	17 (13.3)	1 (3.4)	10 (20.8)	6 (11.8)	
Medication before admission					
Aspirin = 1 (%)	56 (43.8)	5 (17.2)	16 (33.3)	35 (68.6)	<0.001
Indobufen = 1 (%)	26 (20.3)	0 (0.0)	14 (29.2)	12 (23.5)	0.007
Clopidogrel = 1 (%)	64 (50.0)	0 (0.0)	22 (45.8)	42 (82.4)	<0.001
Ticagrelor = 1 (%)	5 (3.9)	0 (0.0)	0 (0.0)	5 (9.8)	0.02
Warfarin = 1 (%)	1 (0.8)	0 (0.0)	1 (2.1)	0 (0.0)	0.432
Noac = 1 (%)	7 (5.5)	0 (0.0)	5 (10.4)	2 (3.9)	0.123
Statins = 1 (%)	96 (75.0)	2 (6.9)	43 (89.6)	51 (100.0)	<0.001
β -Blockers = 1 (%)	87 (68.0)	2 (6.9)	36 (75.0)	49 (96.1)	<0.001
ACE inhibitors = 1 (%)	2 (1.6)	0 (0.0)	0 (0.0)	2 (3.9)	0.216
ARB = 1 (%)	39 (30.5)	0 (0.0)	14 (29.2)	25 (49.0)	<0.001
Aldosterone = 1 (%)	5 (3.9)	0 (0.0)	3 (6.2)	2 (3.9)	0.39
Diuretics = 1 (%)	3 (2.3)	0 (0.0)	3 (6.2)	0 (0.0)	0.077
Digoxin = 1 (%)	1 (0.8)	0 (0.0)	1 (2.1)	0 (0.0)	0.432
Nitroglycerine = 1 (%)	55 (43.0)	0 (0.0)	26 (54.2)	29 (56.9)	<0.001
Treatment					
Antihypertensive therapy = 1 (%)	20 (15.6)	2 (6.9)	10 (20.8)	8 (15.7)	0.264
Lipid-lowering therapy = 1 (%)	46 (35.9)	2 (6.9)	14 (29.2)	30 (58.8)	<0.001
Antidiabetic therapy = 1 (%)	16 (12.5)	0 (0.0)	10 (20.8)	6 (11.8)	0.027
Biochemistry					
Total cholesterol, mmol/L	4.44 (1.17)	4.61 (0.68)	4.46 (1.28)	4.33 (1.28)	0.57
Total Triglycerides, mmol/L	1.94 (1.27)	1.64 (1.08)	1.92 (1.33)	2.12 (1.31)	0.267
HDL-C, mmol/L	1.18 (0.30)	1.34 (0.27)	1.18 (0.32)	1.08 (0.25)	0.001
LDL-C, mmol/L	7.27 (36.01)	12.31 (50.91)	2.72 (0.77)	8.69 (42.48)	0.497
FBG, mmol/L	13.18 (50.88)	20.49 (75.91)	15.01 (59.00)	7.30 (2.80)	0.515
CK, U/L	106.26 (104.45)	108.24 (167.97)	104.20 (52.31)	107.07 (96.60)	0.984
CK-MB, U/L	13.76 (11.38)	17.42 (20.93)	11.94 (4.15)	13.40 (7.48)	0.117
LDH, U/L	179.43 (44.00)	165.49 (35.91)	183.70 (34.07)	183.35 (54.39)	0.152
AST (U/L)	27.59 (34.90)	19.96 (15.70)	29.54 (46.87)	30.09 (29.12)	0.41
ALT (U/L)	29.25 (33.74)	29.57 (48.37)	30.07 (36.36)	28.29 (18.35)	0.965
Urea, mmol/L	6.61 (4.12)	6.70 (6.03)	6.78 (4.59)	6.40 (1.67)	0.896
Crea, mmol/L	95.43 (118.61)	75.30 (60.70)	111.78 (172.81)	91.48 (71.36)	0.409
UA, μ mol/L	370.74 (239.39)	400.71 (478.33)	372.03 (93.21)	352.49 (91.67)	0.69

Blood count

Leucocytes, 10 ⁹ /L	6.25 (1.99)	5.87 (1.57)	6.57 (2.40)	6.17 (1.75)	0.309
Red blood cell count, 10 ¹² /L	4.45 (0.63)	4.34 (0.54)	4.43 (0.59)	4.53 (0.71)	0.4
Haemoglobin, g/dL	132.69 (22.71)	133.07 (14.69)	133.35 (23.18)	131.84 (26.13)	0.943
Platelets, 10 ⁹ /L	229.61 (209.20)	221.10 (48.81)	206.89 (66.86)	255.84 (323.10)	0.496
Neutrophil, 10 ⁹ /L	5.61 (17.58)	3.54 (1.14)	8.46 (28.61)	4.09 (1.44)	0.363
Lymphocytes, 10 ⁹ /L	1.71 (1.34)	1.69 (0.47)	2.00 (2.07)	1.45 (0.51)	0.118
Monocytes, 10 ⁹ /L	0.49 (0.57)	0.62 (1.16)	0.46 (0.17)	0.46 (0.17)	0.381
Eosinophils, 10 ⁹ /L	0.36 (1.47)	0.80 (2.97)	0.23 (0.42)	0.23 (0.46)	0.189
Basophils, 10 ⁹ /L	0.08 (0.21)	0.06 (0.11)	0.05 (0.07)	0.13 (0.31)	0.143
Fibrinogen, mg/dL	3.21 (0.95)	2.89 (0.83)	3.24 (1.03)	3.36 (0.91)	0.091

Normally distributed continuous variables are presented as mean±SD. Categorical data are summarized by n (%). The Chi-square test and continuity-adjusted Chi-square test were used for comparisons of categorical variables. The analysis of variance was used for comparisons of continuous variables.

Table S2. Multivariable Linear Regression Model for the Association of sGPNMB with AS-associated Independent variables at Baseline

Independent variables	$\beta 1^*$	95% CI	P value	$\beta 2^\dagger$	R ²
Coronary heart disease	0.248	0.110 to 0.385	< 0.0001	0.247	0.129
Age	0.283	0.149 to 0.417	< 0.0001	0.283	0.192
Antihypertensive therapy	0.150	0.023 to 0.278	0.021	0.150	0.222
Total Cholesterol	0.151	0.023 to 0.279	0.021	0.151	0.243
Diuretics	0.224	0.080 to 0.368	0.002	0.224	0.261
Heart failure	-0.202	-0.345 to -0.059	0.006	-0.201	0.291
CK-MB	-0.135	-0.261 to -0.008	0.037	-0.135	0.309

Sample Size (n)=182. Other baseline variables were consecutively removed from the model automatically due to coefficients with $P>0.05$. Fisher F test for significance of the model: $F=11.052$, $df=7$, $P<0.0001$. The P Value for the significance of the regression coefficients was determined by a t-test. *Non-standardized coefficients. †Standardized coefficients.

Table S3. Predicted Multivariable Linear Regression Model for Carotid Plaque Severity (based on Gensini score) at Baseline

Independent variables	$\beta 2^\dagger$	95% CI	P value	R ²
Urea	0.278	0.080 to 0.476	0.007	0.147
HDLC	-0.273	-0.467 to -0.078	0.007	0.220
Antidiabetic therapy	-0.226	-0.415 to -0.036	0.020	0.275
sGPNMB	0.218	0.021 to 0.415	0.031	0.319

Sample Size (n)=182. Other baseline variables were consecutively removed from the model automatically due to coefficients with $P>0.05$. Fisher F test for significance of the model: $F=8.649$, $df=4$, $P<0.0001$. The P Value for the significance of the regression coefficients was determined by a t-test. †Standardized coefficients.

Table S4. Features of *Gpnmb*^{R150X} mice (C57/6J)

Characteristics	MALE					FEMALE				
	Overall	WT	HET	<i>Gpnmb</i> ^{R150X}	P-value	Overall	WT	HET	<i>Gpnmb</i> ^{R150X}	P-value
Sample Size (n)	16	4	6	6		17	6	6	5	
Increased Body Weight (g)	15.56 (4.37)	12.46 (4.27)	18.98 (3.58)	13.93 (2.60)	0.026	9.05 (2.51)	9.51 (1.15)	8.97 (2.85)	8.77 (3.33)	0.918
Fat Pad Weight (g)	3.89 (1.15)	3.76 (1.46)	4.33 (0.91)	3.46 (1.21)	0.475	2.07 (1.00)	2.44 (0.52)	2.07 (1.37)	1.81 (0.88)	0.659
Percentage of Fat Pad (%)	9.01 (1.78)	9.06 (2.39)	9.56 (1.26)	8.31 (1.95)	0.547	6.43 (2.00)	7.54 (1.17)	6.32 (2.55)	5.79 (1.78)	0.419
Biochemistry										
Total Cholesterol (mmol/L)	1.90 (0.25)	1.94 (0.36)	1.92 (0.20)	1.84 (0.26)	0.831	1.51 (0.08)	1.57 (0.11)	1.53 (0.06)	1.46 (0.05)	0.071
Total Triglycerides (mmol/L)	0.46 (0.07)	0.46 (0.10)	0.44 (0.06)	0.47 (0.06)	0.81	0.39 (0.05)	0.43 (0.07)	0.37 (0.03)	0.39 (0.04)	0.141
HDL-C (mmol/L)	0.71 (0.19)	0.73 (0.25)	0.73 (0.14)	0.68 (0.24)	0.92	0.41 (0.06)	0.44 (0.05)	0.44 (0.06)	0.37 (0.03)	0.053
LDL-C (mmol/L)	0.17 (0.06)	0.17 (0.09)	0.17 (0.05)	0.18 (0.05)	0.953	0.09 (0.02)	0.10 (0.03)	0.09 (0.01)	0.08 (0.01)	0.319
Blood count										
WBC (10 ⁹ /L)	3.49 (1.63)	3.18 (0.94)	3.68 (2.11)	3.53 (1.71)	0.906	1.95 (1.59)	1.19 (0.20)	1.74 (1.30)	2.78 (2.22)	0.249
Neu # (10 ⁹ /L)	0.94 (0.71)	0.90 (0.70)	0.52 (0.39)	1.46 (0.77)	0.079	0.34 (0.25)	0.29 (0.09)	0.28 (0.15)	0.45 (0.39)	0.461
Lym # (10 ⁹ /L)	2.18 (1.46)	1.96 (0.42)	2.94 (2.04)	1.44 (0.73)	0.239	1.37 (1.20)	0.74 (0.13)	1.23 (0.96)	2.04 (1.64)	0.188
Mon # (10 ⁹ /L)	0.24 (0.29)	0.18 (0.12)	0.13 (0.11)	0.41 (0.47)	0.282	0.09 (0.11)	0.04 (0.03)	0.06 (0.04)	0.16 (0.16)	0.094
Eos # (10 ⁹ /L)	0.12 (0.09)	0.13 (0.11)	0.08 (0.05)	0.16 (0.11)	0.314	0.12 (0.09)	0.12 (0.08)	0.14 (0.14)	0.11 (0.07)	0.847
Bas # (10 ⁹ /L)	0.02 (0.04)	0.01 (0.02)	0.01 (0.02)	0.05 (0.05)	0.198	0.02 (0.03)	0.01 (0.02)	0.04 (0.05)	0.01 (0.01)	0.29
Neu % (%)	27.01 (17.23)	25.80 (15.43)	15.42 (8.80)	41.90 (16.83)	0.024	18.73 (6.05)	24.22 (7.22)	17.32 (4.88)	15.57 (2.69)	0.035
Lym % (%)	62.27 (21.46)	64.48 (19.53)	77.55 (11.02)	42.18 (17.73)	0.01	67.88 (7.75)	61.88 (8.21)	68.05 (6.31)	72.70 (5.88)	0.059
Mon % (%)	6.29 (4.67)	5.15 (1.71)	4.07 (2.90)	9.88 (6.23)	0.095	4.56 (2.57)	3.48 (1.53)	4.10 (2.28)	5.93 (3.22)	0.261
Eos % (%)	3.72 (2.54)	4.00 (3.76)	2.62 (1.73)	4.82 (2.18)	0.373	7.55 (4.42)	9.20 (5.04)	8.52 (4.56)	5.22 (3.31)	0.28
Bas % (%)	0.70 (0.56)	0.58 (0.38)	0.35 (0.26)	1.22 (0.60)	0.017	1.28 (1.04)	1.22 (1.06)	2.02 (0.94)	0.58 (0.68)	0.045
RBC (10 ¹² /L)	9.16 (1.35)	9.64 (1.21)	9.12 (0.96)	8.83 (1.95)	0.695	8.37 (1.15)	8.38 (0.83)	7.77 (1.55)	8.96 (0.64)	0.206
HGB (g/L)	137.27 (18.14)	142.50 (15.42)	135.83 (15.51)	134.80 (25.19)	0.817	128.59 (14.15)	128.00 (13.06)	120.83 (16.98)	136.83 (7.88)	0.146
HCT (%)	44.07 (6.94)	45.48 (6.92)	44.50 (6.36)	42.44 (8.76)	0.818	37.96 (4.58)	38.22 (3.27)	35.63 (6.40)	40.07 (2.40)	0.256
MCV (fL)	48.17 (3.30)	47.00 (1.15)	48.67 (3.08)	48.50 (4.83)	0.738	45.48 (1.02)	45.64 (0.59)	46.08 (1.25)	44.75 (0.63)	0.06
MCH (pg)	15.05 (0.60)	14.80 (0.49)	14.90 (0.32)	15.42 (0.82)	0.237	15.45 (0.95)	15.30 (0.54)	15.75 (1.54)	15.28 (0.33)	0.663
MCHC (g/L)	313.40 (19.80)	314.75 (16.15)	307.33 (19.00)	319.60 (24.91)	0.62	339.94 (16.31)	335.20 (12.07)	342.00 (25.70)	341.83 (6.52)	0.766
RDW-CV (%)	18.05 (2.65)	17.40 (1.73)	18.60 (2.64)	17.90 (3.57)	0.798	14.85 (1.92)	14.82 (1.82)	14.92 (1.43)	14.80 (2.67)	0.995
RDW-SD (fL)	38.21 (8.15)	35.70 (4.50)	39.85 (8.30)	38.24 (10.99)	0.761	29.08 (3.99)	29.00 (3.79)	29.62 (3.06)	28.62 (5.44)	0.919
PLT (10 ⁹ /L)	755.07 (285.06)	775.00 (355.89)	798.33 (292.85)	687.20 (270.65)	0.825	835.47 (394.17)	965.80 (470.17)	731.67 (503.93)	830.67 (190.92)	0.647
MPV (fL)	7.24 (0.71)	7.20 (0.83)	7.52 (0.76)	6.94 (0.56)	0.437	7.08 (0.84)	7.56 (0.97)	6.88 (0.96)	6.87 (0.52)	0.333
PDW	15.89 (0.45)	15.88 (0.64)	15.87 (0.44)	15.92 (0.41)	0.982	15.66 (0.57)	15.72 (0.44)	15.73 (0.80)	15.55 (0.48)	0.848
PCT (%)	0.54 (0.20)	0.55 (0.24)	0.59 (0.20)	0.48 (0.20)	0.696	0.51 (0.26)	0.31 (0.19)	0.52 (0.37)	0.57 (0.13)	0.52

WT, HET, and *Gpnmb*^{R150X} (all on hybrid DBA/2×C57BL/6J-C57BL/6J background) mice were fed a WD for 20 weeks. The variables were presented as mean±SD. The analysis of variance was used for comparisons of continuous variables.

Table S5. Features of *Gpnmb*^{R150X} *ApoE*^{-/-} mice (C57/6J)

Characteristics	MALE					FEMALE				
	Overall	WT <i>ApoE</i> ^{-/-}	HET <i>ApoE</i> ^{-/-}	<i>Gpnmb</i> ^{R150X} <i>ApoE</i> ^{-/-}	<i>P</i> -value	Overall	WT <i>ApoE</i> ^{-/-}	HET <i>ApoE</i> ^{-/-}	<i>Gpnmb</i> ^{R150X} <i>ApoE</i> ^{-/-}	<i>P</i> -value
Sample Size (n)	47	18	12	17		31	10	11	10	
Increased Body Weight (g)	12.10 (3.75)	11.09 (2.63)	12.75 (4.67)	12.23 (3.54)	0.612	7.86 (3.63)	7.61 (4.13)	7.64 (3.13)	8.30 (4.06)	0.898
Fat Pad Weight (g)	1.98 (0.68)	1.28 (0.48)	2.14 (0.73)	2.22 (0.45)	0.025	0.84 (0.28)	0.68 (0.19)	0.96 (0.32)	0.83 (0.27)	0.103
Percentage of Fat Pad (%)	5.74 (1.62)	4.13 (1.49)	6.00 (1.63)	6.42 (1.02)	0.027	3.32 (0.88)	2.83 (0.71)	3.93 (0.88)	2.95 (0.52)	0.014
Biochemistry										
Total Cholesterol (mmol/L)	31.68 (13.56)	41.20 (6.82)	24.79 (16.10)	26.99 (11.84)	0.019	22.94 (8.50)	18.69 (7.81)	29.18 (7.80)	19.89 (6.46)	0.024
Total Triglycerides (mmol/L)	1.45 (1.05)	0.99 (0.60)	2.90 (1.49)	1.32 (0.65)	<0.001	1.58 (0.75)	1.22 (0.37)	1.07 (0.29)	2.33 (0.69)	<0.001
HDL-C (mmol/L)	5.65 (2.86)	6.82 (3.05)	4.73 (1.77)	4.69 (2.65)	0.062	4.19 (1.84)	3.97 (2.38)	4.83 (1.51)	3.91 (1.48)	0.53
LDL-C (mmol/L)	8.33 (4.39)	8.68 (4.27)	7.11 (5.05)	8.45 (4.43)	0.727	7.12 (4.31)	6.43 (4.73)	7.62 (3.65)	7.40 (4.70)	0.828
Blood count										
WBC (10 ⁹ /L)	2.66 (1.42)	2.23 (1.48)	3.15 (1.57)	2.64 (1.13)	0.429	2.43 (2.04)	1.47 (0.86)	3.00 (2.61)	2.81 (2.02)	0.267
Neu # (10 ⁹ /L)	0.75 (0.60)	0.54 (0.39)	0.85 (0.69)	0.89 (0.74)	0.464	0.50 (0.45)	0.36 (0.19)	0.63 (0.64)	0.49 (0.37)	0.484
Lym # (10 ⁹ /L)	1.53 (0.98)	1.38 (1.17)	1.79 (1.02)	1.41 (0.69)	0.659	1.59 (1.32)	0.90 (0.67)	1.89 (1.48)	1.98 (1.50)	0.198
Mon # (10 ⁹ /L)	0.14 (0.12)	0.12 (0.11)	0.16 (0.14)	0.13 (0.11)	0.712	0.11 (0.12)	0.06 (0.06)	0.12 (0.12)	0.16 (0.14)	0.227
Eos # (10 ⁹ /L)	0.21 (0.21)	0.17 (0.10)	0.29 (0.30)	0.17 (0.19)	0.44	0.18 (0.20)	0.13 (0.08)	0.25 (0.29)	0.16 (0.14)	0.45
Bas # (10 ⁹ /L)	0.04 (0.06)	0.02 (0.03)	0.05 (0.06)	0.05 (0.09)	0.401	0.06 (0.11)	0.03 (0.03)	0.12 (0.17)	0.02 (0.02)	0.146
Neu % (%)	27.21 (14.63)	25.69 (14.18)	25.71 (13.03)	30.87 (18.22)	0.751	20.48 (6.18)	24.49 (5.62)	19.72 (6.37)	16.86 (4.21)	0.044
Lym % (%)	56.81 (16.45)	55.82 (19.27)	58.42 (13.47)	56.24 (18.03)	0.947	64.25 (10.66)	58.29 (12.21)	65.09 (8.42)	69.99 (8.96)	0.097
Mon % (%)	5.12 (3.34)	5.49 (3.99)	4.92 (3.47)	4.87 (2.65)	0.922	4.54 (2.18)	3.94 (1.36)	4.12 (1.90)	5.76 (2.97)	0.217
Eos % (%)	9.39 (7.95)	12.09 (10.20)	9.21 (6.58)	6.11 (5.45)	0.343	8.61 (5.52)	10.85 (7.27)	8.18 (3.94)	6.61 (4.78)	0.332
Bas % (%)	1.47 (1.58)	0.91 (0.58)	1.73 (1.43)	1.90 (2.46)	0.416	2.12 (2.43)	2.44 (3.41)	2.89 (2.00)	0.79 (0.82)	0.213
RBC (10 ¹² /L)	9.58 (2.35)	9.05 (1.61)	9.74 (2.31)	10.09 (3.28)	0.681	9.19 (2.10)	8.65 (0.87)	9.56 (3.26)	9.33 (1.12)	0.677
HGB (g/L)	144.75 (34.51)	137.00 (24.35)	150.00 (33.94)	148.71 (47.80)	0.712	140.62 (29.77)	131.88 (12.82)	147.78 (46.03)	141.43 (14.13)	0.565
HCT (%)	44.15 (10.48)	42.04 (7.95)	44.85 (8.70)	46.06 (15.38)	0.747	41.09 (7.87)	39.36 (3.54)	42.32 (12.18)	41.47 (4.31)	0.75
MCV (fL)	46.18 (2.22)	46.41 (1.30)	46.45 (3.36)	45.57 (1.67)	0.708	45.04 (1.47)	45.56 (0.73)	44.94 (2.19)	44.56 (0.77)	0.423
MCH (pg)	15.13 (0.78)	15.16 (0.39)	15.46 (1.22)	14.73 (0.26)	0.197	15.39 (0.83)	15.28 (0.43)	15.64 (1.26)	15.20 (0.37)	0.522
MCHC (g/L)	328.12 (17.94)	326.67 (10.44)	333.50 (27.26)	323.86 (12.58)	0.577	342.17 (16.51)	335.25 (10.32)	348.78 (23.80)	341.57 (6.00)	0.249
RDW-CV (%)	18.55 (4.28)	17.49 (1.74)	21.51 (6.13)	16.51 (2.05)	0.043	16.08 (3.09)	15.72 (3.10)	16.56 (2.81)	15.89 (3.77)	0.852
RDW-SD (fL)	37.99 (10.20)	35.56 (4.35)	44.74 (14.58)	33.41 (5.62)	0.059	31.58 (6.21)	30.95 (6.40)	32.71 (5.34)	30.83 (7.68)	0.8
PLT (10 ⁹ /L)	1171.04 (575.84)	1158.00 (581.94)	1169.57 (600.18)	1189.29 (635.16)	0.995	1021.08 (611.74)	974.00 (389.42)	1205.11 (922.26)	838.29 (175.44)	0.496
MPV (fL)	6.74 (1.13)	6.79 (0.90)	6.86 (1.43)	6.54 (1.17)	0.862	6.75 (0.92)	7.06 (1.03)	6.48 (1.01)	6.73 (0.60)	0.439
PDW	16.05 (1.24)	15.71 (0.38)	16.62 (2.04)	15.83 (0.45)	0.283	15.75 (0.52)	15.72 (0.34)	15.89 (0.68)	15.60 (0.46)	0.553
PCT (%)	0.62 (0.28)	0.67 (0.36)	0.59 (0.25)	0.60 (0.23)	0.872	0.55 (0.25)	0.49 (0.22)	0.58 (0.36)	0.56 (0.12)	0.832

WT *ApoE*^{-/-}, HET *ApoE*^{-/-}, and *Gpnmb*^{R150X} *ApoE*^{-/-} (all on hybrid DBA/2×C57BL/6J-C57BL/6J background) mice were fed a WD for 20 weeks. The variables were presented as mean±SD. The analysis of variance was used for comparisons of continuous variables.

Table S6. Features of *Gpnmb*^{R150X} mice (DBA/2)

Characteristics	MALE				FEMALE			
	Overall	CD	WD	<i>P</i> -value	Overall	CD	WD	<i>P</i> -value
Sample Size (n)	14	7	7		12	6	6	
Increased Body Weight (g)	10.62 (4.18)	9.60 (3.78)	11.65 (4.58)	0.379	10.14 (2.67)	9.08 (2.57)	11.20 (2.52)	0.181
Fat Pad Weight (g)	1.39 (0.57)	1.26 (0.55)	1.51 (0.61)	0.429	1.22 (0.62)	0.86 (0.22)	1.58 (0.70)	0.037
Percentage of Fat Pad (%)	3.70 (1.42)	3.59 (1.46)	3.82 (1.49)	0.777	4.32 (1.66)	3.29 (0.39)	5.34 (1.84)	0.024
Biochemistry								
Total Cholesterol (mmol/L)	1.38 (0.53)	1.37 (0.54)	1.40 (0.57)	0.91	1.44 (0.09)	1.43 (0.07)	1.45 (0.10)	0.707
Total Triglycerides (mmol/L)	0.59 (0.23)	0.52 (0.21)	0.65 (0.26)	0.335	0.79 (0.16)	0.81 (0.19)	0.78 (0.14)	0.749
HDL-C (mmol/L)	0.35 (0.16)	0.28 (0.11)	0.41 (0.18)	0.109	0.28 (0.07)	0.25 (0.05)	0.31 (0.08)	0.184
LDL-C (mmol/L)	0.10 (0.04)	0.09 (0.04)	0.11 (0.04)	0.45	0.12 (0.02)	0.13 (0.02)	0.12 (0.02)	0.472
Blood count								
WBC (10 ⁹ /L)	4.31 (2.54)	2.95 (1.15)	5.67 (2.89)	0.039	11.30 (1.57)	12.02 (0.98)	10.57 (1.85)	0.218
Neu # (10 ⁹ /L)	1.46 (0.91)	1.08 (0.82)	1.83 (0.90)	0.126	3.96 (2.25)	5.44 (2.20)	2.49 (1.05)	0.051
Lym # (10 ⁹ /L)	2.45 (2.00)	1.53 (0.73)	3.38 (2.48)	0.083	5.89 (1.04)	5.38 (1.29)	6.40 (0.43)	0.185
Mon # (10 ⁹ /L)	0.24 (0.17)	0.19 (0.19)	0.28 (0.15)	0.369	0.99 (0.31)	0.81 (0.03)	1.18 (0.38)	0.101
Eos # (10 ⁹ /L)	0.30 (0.14)	0.33 (0.14)	0.27 (0.13)	0.409	0.35 (0.07)	0.29 (0.02)	0.42 (0.02)	<0.001
Bas # (10 ⁹ /L)	0.06 (0.03)	0.05 (0.03)	0.06 (0.03)	0.391	0.09 (0.04)	0.09 (0.05)	0.10 (0.03)	0.86
Neu % (%)	30.59 (16.79)	29.83 (19.59)	31.36 (15.02)	0.873	33.60 (15.58)	44.45 (14.72)	22.75 (5.95)	0.034
Lym % (%)	48.18 (20.77)	48.12 (23.24)	48.24 (19.85)	0.992	53.55 (13.38)	45.70 (14.43)	61.40 (6.70)	0.096
Mon % (%)	5.06 (3.37)	4.94 (4.14)	5.18 (2.73)	0.899	8.82 (2.40)	6.80 (0.23)	10.85 (1.56)	0.002
Eos % (%)	7.71 (3.95)	9.72 (3.99)	5.70 (2.91)	0.053	3.22 (1.14)	2.35 (0.40)	4.10 (0.92)	0.013
Bas % (%)	1.35 (0.75)	1.59 (0.95)	1.12 (0.44)	0.267	0.80 (0.26)	0.70 (0.35)	0.90 (0.12)	0.315
RBC (10 ¹² /L)	6.88 (2.60)	6.54 (2.55)	7.22 (2.81)	0.643	10.32 (0.35)	10.29 (0.21)	10.36 (0.48)	0.771
HGB (g/L)	95.64 (36.20)	91.43 (35.89)	99.85 (38.85)	0.681	141.25 (4.43)	140.00 (1.15)	142.50 (6.35)	0.468
HCT (%)	30.37 (11.50)	29.26 (11.51)	31.49 (12.28)	0.732	42.67 (2.11)	42.10 (0.92)	43.25 (2.94)	0.484
MCV (fL)	38.52 (15.24)	39.33 (16.05)	37.70 (15.63)	0.851	41.40 (3.15)	40.90 (0.00)	41.90 (4.73)	0.687
MCH (pg)	12.04 (4.89)	12.20 (5.07)	11.87 (5.10)	0.907	13.70 (0.84)	13.60 (0.12)	13.80 (1.27)	0.764
MCHC (g/L)	272.62 (108.54)	270.47 (111.62)	274.77 (114.25)	0.944	331.50 (5.32)	333.00 (3.46)	330.00 (6.93)	0.468
RDW-CV (%)	18.95 (7.32)	19.40 (7.67)	18.50 (7.54)	0.829	20.97 (5.34)	16.00 (0.46)	25.95 (0.52)	<0.001
RDW-SD (fL)	37.18 (15.06)	39.38 (16.43)	34.98 (14.51)	0.605	38.05 (10.60)	28.80 (0.81)	47.30 (5.77)	0.001
PLT (10 ⁹ /L)	754.51 (456.99)	713.42 (444.52)	795.60 (500.94)	0.751	761.25 (398.72)	1124.00 (132.79)	398.50 (49.07)	<0.001
MPV (fL)	5.20 (2.02)	5.07 (2.07)	5.33 (2.12)	0.821	6.38 (0.37)	6.25 (0.52)	6.50 (0.12)	0.384
PDW	13.61 (5.56)	13.94 (5.82)	13.29 (5.74)	0.839	15.55 (0.42)	15.80 (0.35)	15.30 (0.35)	0.087
PCT (%)	0.47 (0.29)	0.43 (0.27)	0.50 (0.32)	0.646	0.48 (0.24)	0.70 (0.02)	0.26 (0.04)	<0.001

Gpnmb^{R150X} mice (on hybrid DBA/2×C57BL/6J-DBA/2 background) were fed a CD or WD for 20 weeks. The variables were presented as mean±SD. The analysis of variance was used for comparisons of continuous variables.

Table S7. Features of *Gpnmb*^{R150X} *ApoE*^{-/-} mice (DBA/2)

Characteristics	MALE				FEMALE			
	Overall	CD	WD	P-value	Overall	CD	WD	P-value
Sample Size (n)	19	10	9		20	10	10	
Increased Body Weight (g)	11.69 (4.17)	8.47 (1.27)	14.90 (3.43)	0.002	6.59 (2.15)	5.35 (1.27)	7.83 (2.17)	0.006
Fat Pad Weight (g)	2.26 (0.95)	1.57 (0.21)	2.94 (0.90)	0.005	1.39 (0.68)	0.96 (0.25)	1.86 (0.69)	0.002
Percentage of Fat Pad (%)	6.81 (1.63)	5.87 (1.38)	7.74 (1.35)	0.038	5.23 (2.08)	4.01 (0.87)	6.61 (2.22)	0.005
Biochemistry								
Total Cholesterol (mmol/L)	19.00 (13.75)	8.59 (1.13)	32.38 (9.98)	<0.001	27.44 (8.34)	19.09 (3.28)	33.41 (4.56)	<0.001
Total Triglycerides (mmol/L)	3.38 (2.20)	2.43 (1.08)	4.43 (2.69)	0.045	2.58 (2.09)	1.98 (0.54)	3.19 (2.86)	0.26
HDL-C (mmol/L)	6.62 (2.65)	6.03 (2.04)	7.29 (3.19)	0.315	5.84 (2.92)	4.25 (2.59)	7.42 (2.42)	0.024
LDL-C (mmol/L)	5.40 (4.66)	3.14 (1.44)	7.92 (5.74)	0.021	6.03 (3.93)	3.16 (1.92)	8.89 (3.26)	0.001
Blood count								
WBC (10 ⁹ /L)	4.02 (2.43)	3.42 (3.06)	4.78 (1.01)	0.279	5.00 (2.78)	5.73 (3.31)	4.27 (2.06)	0.253
Neu # (10 ⁹ /L)	1.50 (1.34)	1.40 (1.71)	1.62 (0.73)	0.757	1.23 (0.86)	1.34 (1.03)	1.13 (0.70)	0.609
Lym # (10 ⁹ /L)	2.10 (1.28)	1.74 (1.53)	2.56 (0.72)	0.217	3.22 (2.17)	3.94 (2.42)	2.51 (1.70)	0.144
Mon # (10 ⁹ /L)	0.22 (0.17)	0.15 (0.14)	0.30 (0.18)	0.083	0.26 (0.17)	0.22 (0.16)	0.29 (0.19)	0.377
Eos # (10 ⁹ /L)	0.16 (0.14)	0.09 (0.06)	0.25 (0.16)	0.013	0.19 (0.15)	0.14 (0.14)	0.24 (0.15)	0.151
Bas # (10 ⁹ /L)	0.04 (0.03)	0.03 (0.03)	0.05 (0.04)	0.341	0.10 (0.10)	0.09 (0.12)	0.10 (0.08)	0.827
Neu % (%)	32.73 (13.82)	32.28 (16.65)	33.31 (10.37)	0.888	25.31 (10.80)	23.69 (8.71)	26.93 (12.82)	0.517
Lym % (%)	55.80 (13.82)	57.30 (15.50)	53.87 (12.24)	0.639	63.56 (14.99)	69.06 (10.72)	58.07 (17.09)	0.102
Mon % (%)	6.00 (4.33)	5.88 (5.35)	6.16 (2.95)	0.903	5.21 (3.20)	3.48 (1.31)	6.94 (3.64)	0.011
Eos % (%)	4.48 (3.06)	3.58 (1.99)	5.64 (3.91)	0.189	4.03 (2.93)	2.33 (1.46)	5.72 (3.09)	0.006
Bas % (%)	0.99 (0.59)	0.97 (0.54)	1.01 (0.70)	0.88	1.89 (1.63)	1.44 (1.30)	2.34 (1.86)	0.226
RBC (10 ¹² /L)	9.57 (1.89)	10.13 (2.15)	8.93 (1.44)	0.236	9.78 (1.94)	10.44 (0.85)	9.12 (2.49)	0.13
HGB (g/L)	120.87 (31.33)	120.38 (41.77)	121.43 (15.95)	0.951	132.10 (26.19)	142.30 (11.08)	121.90 (33.08)	0.081
HCT (%)	39.80 (7.15)	41.90 (8.25)	37.40 (5.23)	0.237	40.56 (7.49)	43.01 (3.24)	38.11 (9.73)	0.148
MCV (fL)	41.78 (1.70)	41.52 (0.97)	42.07 (2.33)	0.554	41.62 (1.76)	41.23 (0.61)	42.00 (2.42)	0.342
MCH (pg)	12.98 (2.95)	12.34 (3.95)	13.71 (0.96)	0.387	13.52 (0.37)	13.63 (0.23)	13.40 (0.45)	0.166
MCHC (g/L)	309.80 (67.98)	296.12 (93.59)	325.43 (5.47)	0.425	325.15 (11.24)	330.70 (3.53)	319.60 (13.64)	0.023
RDW-CV (%)	16.16 (3.01)	14.95 (2.09)	17.54 (3.45)	0.097	16.58 (3.46)	14.56 (0.76)	18.59 (3.96)	0.005
RDW-SD (fL)	29.39 (5.20)	27.18 (3.82)	31.93 (5.67)	0.076	30.16 (7.36)	26.29 (1.28)	34.02 (8.92)	0.014
PLT (10 ⁹ /L)	855.93 (331.65)	899.62 (413.15)	806.00 (228.17)	0.604	824.85 (280.90)	963.30 (155.18)	686.40 (316.07)	0.023
MPV (fL)	6.38 (0.69)	6.11 (0.73)	6.71 (0.48)	0.081	6.36 (0.63)	6.48 (0.39)	6.23 (0.80)	0.386
PDW	15.59 (0.25)	15.66 (0.24)	15.51 (0.25)	0.269	15.83 (0.43)	15.75 (0.17)	15.91 (0.59)	0.418
PCT (%)	0.50 (0.21)	0.47 (0.25)	0.54 (0.15)	0.551	0.53 (0.19)	0.62 (0.11)	0.44 (0.21)	0.029

Gpnmb^{R150X} *ApoE*^{-/-} mice (on hybrid DBA/2×C57BL/6J-DBA/2 background) were fed a CD or WD for 20 weeks. The variables were presented as mean±SD. The analysis of variance was used for comparisons of continuous variables.

Table S8. Physicochemical characterization of siRNA-LNPs

Physicochemical Characterization	siNC-LNP	siGpnmb-LNP
Size (nm)	130.12±7.02	146.30±11.48
Polymer Dispersity Index (PDI)	0.15	0.17
Zeta Potential (mV)	5.35±0.97	7.12±1.53
Carrier Concentration (mg/mL)	10.00	10.00
Nucleic Acid Concentration (mg/mL)	0.1947	0.1933
Drug Loading Efficiency (%)	1.95%	1.93%

Physicochemical characterization of siNC-LNPs and siGpnmb-LNP

Table S9. Hematological analysis of *ApoE*^{-/-} mice injected with LNPs-siRNA

Indicators	LNPs-siNC	LNPs-siGpnmb	P Value
WBC (10 ⁹ /L)	6.110±2.397	4.113±1.646	0.5079
Neu # (10 ⁹ /L)	2.225±0.6902	2.090±0.7876	0.9000
Lym # (10 ⁹ /L)	3.178±1.618	1.995±0.8055	0.5664
Mon # (10 ⁹ /L)	0.5233±0.1936	0.3767±0.1701	0.5818
Eos # (10 ⁹ /L)	0.2800±0.1458	0.1017±0.06019	0.2575
Bas # (10 ⁹ /L)	0.1560±0.09755	0.0750±0.04201	0.4369
RBC (10 ¹² /L)	9.547±1.455	7.197±0.5030	0.1579
HGB (g/L)	136.3±21.05	103.0±7.716	0.1680
HCT (%)	38.45±5.620	29.55±2.417	0.1764
MCV (fL)	40.45±0.7122	40.93±0.6712	0.6320
MCH (pg)	14.25±0.1648	14.25±0.2363	>0.9999
MCHC (g/L)	352.5±4.595	348.7±3.242	0.5110
RDW-CV (%)	19.20±1.290	16.95±0.3433	0.1228
RDW-SD (fL)	35.15±2.829	31.07±1.001	0.2035
PLT (10 ⁹ /L)	868.5±61.16	1222±124.8	0.0293*
MPV (fL)	6.300±0.3651	6.017±0.2469	0.5348
PDW (fL)	15.95±0.2717	15.37±0.2201	0.1262
PCT (%)	0.5480±0.05260	0.6724±0.05687	0.1432

Data were compared by an unpaired two-sided Student's t-test. **p* < 0.05.