SUPPLEMENTAL MATERIAL

Extended Methods

Bone marrow transplantation

At 8 weeks of age, female *Ldlr*$^{-/-}$ mice were lethally irradiated with 1 dose of 9.12 Gy from acesium g source. At 24 h after irradiation, the *Ldlr*$^{-/-}$ mice were transplanted with chimeric 5-10*10^{6} *Tet2*$^{-/-}$ bone marrow (BM) cells containing 10% CD45.2 *Abro1*$^{-/-}$, *Tet2*$^{+/-}$, *Tet2*$^{-/-}$, *Tet2*$^{+/-}$*Abro1*$^{-/-}$ or *Tet2*$^{-/-}$*Abro1*$^{-/-}$ and 90% CD45.1 wild type cells. A control group was transplanted with mixed bone marrow from 10% littermate control CD45.2 Tet2$^{+/+}$ and 90% CD45.1 wild type bone marrow cells. Mice were allowed to recover for 5 weeks after BM transplantation before Western-type diet (WTD; Harlan Teklad TD88137) feeding for 8 weeks.

Atherosclerosis studies

Ldlr$^{-/-}$ mice were transplanted with BM from indicated mice and fed WTD. After 2 weeks of WTD, mice with similar body weights were randomized into two different groups that were respectively injected intraperitoneally with HL (1 mg/kg) or vehicle control (DMSO/PBS) every second day for 6 weeks mice then were sacrificed after a total of 8 weeks of WTD. After the indicated period on WTD, mice were sacrificed and hearts were perfused with PBS, isolated, and fixed in phosphate-buffered formalin. Subsequently, hearts were dehydrated and embedded in paraffin, and were cross sectioned throughout the aortic root area. Hematoxylin-eosin staining was performed on the sections and the average from 6 sections for each animal was used to determine lesion size. Lesion size and necrotic area were quantified bymorphometric analysis using Image-Pro Plus software (Media Cybernetics, USA). Morphological analysis of fibrous cap thickness was performed with a Masson trichrome stain kit (Maixin-Bio, Liaoning, China) and was quantified by choosing the largest necrotic core from duplicate sections and measuring the thickness of the thinnest part of the cap.

Immunofluorescence staining on atherosclerotic plaques

Paraffin-embedded slides were deparaffinized and rehydrated in Trilogy (Cell MARQUE 920P-09). The antibodies were used for the staining including anti-IL1β (abcam, ab9722 1:200). The sections were incubated with primary antibodies overnight at 4˚C then incubated with secondary antibodies for 30 min. Sections were mounted using DAPI. In all immunofluorescence staining, isotype matched normal IgG were used as the negative control. For staining of neutrophil extracellular traps, paraffin sections were incubated in Tris-Base EDTA at pH 9.0 (15-20 min; pressure cooker) for antigen retrieval. Then, sections were blocked in PBS containing 10% goat serum for 30 min at 4°C. Subsequently, sections were incubated overnightat 4°C with biotinylated myeloperoxidase (MPO) (1:30; R&D systems; BAF3667) or Ly6G (1:200; BioLegend; 127602). When citrullinated histones were stained, sections were concomitantly incubated with Anti-Histone H3 (citrulline R2+R8+R17) antibody (1:300; Abcam; ab5103). For MPO staining, the sections were then incubated with Streptavidin Alexa Fluor 488 (1:200; Invitrogen/Life Technologies; S11223). Anti-rat CF 488A (1:200) was used as secondary antibody for Ly6G staining. When citrullinated histones were stained, sections were concomitantly incubated with Alexa-647 (1:200; Invitrogen; A-21447). Sections were mounted using ProLong Gold Antifade Mountant with DAPI (Thermofisher; P3693) and imaged using a Leica DMI6000B microscope running Leica software. The MPO or Ly6G positive area was quantified using Image-Pro Plus software (Media Cybernetics, USA). The overlap of MPO staining with citrullinated histone staining or Ly6G staining with citrullinated histone staining was assessed as neutrophil extracellular traps and quantified using Image-Pro Plus software (Media Cybernetics, USA).

Flow cytometry

For quantification of blood myeloid cells, blood was collected by tail bleeding into EDTA coated tubes and immediately put on ice. Red blood cells (RBCs) were lysed (BD Pharm Lyse, BD Bioscience) and white blood cells were centrifuged, washed, and resuspended in FACS buffer.Cells were stained with a cocktail of antibodies against CD45.1 (FITC anti-mouse CD45.1, Biolegend, 110706) and CD45.2 (APC/Cyanine7 anti-mouse CD45.2, Biolegend, 109824). The expansion of *Tet2*$^{-/-}$ (*Tet2*$^{-/-}$ allele burden) was calculated as percentage of CD45.2^{+} white blood cells in total CD45^{+} cells (% of CD45^{+} cells) in blood. For the human embryonic stem cells (ESCs), anti-CD45 (1:100 dilution, BioLegend, 304006,) and anti-CD68 (1:100 dilution, BioLegend, 333810) were used to characterize the cells. Flow cytometry was performed using the LSRII (Beckton Dickinson) and data were analyzed using FlowJo software (Beckton Dickinson). Isotype matched normal IgG was used as the control in each flow cytometry assay.

Isolation of Ly6G^{+} neutrophils and Ly6G^{-}CD11b^{+} monocytes

Spleens were mashed on a 40 μm filter and red blood cells were lysed (BD Pharm Lyse, BD Bioscience). First, Ly6G^{+} neutrophils were isolated, using Ly6G^{+} (#130-120-337) coated microbeads, and then, from the same sample, Ly6G^{-}CD11b^{+} monocytes/macrophages were isolated, using CD11b^{+} (#130-049-601) coated microbeads (Miltenyi Biotec). Ly6G^{-}CD11b^{+} monocyte/macrophages were separate into CD45.1^{+} and CD45.2^{+} fractions using Magnisort mouse CD45.2 positive selection kit (#8802-6849) from Thermo Fisher.

Blood and serum analysis

Complete blood counts were performed using whole blood collected from facial vein bleeding in EDTA coated tube and then analyzed with FORCYTE Veterinary Hematology Analyzer (Oxford Science, Inc.) Mouse plasma was isolated through centrifugation of blood at 12,000g for 10 min at 4°C. Total plasma cholesterol was determined using a cholesterol E assay (Wako, 999-02601).

Bone marrow culture

Bone marrow was flushed from hindlimbs with Hanks balanced salt solution (HBSS) and filtered in 60μm cell filters on ice. Cells were centrifuged 800 g for 10 minutes at 4 C and suspended in DMEM with 10% FBS and 20% L-cell media, 100 U/ml Penicillin/Streptomycin (Thermo Fisher, 15140148). Bone marrow cells were then incubated in non-tissue culture treated flasks for 5 days and plated into new tissue culture dishes overnight forthe indicated assays.

Human embryonic stem cell (hESC) culture

TET2$^{-/-}$ HUES8 hESCs were previously generated through CRISPR/Cas9 gene editing.[30] Human hESCs were cultured on mitotically inactivated MEFs with hESC media supplemented with 6ng/ml FGF2, as described.[49] Hematopoietic lineage specification was performed following a previously described spin-embryoid body-based protocol to generate hematopoietic progenitor cells through a hemogenic endothelium intermediate.[49] On day 10, the cells were transferred to macrophage differentiation culture consisting of StemPro-34 SFM medium with 1% nonessential amino acids (NEAA), 1 mM L-glutamine and 0.1mM β-mercaptoethanol (2ME), supplemented with 100 ng/ml macrophage colony-stimulating factor (M-CSF) and 25 ng/ml interleukin 3 (IL-3) for 11 days with media changes every two days.

Lentivirus production for DUSP10 overexpression or targeted methylation editing

Fuw-dCas9-Tet1CD-P2A-BFP (Addgene plasmid: 108245), Fuw-dCas9-dead Tet1CDP2A-BFP (Addgene plasmid: 108246) and pgRNA-modified (Addgene plasmid #84477) were purchased. The *Dusp10* gRNA expression plasmid was cloned by inserting annealed oligos (For: TTGG ACCCACTAGCGGGTCCGAGCCGG; Rev: AAAC CCGGCTCGGACCCGCTAGTGGGT) into modified pgRNA plasmid with AarI site.[32,33] Lentiviruses expressing *Dusp10* gRNA and Fuw-dCas9-Tet1CD-P2A-BFP or Fuw-dCas9-dead Tet1CDP2A-BFP were produced by transfecting HEK293T cells with together with standard packaging vectors (pmD2.G, pRSV-REV and pMDLg/pRRE) followed by ultra-centrifugation-based concentration. For overexpression of

human DUSP10, pLX-302 (Addgene plasmid: 25896) and pLX-302-MKP5-V5 puro (Addgene plasmid #87770) were purchased. Lentiviruses expressing pLX-302 (empty vector) or pLX-302-MKP5-V5 puro (pLX-DUSP10) were produced as described above. BMDMs were centrifuged at 900g at 20 C and incubated with lentiviruses for 24h in complete growth medium supplemented with 8 μg/ml polybrene (Sigma, TR-1003). 24 h later, cells were supplemented with fresh media for 2 additional days.

siRNA-mediated gene silencing

Scrambled siRNA control (Dharmacon, D-001810-10-20) and siRNAs against *Dusp10* (Dharmacon, L-060807-00-0005) or *Brcc3* (Dharmacon, L-060013-01-0010) were transfected into BMDMs using Lipofectamine RNAiMAX (Life Technologies) at 40 nM of siRNA in 24-well or 96 well plates following the manufacturer's instructions.

Acetylated LDL preparation

LDL was acetylated (acLDL) by the method of Fraenkel-Conrat as described.[22]In summary, 1 ml of 0.15 M NaCl containing 16 mg of LDL protein was added to 1 ml of a saturatedsolution of sodium acetate with continuous stirring in an ice-water bath. Next, acetic anhydride was added in multiple small aliquots while stirring. After the addition of a total mass of acetic anhydride equal to 1.5 times the mass of protein used, the mixture was stirred for an additional 30min without further additions. The reaction solution was then dialyzed for 48 hr at 4ºC with buffer containing 0.15M NaCl and 0.3 mM EDTA, pH, 7.4.

Inflammasome assays

Bone marrow derived macrophages (BMDMs) were preincubated with LPS (20ng/mL), for 3 hours then incubated with 2 mM ATP or 10 μg/ml Nigericin for 1h. Alternatively, BMDMs were primed with LPS (20ng/mL) and IFN-γ (2ng/mL), for 3h and treated with 25 μg/ml oxidixed LDL (oxLDL) for additional 16h. At the end of the treatment, IL-1β in the media was measured using ELISA kits (R&D Systems; DY401). Data were normalized to protein concentration of cell lysates. For mechanistical inflammasome assays, treatments of various compounds were done as listed below; 1 μM SP600125 (SelleckChem, S1460) for 30 min prior to LPS, 1 μM G5 (Ubiquitin isopeptidase inhibitor I, Sigma, 662125-10MG) for 30 prior to ATP or Nigericin, 25 nM Holomycin (Santa Cruz, sc-490291) for 30 prior to ATP or Nigericin.

Methylated DNA capture

DNA was isolated using the PureLink Genomic DNA Kit (Thermo Fisher Scientific Cat#K182001). Next, using 1μg of DNA from each sample, methylated DNA was captured and detected by antibodies in the Methylamp Methylated DNA Capture Kit (EPIGENTEK), then purification of methylated DNA was isolated following the manufacturer's protocol. PCR was conducted using primers targeting the promoter of *Dusp1,4,6* and *10*, and the data were quantified as fold-enrichment of methylated DNA in the Control *Csf1r* promoter. IgG antibodies supplied in the kit was using as the negative control which do not recognize methylated DNA. Primers for used for MeDIP analysis are as follows: *Dusp1* MeDIP (For: AGA AGG ACG TCT CAA CTCT CG; Rev: AAG GGG AGT GGG TAG TGA GA), *Dusp4* MeDIP (For: CAC CCG CAA CGA TCT CTA C; Rev: AAC GGA GAC CTA GAG GAA GAA), *Dusp6* MeDIP (For: CCA GGC AGT CCA CCA GTC; Rev: CCA ACC CGG TCC TCC TTT AG) and *Dusp10* MeDIP (For: GTT CGG GGA ATC GGG AG; Rev: CGG GTT GAA CAG CCA GAA TG).

qRT-PCR

To assess mRNA expression, RNA from BMDMs was isolated using a Qiagen RNeasy kit and cDNA was synthesized using kits from Thermo Scientific (Maxima First Strand cDNA synthesis kit; 1642). Initial differences in RNA quantity were corrected for using the housekeepinggene m36B4. SYBR Green Master Mix was from Applied Biosystems (by ThermoScientific; 4385612) and qPCR was run on a StepOne Plus Real-time PCR Systems from Applied Biosystems.

qRT-PCR was conducted for specific genes and normalized to m36B4. Primers for qRT-PCR assays in murine samples are as follows: *Il1b* (For: TGT GAA TGC CAC CTT TTG ACA; Rev: GGT CAA AGG TTT GGA AGC AG), *Nlrp3* (For: ATT ACC CGC CCG AGA AAG G; Rev: TCG CAG CAA AGA TCC ACA CAG), *Il6* (For: ACA ACC ACG GCC TTC CCT ACTT; Rev: CAC GAT TTC CCA GAG AAC ATGTG), *Brcc3* (For: CTG CCG TCC ATT GAG ATT ACG; Rev: TCA GGA ACC TGC TCG AAT CAT), *Dusp1* (For: GTT GTT GGA TTG TCG CTC CTT; Rev: TTG GGC ACG ATA TGC TCC AG), *Dusp2* (For: TGC TGG GGC CGA AAA TAG C; Rev: CAT AGA TCG GAA CTC ACC TGG T), *Dusp3* (For: TCT GTG GCT CAG GAC ATC AC; Rev: GGC CCT TTC AAA GTA AGC ACT G), *Dusp4* (For: GTA CAT CGA CGC AGT AAA GGA C; Rev: GCT TGA CGA ACT CAA AAG CCT C), *Dusp5* (For: GGG GTA TGA GAC CTT CTA CTC AC; Rev: GCG TGG TAG GCA CTT CCA A), *Dusp6* (For: ATA GAT ACG CTC AGA CCC GTG; Rev: ATC AGC AGA AGC CGT TCG TT), *Dusp7* (For: GTG CTG CTC TAC GAC GAG G Rev: GCT CAG AGT ATT CCG TCT GGA), *Dusp8* (For: CCG AGG AAG GTG ATG GAC G; Rev: CAC CAG CTT TGA ACA GCA GAT A), *Dusp9* (For: GGA GGC CAT TGC ATT CAT TGA; Rev: GCA TCG TTG AGT GAG AGG TGA), *Dusp10* (For: CCA TCT CCT TTA GAC GAC AGG G; Rev: GCT ACC ACT ACC TGG GCT G), *Dusp12* (For: ACT GAA ACT GTA TGA GGC AAT GG; Rev: CCT GTG AAA TGG TAG TTG GGT C), *Dusp13* (For: CAG TCT GCC CTT GGC ATT TAC; Rev: CCT CTT CTC TTA GGG AGC ACA G), *Dusp16* (For: TTT ATG GGC CAA CTC ATG GAC; Rev: CAG CAG CTT CAG TTT GCT CTT), *Dusp18* (For: CTT CCC AGT TCA GAT CCC CCA; Rev: AGT AGG AGC TTG TTG TTG GCA), *Dusp19* (For: GGT GAC CAC GCT AAC TGG AAA; Rev: CAC ATA GCC ACA ACC ACC C), *Dusp22* (For: ACG CAA GAG ATG CAG AAC AGT; Rev: GCC GCT GGA ATA CAC AGG T), *Dusp23* (For: ATC GAC CAA TTT GTG AAG ATC GT; Rev: TCC TGT TCA TAC GTC TCA ATG GA). Primers for qRT-PCR assays in human samples are as follows: *DUSP1* (For: ACC ACC ACC GTG TTC AAC TTC; Rev: TGG GAG AGG TCG TAA TGG GG), *DUSP2* (For: TGC CCC AAC CAC TTT GAG G; Rev: AGT CAA TGA AGC CTA TGG CCT), *DUSP3* (For: AAG GAC TCC GGC ATC ACA TAC; Rev: AAG CCT GGT CAA TGA AGT CGG), D*USP4* (For: GGC GGC TAT GAG AGG TTT TCC; Rev: TGG TCG TGT AGT GGG GTC C), *DUSP5* (For: GCG ACC CAC CTA CAC TAC AAA; Rev: CTT CAT AAG GTA AGC CAT GCA GA), *DUSP6* (For: GAA CTG TGG TGT CTT GGT ACA TT; Rev: GTT CAT CGA CAG ATT GAG CTT CT) and *DUSP10* (For: TGA AGC ACA CTC GGA TGA CC; Rev: CCT CGA ACT CTA GCA ACT GCC).

Immunoprecipitation

To detect NLRP3 ubiquitination, cells were lysed in lysis buffer (M-PER™ Mammalian Protein Extraction Reagent, Thermo Fisher, 78505). Endogenous NLRP3 was immuno- precipitated with anti-NLRP3 (Adipogen, AG-20B-0014-C100) and Dynabeads™ Protein A Immunoprecipitation Kit (Thermo Fisher, 10006D). Immunoprecipitated complexes were washed in lysis buffer and proteins were eluted in Laemmli buffer (Boston Products, BP-111R).

Immunoblotting

BMDMs or Ly6G$^-$CD11b$^+$ monocytes/macrophages were lysed in lysis buffer containing protease/phosphatase inhibitor on ice for 30 mins and then centrifuged at 14,000g for 5 minutes. Protein lysates were separated by 4-20% gradient SDS-PAGE andtransferred to nitrocellulose membranes. Then the membranes were blocked with 5% non-fat milk in TBS-T and incubated with primary antibodies, anti-Caspase-1 (14-9832-82, eBioScience, 1:2000), anti-GSDMD (Genentech, 1:1000), anti-IL-1β (ab9722, Abcam, 1:1000), anti-NLRP3 (15101S, Cell Signaling, 1:1000), anti-Ubiquitin (Cell signaling 43124, 1:1000), anti-p- SAPK/JNK (Thr183/Tyr185) (Cell signaling 4668S, 1:1000), anti-SAPK/JNK (Cell signaling 9252S,

1:2000), anti-p-Erk (1/2) (Cell signaling 4370S, 1:1000), anti-Erk (1/2) (Cell signaling 4695S, 1:2000), anti-p-p38 MAPK (Cell signaling 4511S, 1:1000), anti-p38 MAPK (Cell signaling 8690S, 1:2000), and β-actin (Cell signaling 4970S, 1:5000) at 4°C overnight and detected using HRP-conjugated secondary antibodies.

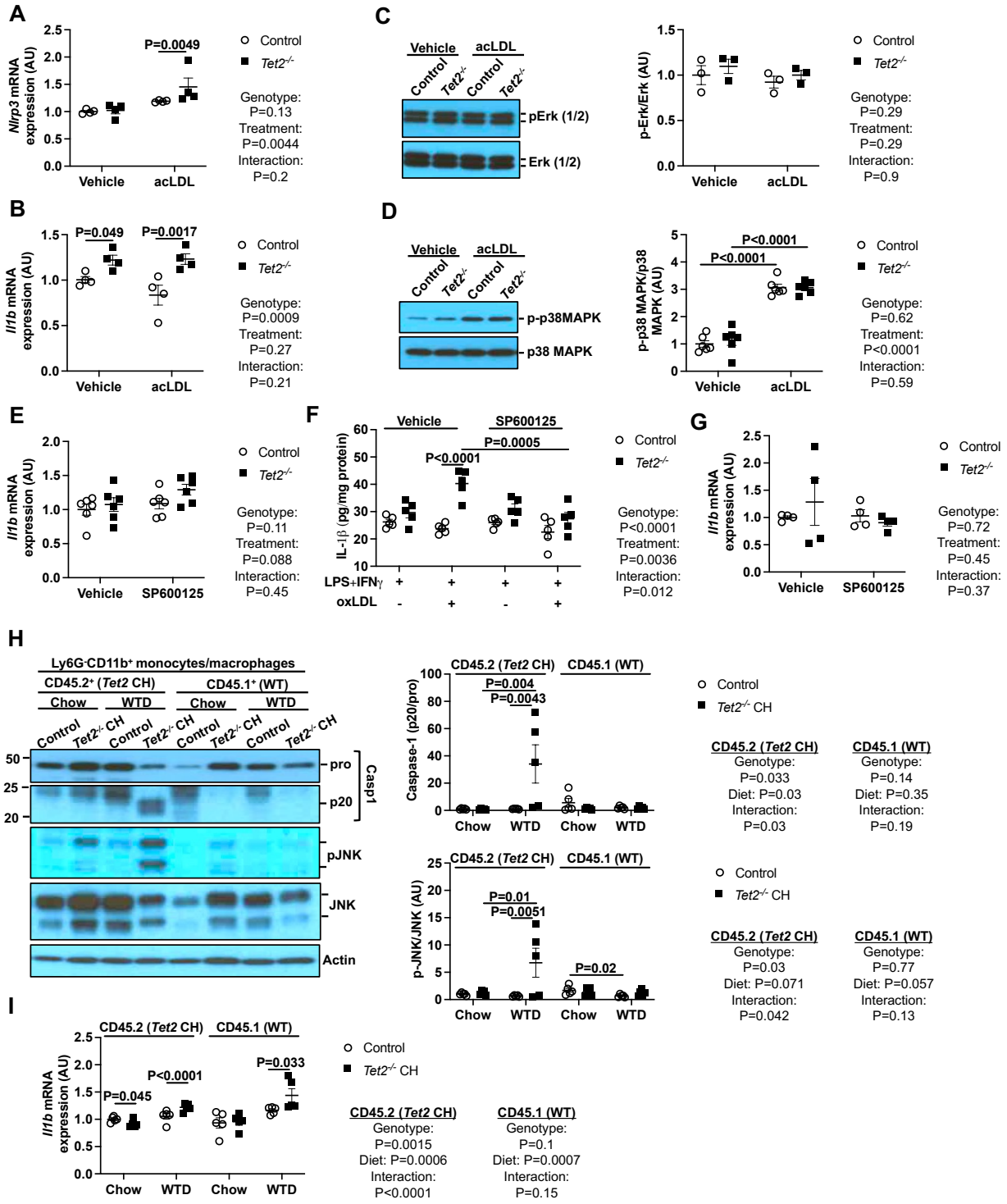

Figure S1. Inflammasome priming is slightly elevated with no changes in Erk and p38 MAPK phosphorylation in *Tet2*$^{-/-}$ BMDMs. (A) *Nlrp3* mRNA expression in control and *Tet2*$^{-/-}$ BMDMs that were primed with LPS for 3h. **(B)** *Il1b* mRNA expression in control and *Tet2*$^{-/-}$ BMDMs that were primed with LPS for 3h. **(C)** Immunoblot analysis of Erk (1/2) phosphorylation in vehicle and acLDL loaded in control and *Tet2*$^{-/-}$ BMDMs. **(D)** Immunoblot analysis of p38 MAPK phosphorylation in vehicle and acLDL loaded in control and *Tet2*$^{-/-}$ BMDMs. (E) *Il1b* mRNA expression in pre-treated with SP600125 and LPS primed control and *Tet2*$^{-/-}$ BMDMs. **(F-G)**

Control and *Tet2*$^{-/-}$ BMDMs that were pretreated with JNK inhibitor SP600125 for 30 min and primed with LPS and IFN-γ for 3h and treated with oxLDL for additional 16h. **(F)** IL-1β secretion. **(G)** *Il1b* mRNA expression. **(H)** Immunoblot of intracellular Caspase-1 cleavage and JNK (Thr183/Tyr185) phosphorylation in Ly6G^{-}CD11b^{+}CD45.1^{+} (WT) or Ly6G^{-}CD11b^{+}CD45.2^{+} (*Tet2* CH) monocytes/macrophages. **(I)** *Il1b* mRNA expression in Ly6G^{-}CD11b^{+}CD45.1^{+} (WT) or Ly6G^{-}CD11b^{+}CD45.2^{+} (*Tet2* CH) monocytes/macrophages isolated from *Ldlr*$^{-/-}$ mice that were transplanted with bone marrow mixture of WT or 10%*Tet2*$^{-/-}$/90%WT and fed with chow or WTD for 4 weeks. ****P<0.0001, ***P<0.001, ** P<0.01, *P<0.05 by *t*-test two-way ANOVA with Sidak's multiple comparison test.

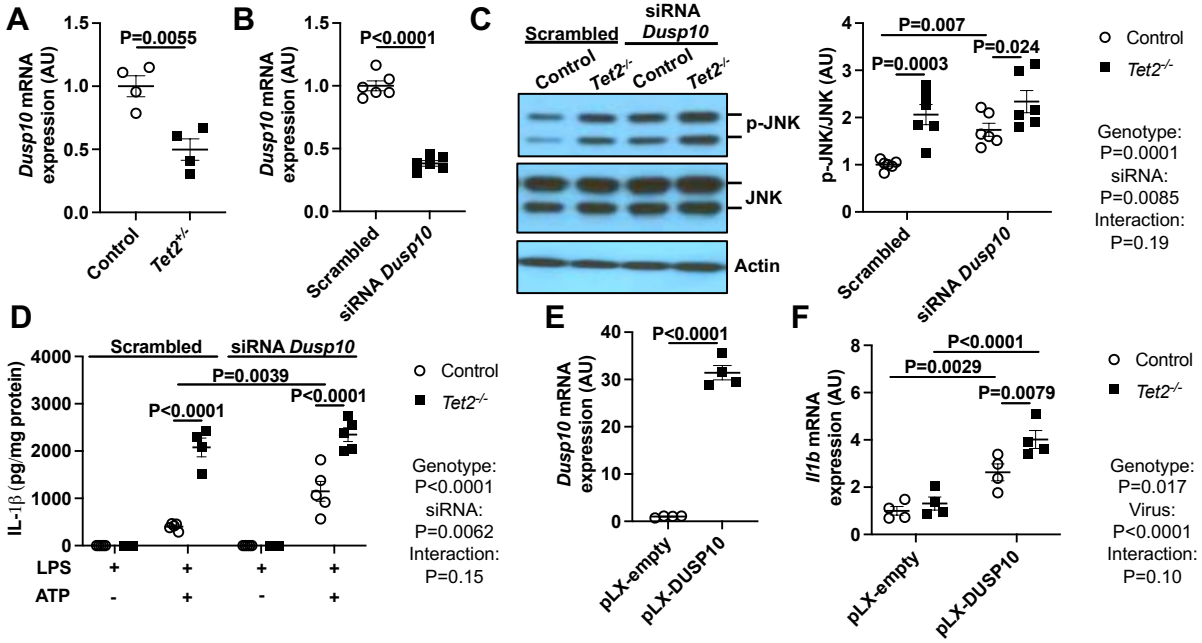

Figure S2. *Dusp10* downregulation elevates inflammasome activation. (A) *Dusp10* mRNA expression in control and *Tet2*$^{+/-}$ BMDMs. **(B-D)** Control and *Tet2*$^{-/-}$ BMDMs were transfected with control (Scrambled) or siRNA against *Dusp10* for 48h. **(B)** *Dusp10* mRNA expression. **(C)** Immunoblot of JNK (Thr183/Tyr185) phosphorylation. **(D)** IL-1β secretion from cells that were primed with LPS for 3h and treated with ATP for an additional 1h. **(E-F)** Control or *Tet2*$^{-/-}$ BMDMs were infected with control (pLX-empty) or DUSP10 lentiviruses for 72h. **(E)** *Dusp10* mRNA expression in control BMDMs. **(F)** *Il1b* mRNA expression in LPS primed control or *Tet2*$^{-/-}$ BMDMs. ****P<0.0001, ***P<0.001, ** P<0.01, *P<0.05 by *t*-test **(A-B, E)** and two-way ANOVA with Sidak's multiple comparison test **(C-D, F)**.

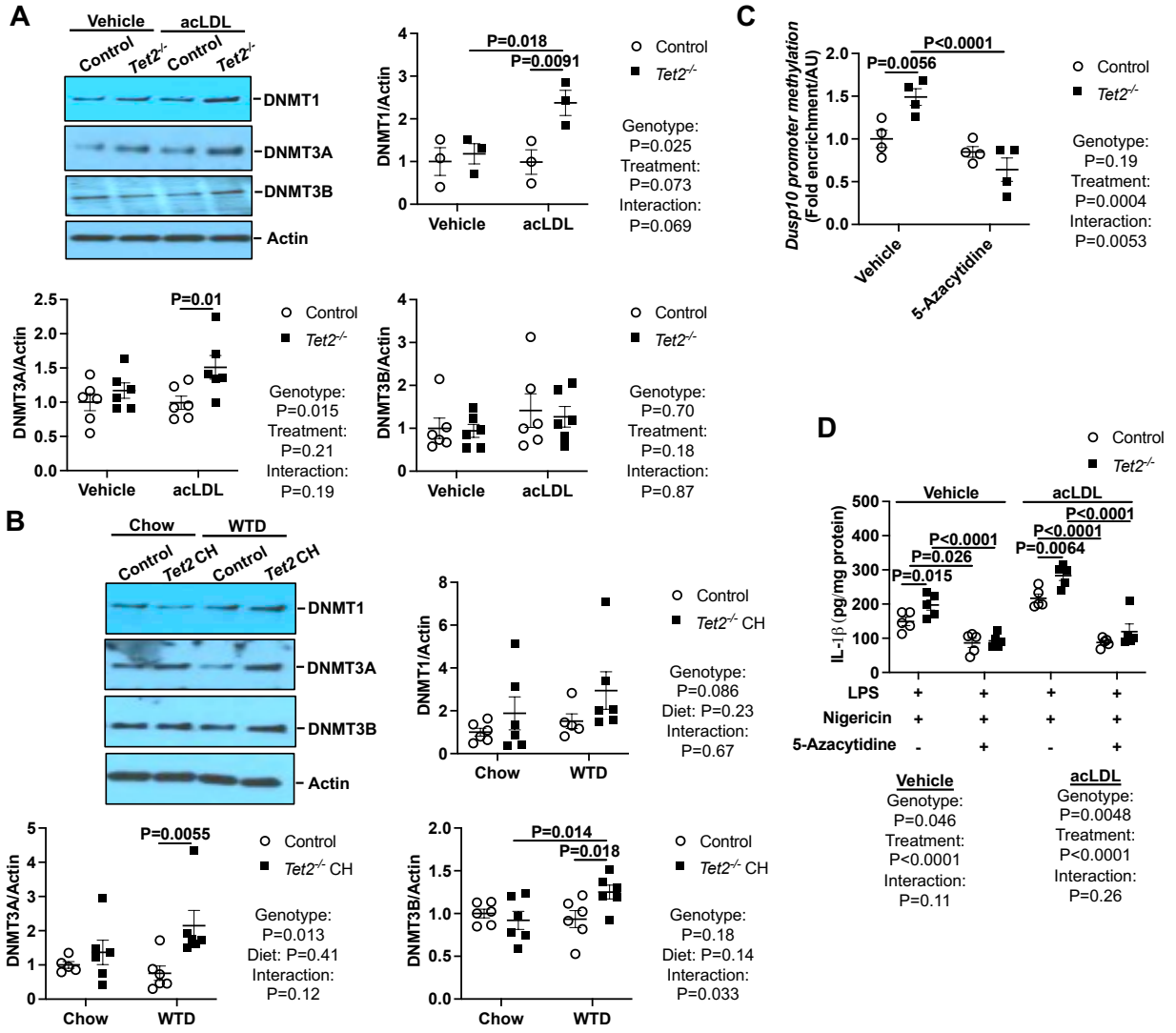

Figure S3. Cholesterol loading elevates inflammasome activation by increasing DNMTs in *Tet2* deficiency. **(A)** Immunoblot of DNMT1, DNMT3A and DNMT3B in vehicle or acLDL loaded control and *Tet2*$^{-/-}$ BMDMs. **(B)** Immunoblot of DNMT1, DNMT3A and DNMT3B in Ly6G^{-}CD11b^{+} splenic monocytes/macrophages from *Ldlr*$^{-/-}$ mice following transplantation of WT or 10%*Tet2*$^{-/-}$/90%WT BM and fed with chow or WTD. **(C)** meDIP analysis of *Dusp10* promoter methylation in control or *Tet2*$^{-/-}$ BMDMs that were pretreated with 5-Azacytidine or DMSO for 1 hour and then incubated with acLDL for 16h. **(D)** IL-1β secretion from control and *Tet2*$^{-/-}$ BMDMs that were pretreated with 5-Azacytidine or DMSO for 1 hour and then incubated with vehicle or acLDL for 16h. Then, BMDMs were primed with LPS for 3h and treated with Nigericin for an additional 1h. ****P<0.0001, ***P<0.001, ** P<0.01, *P<0.05 two-way ANOVA with Sidak's multiple comparison test.

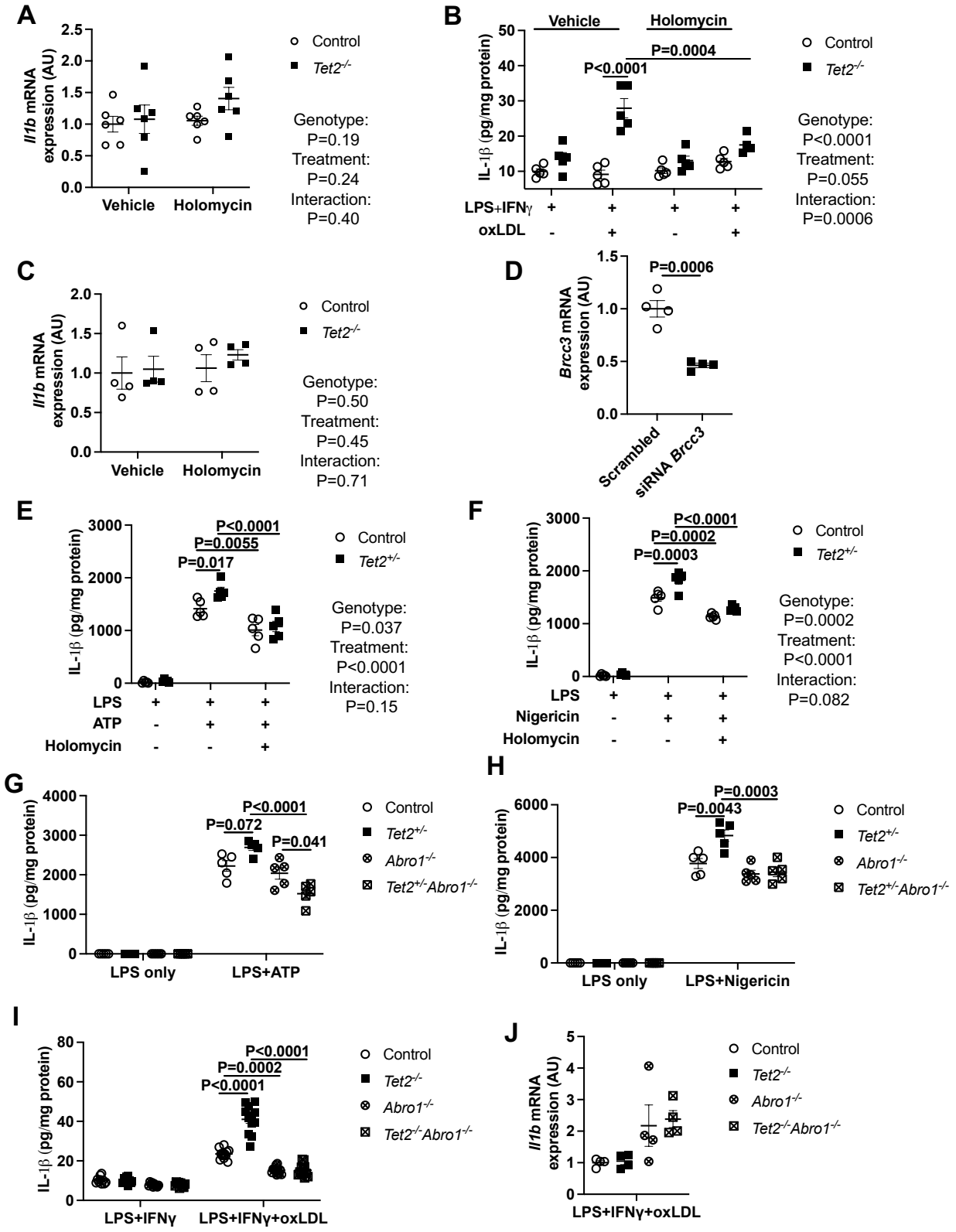

Figure S4. BRCC3-mediated NLRP3 deubiquitylation is essential for inflammasome activation in *Tet2* deficiency. (A) *Il1b* mRNA expression in control and *Tet2*$^{-/-}$ BMDMs primed with LPS for 3h and treated with Holomycin for additional 30 min. **(B-C)** Control and *Tet2*$^{-/-}$

BMDMs were primed with LPS and IFN-γ for 3h and treated with holomycin (HL) for 30 min and treated with oxLDL for additional 16h. **(B)** IL-1β secretion. **(C)** *Il1b* mRNA expression. **(D)** *Brcc3* mRNA expression in BMDMs transfected with control (Scrambled) or siRNA against *Brcc3* for 48h. **(E-F)** IL-1β secretion from control and *Tet2*$^{+/-}$ BMDMs that were primed with LPS for 3h and treated with Holomycin for 30 min and treated with ATP **(E)** or Nigericin **(F)** for an additional 1h. **(G-H)** IL-1β secretion from control, *Tet2*$^{+/-}$, *Abro1*$^{-/-}$ and *Tet2*$^{+/-}$*Abro1*$^{-/-}$ BMDMs that were primed with LPS for 3h and treated with ATP **(G)** or Nigericin **(H)** for an additional 1h. **(I-J)** Control, *Tet2*$^{-/-}$, *Abro1*$^{-/-}$ and *Tet2*$^{-/-}$*Abro1*$^{-/-}$ BMDMs that were primed with LPS and IFN-γ for 3h and treated with oxLDL for additional 16h. **(I)** IL-1β secretion. **(J)** *Il1b* mRNA expression. ****P<0.0001, ***P<0.001, ** P<0.01, *P<0.05 by *t*-test **(D)**, one-way ANOVA coupled with Tukey's comparison test **(G-J)** and two-way ANOVA with Sidak's multiple comparison test **(A-C, E-F)**.

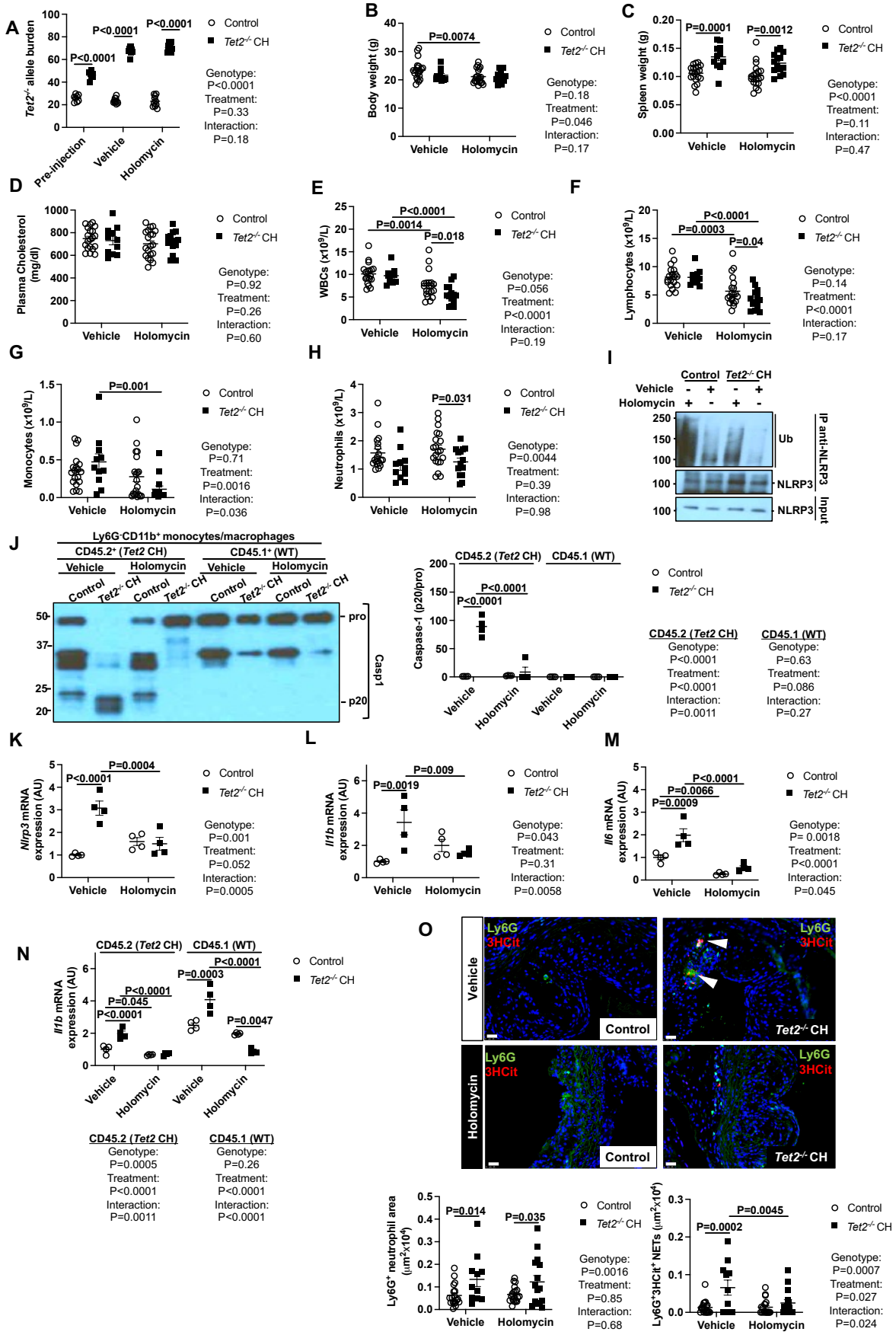
A
Tet2-/- allele burden
P<0.0001
P<0.0001
P<0.0001
Pre-injection
Vehicle
Holomycin
Control
Tet2-/- CH
Genotype: P<0.0001
Treatment: P=0.33
Interaction: P=0.18
B
Body weight (g)
P=0.0074
Vehicle
Holomycin
Genotype: P=0.18
Treatment: P=0.046
Interaction: P=0.17
C
Spleen weight (g)
P=0.0001
P=0.0012
Genotype: P<0.0001
Treatment: P=0.11
Interaction: P=0.47
D
Plasma Cholesterol (mg/dl)
Genotype: P=0.92
Treatment: P=0.26
Interaction: P=0.60
E
WBCs (x10^9/L)
P<0.0001
P=0.0014
P=0.018
Genotype: P=0.056
Treatment: P<0.0001
Interaction: P=0.19
F
Lymphocytes (x10^9/L)
P<0.0001
P=0.0003
P=0.04
Genotype: P=0.14
Treatment: P<0.0001
Interaction: P=0.17
G
Monocytes (x10^9/L)
P=0.001
Genotype: P=0.71
Treatment: P=0.0016
Interaction: P=0.036
H
Neutrophils (x10^9/L)
P=0.031
Genotype: P=0.0044
Treatment: P=0.39
Interaction: P=0.98
I
Control
Tet2-/- CH
Vehicle
Holomycin
Ub
NLRP3
NLRP3
IP anti-NLRP3
Input
J
Ly6G-CD11b+ monocytes/macrophages
CD45.2+ (Tet2 CH)
CD45.1+ (WT)
pro
p20
Casp1
Caspase-1 (p20/pro)
P<0.0001
P<0.0001
CD45.2 (Tet2 CH)
Genotype: P<0.0001
Treatment: P<0.0001
Interaction: P=0.0011
CD45.1 (WT)
Genotype: P=0.63
Treatment: P=0.086
Interaction: P=0.27
K
Nlrp3 mRNA expression (AU)
P=0.0004
P<0.0001
Genotype: P=0.001
Treatment: P=0.052
Interaction: P=0.0005
L
Il1b mRNA expression (AU)
P=0.009
P=0.0019
Genotype: P=0.043
Treatment: P=0.31
Interaction: P=0.0058
M
Il6 mRNA expression (AU)
P<0.0001
P=0.0066
P=0.0009
Genotype: P= 0.0018
Treatment: P<0.0001
Interaction: P=0.045
N
Il1b mRNA expression (AU)
CD45.2 (Tet2 CH)
CD45.1 (WT)
P<0.0001
P=0.0003
P<0.0001
P=0.045
P<0.0001
P=0.0047
CD45.2 (Tet2 CH)
Genotype: P=0.0005
Treatment: P<0.0001
Interaction: P=0.0011
CD45.1 (WT)
Genotype: P=0.26
Treatment: P<0.0001
Interaction: P<0.0001
O
Vehicle
Holomycin
Ly6G
3HCit
Control
Tet2-/- CH
Ly6G+ neutrophil area (μm2x10^4)
P=0.014
P=0.035
Genotype: P=0.0016
Treatment: P=0.85
Interaction: P=0.68
Ly6G+3HCit+ NETs (μm2x10^4)
P=0.0045
P=0.0002
Genotype: P=0.0007
Treatment: P=0.027
Interaction: P=0.024

Figure S5. Inhibition of NLRP3 deubiquitylation decreases NETosis and atherosclerosis in *Tet2* CH mice. *Ldlr*$^{-/-}$ mice were transplanted with bone marrow mixture of WT or 10%*Tet2*$^{-/-}$ /90%WT and fed WTD for 2 weeks. After feeding the WTD for 2 weeks, mice were injected intraperitoneally with Holomycin (1mg/kg) or vehicle control for 6 weeks. Mice then were sacrificed after a total of 8 weeks of WTD. **(A)** *Tet2*$^{-/-}$ allele burden based on flow cytometry analysis of blood CD45.2^{+} white blood cells (% of CD45^{+} cells). **(B)** Body weight **(C)** Spleen weight. **(D)** Plasma total cholesterol analysis. **(E-H)** Blood cell counts. **(E)** White blood cell counts **(F)** Lymphocyte counts. **(G)** Monocyte counts. **(H)** Neutrophil counts. **(I)** Immunoblot of NLRP3 deubiquitylation in cell lysates immunoprecipitated with anti-NLRP3 in Ly6G^{-}CD11b^{+} monocytes/macrophages. **(J)** Immunoblot of intracellular Caspase-1 cleavage in Ly6G^{-}CD11b^{+}CD45.1^{+} (WT) or Ly6G^{-}CD11b^{+}CD45.2^{+} (*Tet2* CH) monocytes/macrophages. **(K)** *Nlrp3* mRNA expression in Ly6G^{-}CD11b^{+} monocytes/macrophages. **(L)** *Il1b* mRNA expression in Ly6G^{-}CD11b^{+} monocytes/macrophages. **(M)** *Il6* mRNA expression in Ly6G^{-}CD11b^{+} monocytes/macrophages. **(N)** *Il1b* mRNA expression in Ly6G^{-}CD11b^{+}CD45.1^{+} (WT) or Ly6G^{-}CD11b^{+}CD45.2^{+} (*Tet2* CH) monocytes/macrophages. **(O)** Neutrophils were stained in atherosclerotic lesions using Ly6G and Ly6G^{+} percentages of lesion size was quantified. Concomitantly, lesions were stained for 3HCit. To assess NETs, the overlap of Ly6G and 3HCit was quantified as percentage of the total lesion area. Representative pictures are shown. Scale bars: 25 μm. ****P<0.0001, ***P<0.001, ** P<0.01, *P<0.05 by t-test two-way ANOVA with Sidak's multiple comparison test.

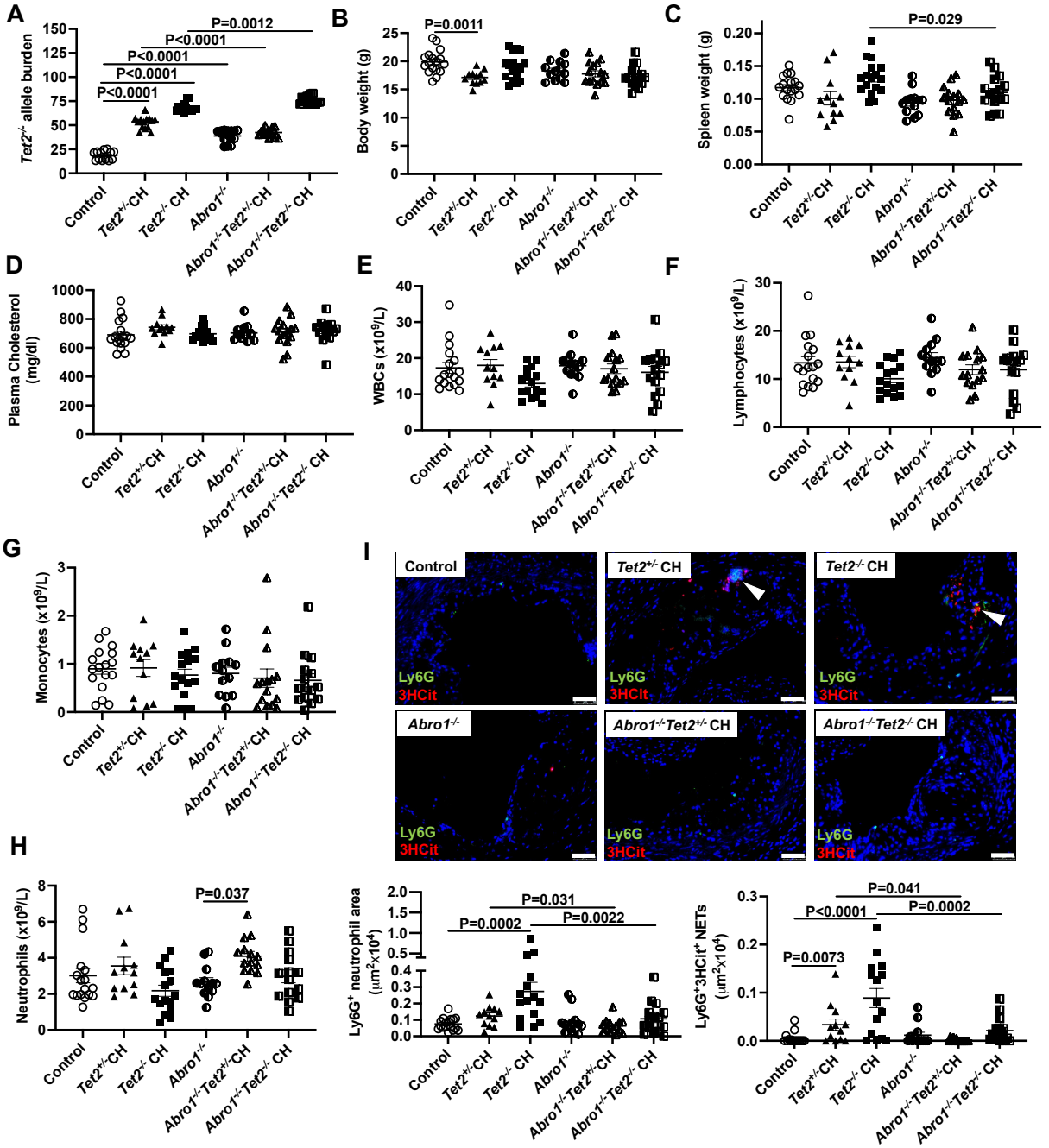

Figure S6. ***Abro1*** **deficiency decreases NETosis and atherosclerosis in** ***Tet2*** **CH mice.** *Ldlr*$^{-/-}$ mice were transplanted with bone marrow mixture WT, 10%*Abro1*$^{-/-}$/90%WT, 10%*Tet2*$^{+/-}$/90%WT, 10%*Tet2*$^{-/-}$/90%WT, 10%*Tet2*$^{+/-}$*Abro1*$^{-/-}$/90% WT or 10%*Tet2*$^{-/-}$*Abro1*$^{-/-}$/90% WT. After 5 weeks of recovery time, they were fed with WTD and then were sacrificed after a total of 8 weeks of WTD. **(A)** *Tet2*$^{-/-}$ allele burden based on flow cytometry analysis of blood CD45.2^{+} white blood cells (% of CD45^{+} cells). **(B)** Body weight **(C)** Spleen weight. **(D)** Plasma total cholesterol analysis. **(E-H)** Blood cell counts. **(E)** White blood cell counts. **(F)** Lymphocyte counts. **(G)** Monocyte counts. **(H)** Neutrophil counts. **(I)** Neutrophils were stained in atherosclerotic lesions using Ly6G and Ly6G^{+} percentages of lesion size was quantified. Concomitantly, lesions were stained for 3HCit. To assess NETs, the overlap of Ly6G and 3HCit was quantified as percentage of the total lesion area. Each datapoint represents an individual mouse. Representative pictures are

shown. Scale bars: 50 μm. ****P<0.0001, ***P<0.001, ** P<0.01, *P<0.05 by one-way ANOVA coupled with Tukey's comparison test for 4 groups (Control, *Abro1*$^{-/-}$, *Tet2*$^{+/-}$, *Tet2*$^{+/-}$*Abro1*$^{-/-}$) or (Control, *Abro1*$^{-/-}$, *Tet2*$^{-/-}$ and *Tet2*$^{-/-}$*Abro1*$^{-/-}$).