## Online Methods

### Mice

C57Bl/6J Tet2-deficient mice ($Tet2^{-/-}$ and $^{+/-}$) (1), C57Bl/6J LysM-Cre mice, C57Bl/6J Tet2 floxed mice (2) and C57Bl/6 Cd45.1 Pep Boy mice were obtained from Jackson Laboratories. Mice with myeloid-restricted Tet2 ablation were generated by crossing Tet2-floxed mice (Tet2 flox/flox) with LysM-Cre mice. Male mice were used for the *in vivo* experiments unless otherwise noted. Mice were maintained on a 12-h light/dark schedule in a specific pathogen-free animal facility and given food and water *ad libitum*. The number of mice included in each study is indicated in the figures or the associated legends. The Institutional Animal Care and Use Committee (IACUC) of Boston University approved all study procedures.

### Cell Culture

Bone marrow-derived macrophages (BMDM) were isolated and cultured in alpha-MEM supplemented with 10% FBS and penicillin/streptomycin/L-glutamine (Complete Media). Bone marrow was flushed from the tibia and femurs of female Tet2 KO (n=3) and littermate controls (n=4) at 10 weeks of age. Following lysis of red blood cells (BioLegend), cells were washed and cultured overnight in Complete Media in the presence of M-CSF (100 ng/mL). Differential plating was used to purify monocytes, that were identified as those cells unattached to tissue culture plastic following 16hrs of culture. Macrophage proliferation and differentiation was induced by 2 days of culture in Complete Media in the presence of M-CSF. Cells were differentiated for the indicated periods of time and were detached by trypsin and scraping. RNA was isolated from pelleted cells using Qiazol and the miRNeasy Micro Kit (Qiagen) according to the manufacturer's instructions. Equal amounts of RNA were transcribed using a High Capacity

Reverse transcription kit (Applied Biosystems) according to the manufacturer's instructions. SYBR-based detection was used to detect transcripts via qPCR through analysis on a ViiA7 (Applied Biosystems). Fold changes were calculated using the ΔΔCT method and normalized to *36b4*.

### *In vivo* inhibition of the NLRP3 inflammasome

MCC950, a small molecule inhibitor of the NLRP3 inflammasome, was synthesized as previously described (22) or purchased from Selleckchem.com (Online Figure 5). It was diluted in PBS and delivered *in vivo* at a dose of 5 mg/kg/day via subcutaneous mini-osmotic pumps (Alzet 2004), starting 1 weeks after LAD ligation or TAC surgeries. Control mice were infused with PBS. The period of infusion is indicated in the figures or associated legends.

### Competitive bone marrow transplantation

6-8 week old lethally irradiated C57Bl/6 Cd45.1 Pep Boy recipients were transplanted with suspensions of BM cells containing 10% $Cd45.2^{+}$ $Tet2^{-/-}$ cells and 90% $Cd45.1^{+}$ $Tet2^{+/+}$ cells (10% KO-BMT mice), or 10 % $Cd45.2^{+}$ $Tet2^{+/+}$ cells and 90% $Cd45.1^{+}$ $Tet2^{+/+}$ cells (10% WT-BMT mice). BM cells were isolated from femurs and tibias of donor 6-8 week old mice after euthanasia. Donor $Cd45.2^{+}$ cells were obtained from $Tet2^{+/+}$ or $^{-/-}$ littermates; donor $Cd45.1^{+}$ cells were obtained from Pep Boy mice. Recipient mice were irradiated in a pie cage (Braintree Scientific) to limit mobility and ensure an equal dose of irradiation, and were exposed to two radiation doses of 450 rad four hours apart using an X-RAD 320 Biological Irradiator. After the second irradiation, each recipient mouse was injected with $5x10^{6}$ BM cells via the retro-orbital vein plexus. Sterilized caging, food and water were provided during the first 14 days post-

transplantation, and water was supplemented with antibiotics (Sulfatrim). 8 weeks after BMT, mice underwent cardiac surgery.

**Hematopoietic parameter measurements**

Peripheral blood cells were obtained from retro-orbital vein and collected in EDTA-coated tubes (BD). Hematopoietic parameters were analyzed by Hemavet 950FS (Drew Scientific).

**Flow cytometry analyses of blood and tissue samples**

Peripheral blood:

Antibodies: The following antibodies were used for flow cytometric analyses: anti-CD45.2-eFluor,104 (eBioscience), anti-CD45.1-PE-Cy7, A20 (eBioscience), anti-CD115-PE, AFS98 (eBioscience) anti-CD4-FITC, RM4-5 (eBioscience), anti-CD3e-PE-eFluor610, 145-2C11 (eBioscience), anti-CD8a-BV510, 53-6.7 (BioLegend), anti-Ly6C-APC, AL-21 (BD Pharmingen$^{TM}$), anti-CD45R-APC-Cy7, RA-6B2 (BD Pharmingen$^{TM}$), anti-Ly6G-PerCP-Cy5.5, 1A8 (BD Pharmingen$^{TM}$), anti-CD43-BUV737, S7 (BD Horizon$^{TM}$). Staining strategies: Peripheral blood cells were obtained from retro-orbital vein. Red blood cells were lysed with 1X RBC Lysis Buffer (eBioscience$^{TM}$) for 5 minutes on ice followed by the 10 minutes incubation with Fc blocker (1:50) on ice. Incubation with antibodies were done for 20 minutes at room temperature in the dark. Dead cells were excluded from analysis by DAPI staining.

Cardiac immune cells:

Antibodies: For myeloid cell staining, cell suspensions were labeled with anti-CD45-Pacific Blue, 30-F11 (BioLegend), anti-CD11b-APC-Cy7, M1/70 (BioLegend), anti-Ly6G-PE, 1A8

(BioLegend), anti-Ly6C-FITC, HK1.4 (BioLegend), and anti-F4/80-PE-Cy7, BM (BioLegend). For lymphoid cell staining, cells were labeled with anti-CD45-Pcific Blue, 30-F11 (BioLegend), anti-CD3e-PE-eFluor610, 145-2C11 (eBioscience), anti-CD4-FITC, RM4-5 (eBioscience), anti-CD8a-BV510, 53-6.7 (BioLegend), anti-CD11b-AF700, M1/70 (BioLegend), anti-CD45R/B220-PE-Cy7, RA3-6B2 (BioLegend), anti-CD19-APC-Cy7, 6D5 (BioLegend).

Staining strategies: Heart was extensively flushed with PBS to avoid blood contamination and then excised. Remote myocardium was separated from infarct and marginal zone as indicated in Online Figure 2a, minced with scissors and digested in collagenase I (450 U/ml), collagenase XI (125 U/ml), DNase I (60 U/ml), and hyaluronidase (450 U/ml) (catalog #C0130, C7657, D4513, and H3506, respectively, Sigma-Aldrich) at 225 rpm at 37℃ for 50 minutes (3). TAC-induced hypertrophied myocardium was digested in the same method. Hearts were subsequently homogenized through a 70-μm nylon mesh (Fisher Scientific). Incubation with antibodies were done for 20 minutes at room temperature in the dark. Dead cells were excluded from analysis by DAPI staining. 123count eBeads™ Counting Beads (BD Bioscience) was used for data acquisition.

Bone marrow cells: Antibodies and strategies: Bone marrow cells were flushed out from bones (femur and tibia). Red blood cells were lysed with 1X RBC Lysis Buffer (eBioscience™) for 5 minutes on ice . For hematopoietic stem/progenitor cell staining, cells were labeled with biotin-conjugated anti-mouse antibodies directed against CD11b, M1/70 (BioLegend), Gr-1, RB6-8C5 (BioLegend), Ter-119, TER-119 (BioLegend), CD45R/B220, RA3-6B2 (BioLegend), CD3e, 145-2C11 (BioLegend), and CD127, A7R34 (BioLegend) followed by a labeling with an anti-

biotin PE-conjugated streptavidin antibody (BioLegend), anti-c-kit-APC, 2B8 (BioLegend), anti-Sca-1-PE-Cy7, D7 (BioLegend), anti-CD16/32-APC-Cy7, 93 (BioLegend), anti-CD34-FITC, RAM34 (eBioscience), and anti-CD115-BV421, AFS98 (BioLegend). For neutrophil and monocyte staining, anti-CD11b-APC-Cy7, M1/70 (BioLegend), anti-CD115-APC, AFS98 (BioLegend), anti-Ly6G-PE, 1A8 (BioLegend), anti-I-A/I-E (MHC-class II)-AF700, M5/114.15.2 (BioLegend) were used. Dead cells were excluded from analysis by DAPI staining.

BD LSR II Flow Cytometer (BD Bioscience) was used for data acquisition. Cells were defined as described in Online Figure 1 (peripheral blood cells), Online Figure 2 (cardiac immune cells), and Online Figure 3 (bone marrow hematopoietic stem/ progenitor cells). Data were analyzed with FlowJo Software.

**Experimental LAD ligation**

Mice initially underwent partial (10%) bone marrow reconstitution with Tet2-deficient cells or wild type cells following lethal irradiation, followed by permanent LAD ligation after 8 weeks of recovery. For myeloid-restricted Tet2 ablation, LAD ligation was performed when mice were 8-12 weeks old. Surgery was performed as previously described (4) with some modifications. Briefly, following anesthetization (isoflurane inhalation) and tracheal intubation, the chest cavity was open from the 4$^{th}$ intercostal space. Left ascending coronary artery was ligated tightly with a tapered 8-0 vicryl suture (J401G, Ethicon) under microscopy. Myocardial ischemia was confirmed by ST-T segment elevation in electrocardiogram and color changes in the segment of left ventricle subjected to coronary flow occlusion. To close the wound, braided 6-0 vicryl suture (J212H, Ethicon) was used. Post-surgery, mice were monitored every day for 3 days, and treated

with an intraperitoneal injection of buprenorphine (0.1mg/kg) twice a day. Mice that died within 12 hours of surgery were excluded from analysis, and perioperative survival rate in this study was more than 95%. Surgery to each groups of mice was performed by an individual who was blinded to the identity of the mouse genotype.

**Transverse aortic constriction (TAC)**

Surgery was performed as previously described (5). Briefly, mice were anaesthetized with isoflurane inhalation. After the chest cavity was exposed by cutting open the proximal portion of the sternum, aortic constriction was produced by ligation of the transverse thoracic aorta between the innominate artery and left common carotid artery using a 27-gauge blunt needle and 7-0 silk suture. All mice were treated twice daily with buprenorphine (0.1 mg/kg) for 2 days, starting on the day of the surgery. Sham-operated mice without constriction served as controls. Surgery to each groups of mice was performed by an individual who was blinded to the identity of the mouse genotype.

**Echocardiography**

Cardiac function was assessed several times before and after the surgery (MI and TAC), at indicated in time points, using Vevo2100 ultrasound system equipped with MS550D probe (VisualSonics, Fujifilm). Mice were anesthetized with isoflurane at a concentration of 5% (induction) and 1-1.5% (maintenance). Each animal was placed on the heating table in a supine position with the extremities tied to the table through four electrocardiography leads. The chest was shaved using chemical hair remover, and ultrasound gel was applied to the thorax surface to optimize the visibility of the cardiac chambers. For MI study, left ventricular ejection fraction

(LVEF), LV systolic and diastolic volume were measured from long-axis view by tracing end-diastolic and end-systolic endocardium. For TAC study, LV posterior wall thickness diameter (LVPWTd) and fractional shortening (FS, %) were measured from M-mode images obtained by short-axis view visualizing both papillary muscles. Measurements were performed by an individual who was blinded to the identity of the experimental groups of mice.

**Measurement of the initial infarct size**

Mice were sacrificed 2 days after LAD ligation. Hearts were perfused with 20 ml of PBS from the apex of the heart as well as right ventricle to remove the peripheral blood. The hearts were excised and frozen in -20℃ domestic freezer for 2 hours, followed by sectioning into 2 mm slices from the ligation site. Hearts were incubated with 1% 2, 3, 5-triphenyltetrazolium chloride (TTC) in PBS for 15 minutes at 37℃. The size of infarct area was determined by computerized planimetry using Image J software.

**Histology**

The heart tissues were obtained at indicated time course after LAD ligation or TAC surgery. Heart tissues were perfused with cold PBS from apex and fixed in 10% formalin overnight and embedded in paraffin. About 7-μm-thick sections were de-paraffinized and rehydrated. Mason's trichrome staining was performed according to the manufacturer's instructions (Sigma-Aldrich). For Picrosirius red staining, sections were incubated with freshly prepared staining buffer (1.2%/w picric acid in water, 0.1%/w Fast Green FCF and 0.1%/w Direct Red 80 solved in PBS) for 1 h at room temperature (all products from Sigma-Aldrich). Sections were washed briefly in $dH_2O$ and dehydrated. The slides were mounted by coverslip using Permount mounting

medium (Fisher Scientific). The images were analyzed by ImageJ software (NIH) for quantification of fibrosis. Myocardial fibrosis size was expressed as a percentage of total LV area.

To measure cardiomyocyte cross-sectional area (CSA), heart sections were stained using Alexa Fluor 488 conjugated-WGA (Life Technologies). An operator who was blinded to genotype quantified cardiomyocyte CSA by computer-assisted morphometric analysis of microscopy images acquired on a Keyence BZ-9000 microscope. The average CSA of randomly selected 50-80 round-shaped cardiomyocytes per each sample was used for analysis.

Cell Proliferation was assessed by double immunofluorescent staining with monoclonal antibodies against the proliferating cell antigen Ki-67 (rabbit IgG, clone SP6, Vector Laboratories, 1:100 dilution) and the macrophage maker Mac3 (rat IgG, clone M3/84, Santa Cruz Biotechnology, 1:400 dilution). After deparaffinization, antigen unmasking with citric acid buffer was performed. Avidin/biotin blocking was performed by using avidin/biotin blocking kit following manufacturer's protocol (Vector Laboratories). Sections were blocked with 2.5% goat serum for 1h and then incubated with primary antibodies at 4℃ overnight. Ki-67 was visualized with biotinylated anti-rabbit IgG following fluorescein labelled streptavidin (Vector Laboratories) and Mac3 with Alexa Flour 594-conjugated anti-rat IgG (Life Technologies). DAPI was used to detect nuclei.

For IL-1β staining, deparaffinization, antigen unmasking with citric acid buffer was performed, followed by blocking with 2.5% goat serum for 1h. Sections were incubated with primary

antibody specific for IL-1β (polyclonal rabbit IgG, Bioss, 1:100 dilution), and Mac3 (rat IgG, clone M3/84, Santa Cruz Biotechnology, 1:400 dilution) for overnight at 4℃. IL-1β was visualized with biotinylated anti-rabbit IgG following fluorescein labelled streptavidin (Vector Laboratories) and Mac3 with Alexa Flour 594-conjugated anti-rat IgG (Life Technologies). Nuclei were stained with DAPI and slides were incubated with Sudan Black B (Sigma-Aldrich) to reduce autofluorescence.

Fluorescent images were taken by confocal microscope LSM710 (Zeiss) or a BZ-9000 Keyence microscope. Fluorescent signal was quantified as relative integrated fluorescence intensity by using ImageJ software (NIH).

**Gene expression analysis by qRT-PCR.**

Total RNA from tissues and cultured cells was isolated using QIAzol reagent and RNeasy kits (Qiagen). RNA (0.5-1.2 μg) was reverse transcribed with QuantiTect Reverse Transcription Kit (Qiagen). qRT-PCR was performed with Power SYBR® Green reagent (ThermoFisher Scientific) in a ViiA7 PCR system. Primers for mouse gene expression studies are shown in the Online Table. Results were analyzed with the ΔΔCt method. *36b4* or *18S rRNA* were used as reference genes for normalization.

**References**

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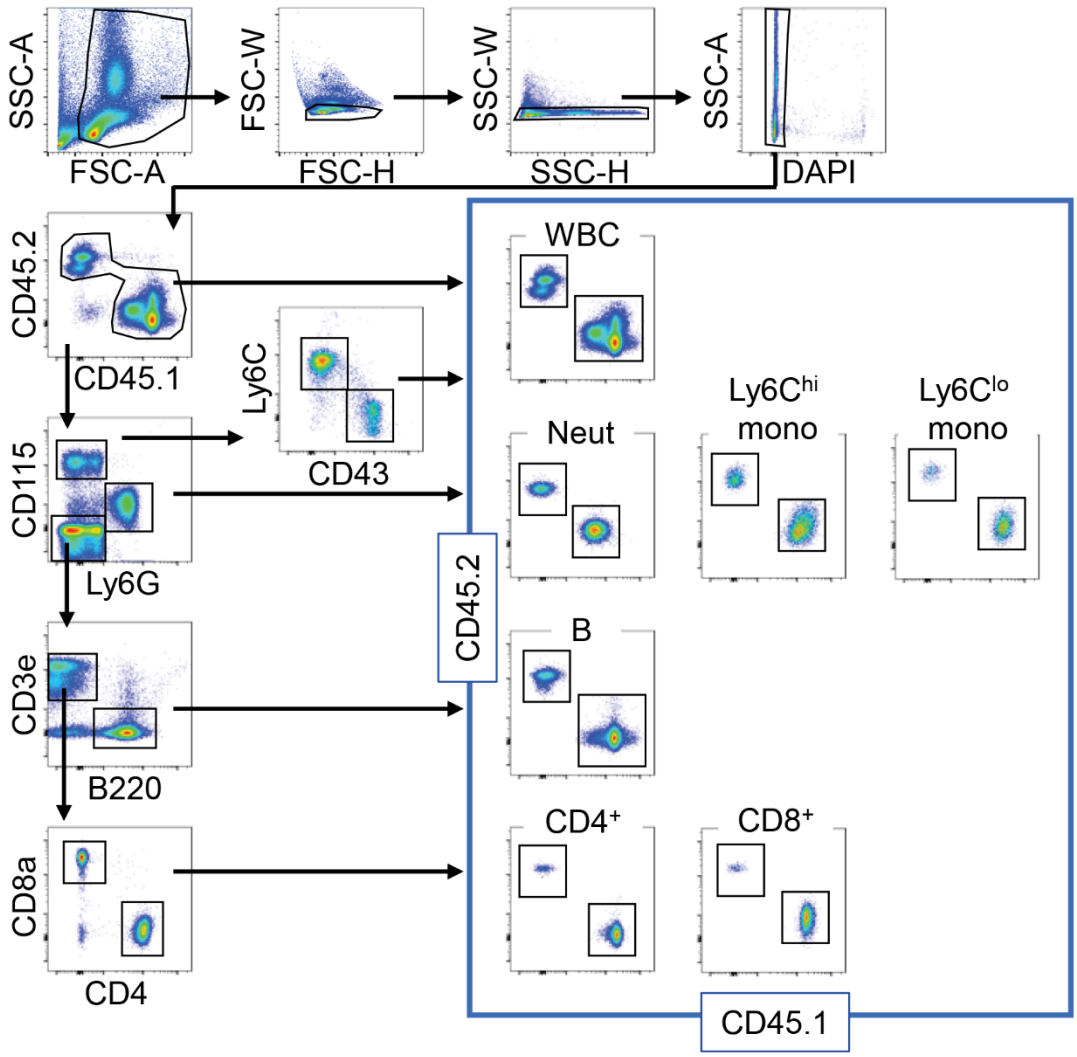
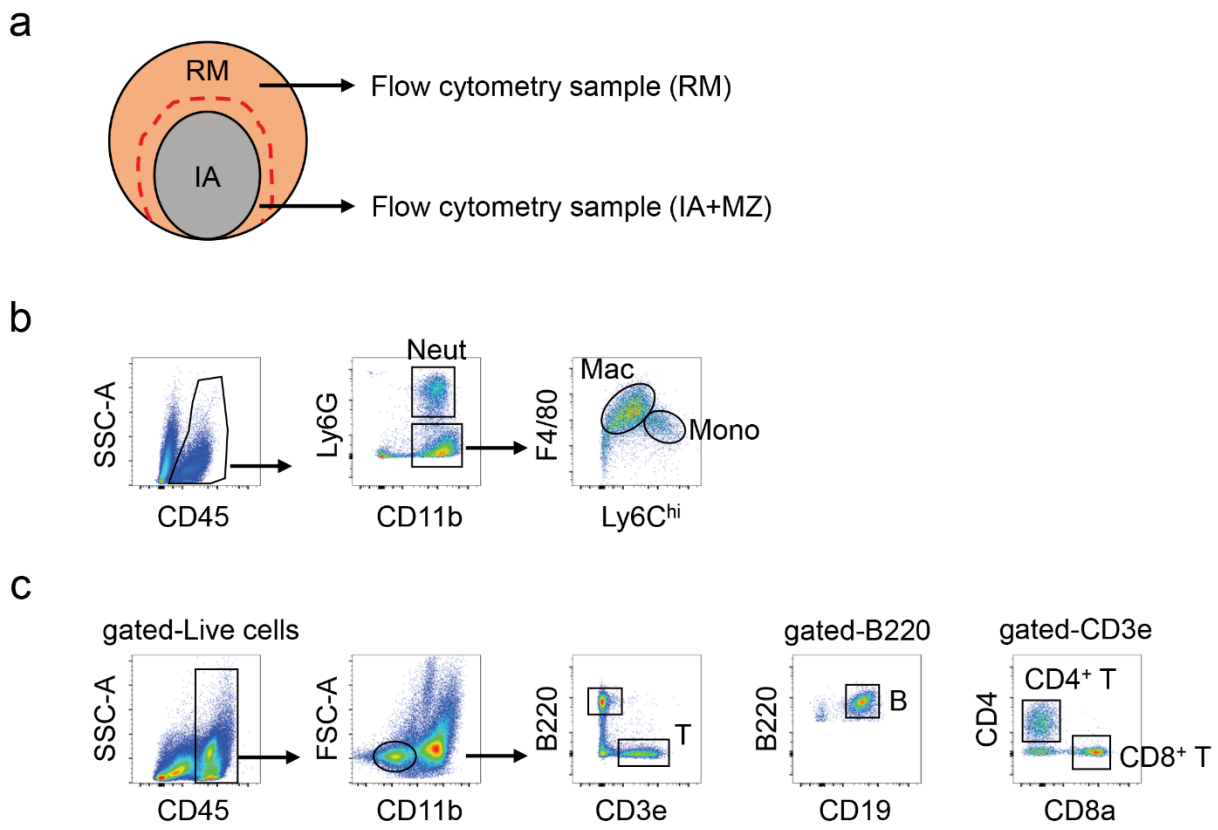
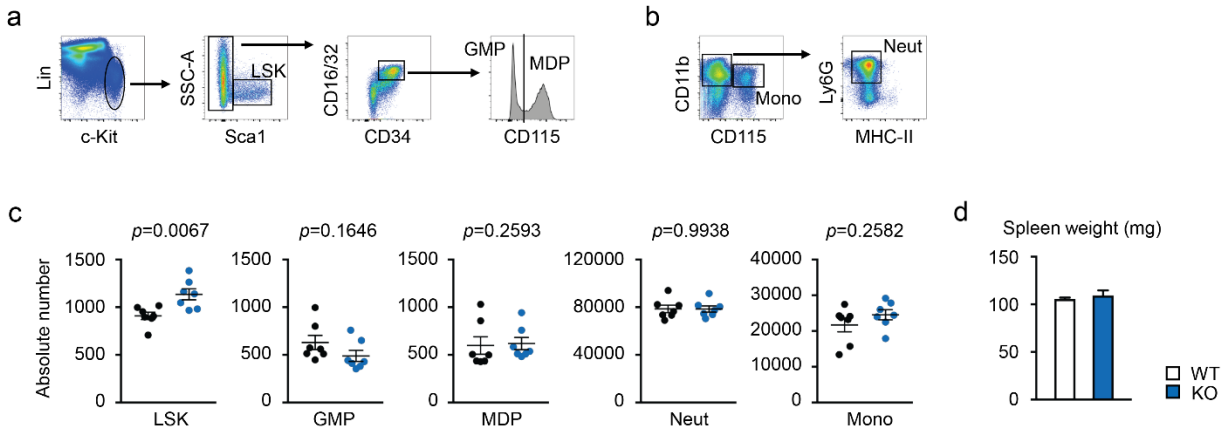
3. Anzai A, Choi JL, He S et al. The infarcted myocardium solicits GM-CSF for the detrimental oversupply of inflammatory leukocytes. J Exp Med 2017;214:3293-3310.
4. Maruyama S, Nakamura K, Papanicolaou KN et al. Follistatin-like 1 promotes cardiac fibroblast activation and protects the heart from rupture. EMBO Mol Med 2016;8:949-66.
5. Shibata R, Ouchi N, Ito M et al. Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat Med 2004;10:1384-9.



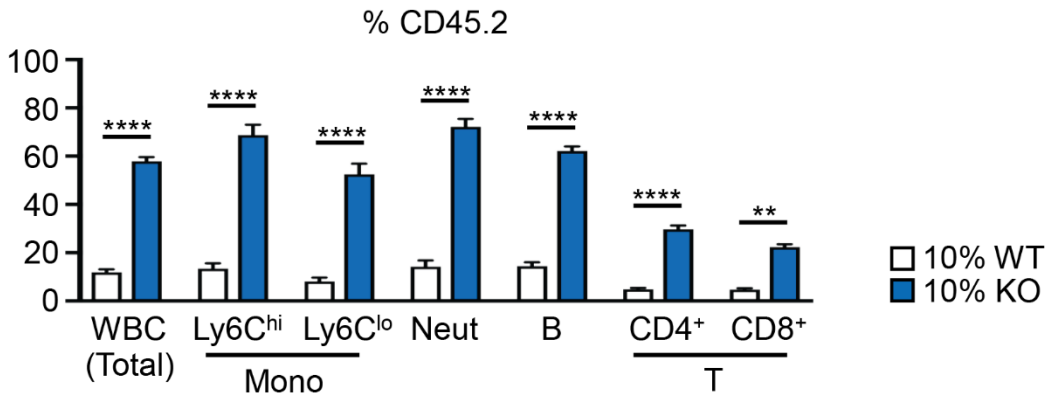

**Online Figure 1. Flow cytometry gating strategy of peripheral blood after competitive BMT.** Cells were defined as: (i) total white blood cells ($CD45^+$), (ii) $Ly6C^{hi}$ monocytes ($CD115^{high}$, $Ly6G^-$, $CD43^{low}$, $Ly6C^{high}$), (iii) $Ly6C^{lo}$ monocytes ($CD115^{high}$, $Ly6G^-$, $CD43^{high}$, $Ly6C^{low}$), (iv) neutrophils ($CD115^{low}$, $Ly6G^+$), (v) B cells ($CD3e^-$, $B220^+$), (vi) T cells ($CD3e^+$, $B220^-$, $CD4/8^+$). CD45.1 and CD45.2 were used to determine the chimerism in each population. BMT: bone marrow transfer. WBC: white blood cells, Neut: neutrophils, Mono: monocytes, B: B cells, T: T cells.



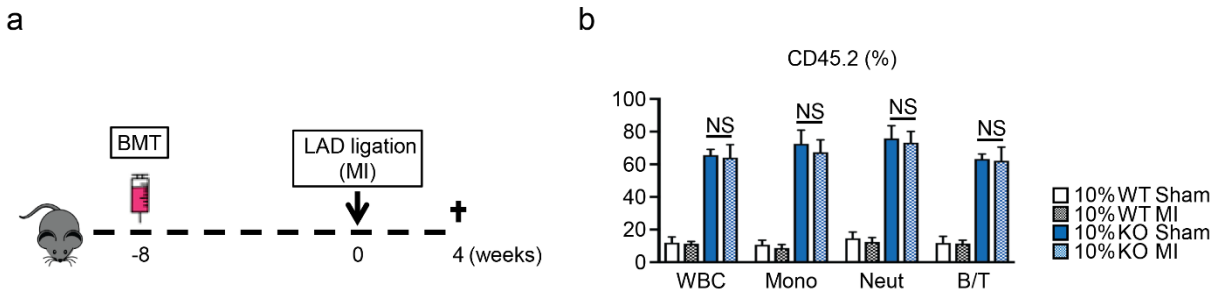

**Online Figure 2. Flow cytometry gating strategy of cardiac tissues. a.** scheme of the sampling of heart tissue after LAD ligation. Hearts were divided into remote area and infarct area with marginal zone. **b.** Myeloid panel of infarct area (6 days after MI). **c.** Lymphoid panel of infarct area (14 days after MI). Cells were defined as: (i) total white blood cells ($CD45^+$), (ii) neutrophils ($CD11b^+$, $Ly6G^+$), (iii) $Ly6C^{hi}$ monocytes ($CD11b^+$, $Ly6G^-$, $Ly6C^{hi}$, $F4/80^{lo}$), (iv) macrophages ($CD11b^+$, $Ly6G^-$, $Ly6C^{lo}$, $F4/80^{hi}$), (v) B cells ($CD11b^-$, $CD3e^-$, $B220^+$, $CD19^+$), (vi) T cells ($CD11b^-$, $CD3e^+$, $B220^-$, $CD4/8^+$). RM: remote area, IA infarct area, MZ: marginal zone, MI: myocardial infarction, Neut: neutrophils, Mac: macrophages, Mono: monocytes, B: B cells, T: T cells.



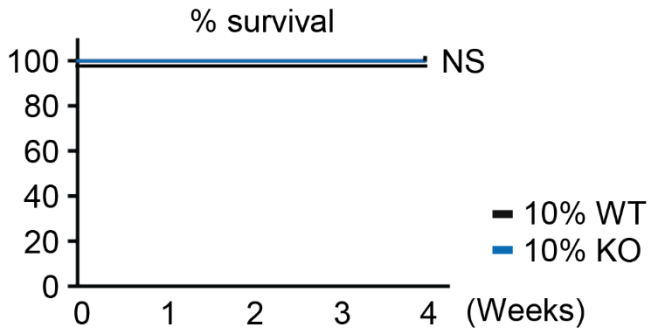

**Online Figure 3. Increased LSK cells in the bone marrow of donor 6-8 week old Tet2-deficient mice. a.** Flow cytometry gating strategy of bone marrow hematopoietic stem/ progenitor cells. **b.** Flow cytometry gating strategy of bone marrow myeloid cells. Cells were defined as: (i) LSK cells ($Lin^-$, $c\text{-}Kit^+$, $Sca1^+$), (ii) GMP ($Lin^-$, $c\text{-}Kit^+$, $Sca1^-$, $CD34^+$, $CD16/32^{hi}$, $CD115^-$), (iii) GMP ($Lin^-$, $c\text{-}Kit^+$, $Sca1^-$, $CD34^+$, $CD16/32^{hi}$, $CD115^+$), (iv) monocytes ($CD11b^+$, $CD115^+$), (v) neutrophils ($CD11b^+$, $CD115^-$, $Ly6G^+$, $MHC\text{-}II^-$). **c.** The number of each populations in $2.5x10^6$ bone marrow cells from Tet2-deficient mice (n=7) and wild type mice (n=7). All mice are 6-8 weeks old. Statistical significance of difference was evaluated by two-tailed unpaired Student's *t* tests or by Mann Whitney U tests for data which failed to pass the Shapiro-Wilk normality test. **d.** The weight of the spleen from Tet2-deficient mice (n=5) and wild type mice (n=5) to show there is no significant difference between both genotypes at this age. Statistical analysis was evaluated by two-tailed unpaired Student's *t* test with Welch's correction. GMP: granulocyte-macrophage progenitors, MDP: monocyte-dendritic cell progenitors, Neut: neutrophils, Mono: monocytes.




**Online Figure 4. Tet2-deficient hematopoietic stem cells display a greater repopulating ability in *vivo*. a.** Tet2-KO bone marrow cells ($Cd45.2^+$) display a competitive advantage over wild type competitor cells ($Cd45.1^+$) in their ability to expand into multiple blood cell lineages *in vivo*. Peripheral blood was obtained 8 weeks after BMT from 10% WT-BMT (n=11) mice and 10% KO-BMT mice (n=10). Statistical analysis was evaluated by multiple *t* tests. **p<0.01, ****p<0.0001. WBC: white blood cells, Mono: monocytes, Neut: neutrophils, B: B cells, T: T cells.

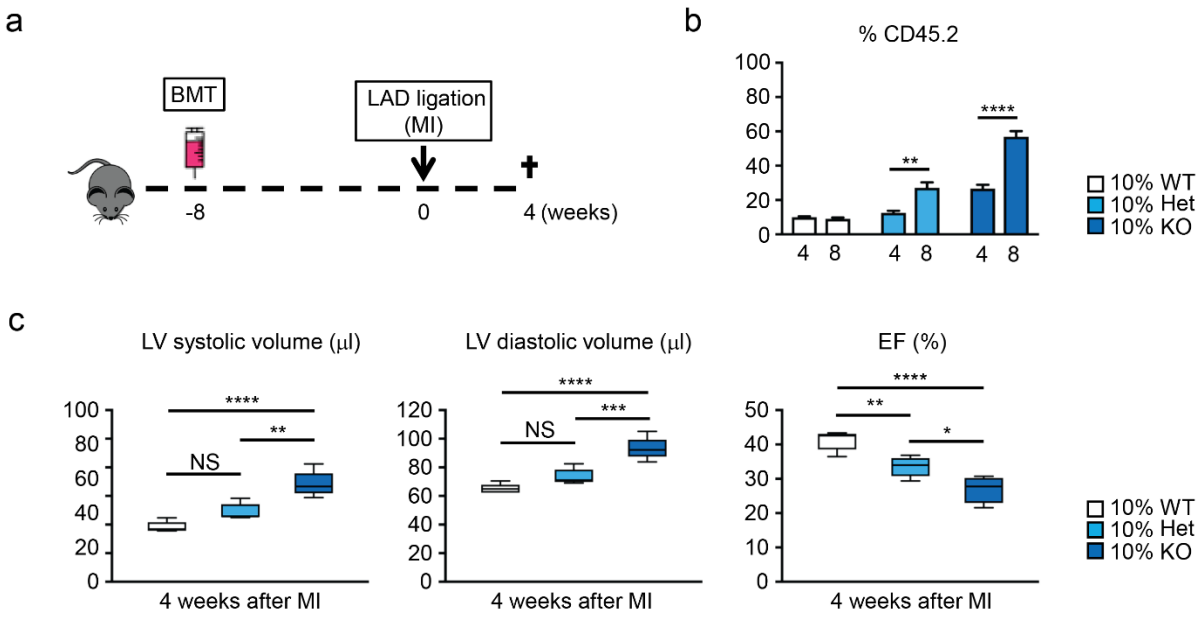



**Online Figure 5. LAD ligation does not affect Tet2-deficient peripheral blood chimerism. a.** Scheme of the experimental study. Mice underwent partial (10%) bone marrow reconstitution with Tet2-deficient cells or WT cells following lethal irradiation. After 8 weeks of recovery, mice underwent permanent LAD ligation (MI). Blood chimerism was analyzed by flow cytometry at 4 weeks after ligation. **b.** The percentage of the $CD45.2^{+}$ cells in different peripheral blood lineages. Sample sizes were n=5 for 10% WT-BMT/sham, n=4 for 10% KO-BMT/sham, n=5 for 10% WT-BMT/MI, n=5 for 10% KO-BMT/MI. Statistical significance was evaluated by two-way ANOVA with Tukey's multiple comparison tests. NS: not significant. HSPC: hematopoietic stem progenitor cells, WT: wild type, KO: knockout, LAD: left anterior ascending artery, MI: myocardial infarction, WBC: white blood cells, Neut: neutrophils, Mono: monocytes, B: B cells, T: T cells.

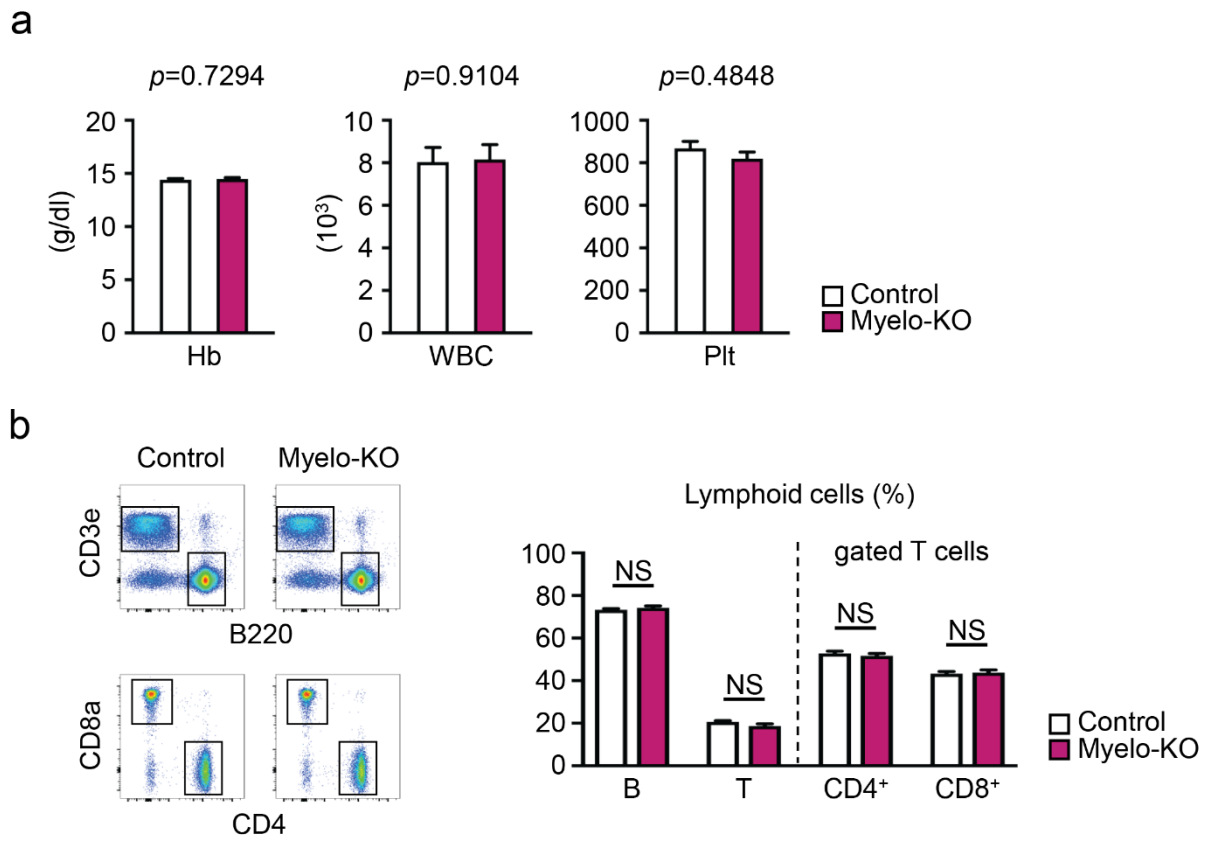



**Online Figure 6. Survival curves of the mice with partial BMT after LAD ligation.**

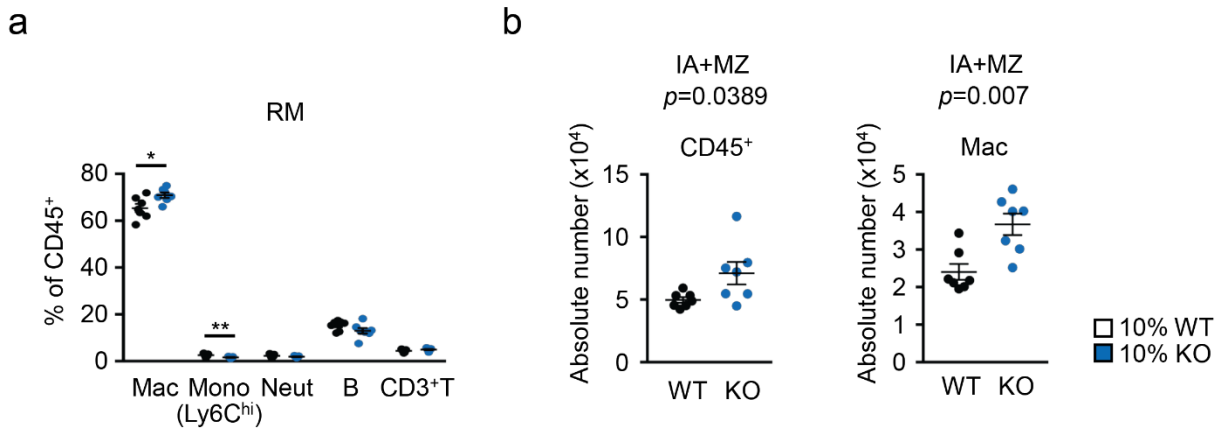
WT: wild type, KO: knockout, NS: not significant. The statistical analysis of Kaplan-Meier Curve was evaluated by log-rank test.



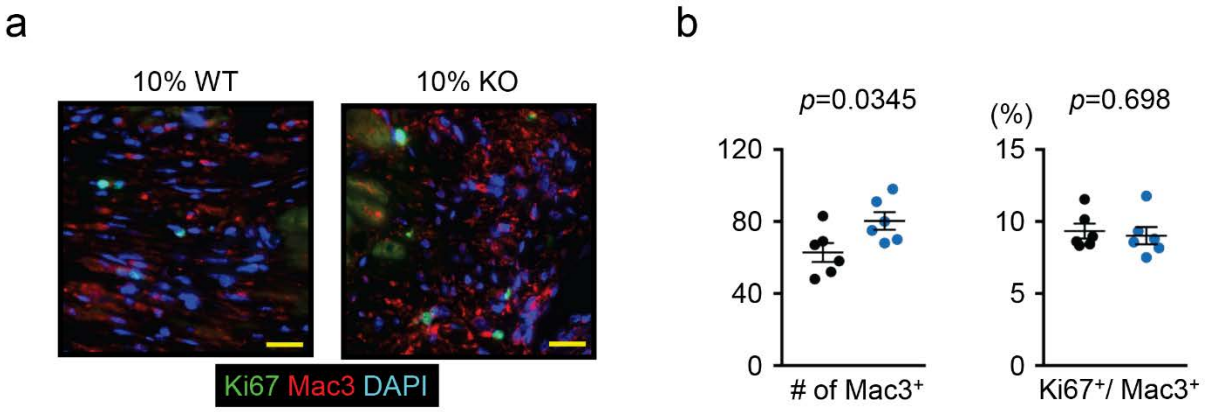

**Online Figure 7. Dose-dependent impact of HSPC Tet2-deficiency on post-MI cardiac remodeling. a.** Scheme of the experimental study. Mice underwent partial (10%) bone marrow reconstitution with Tet2-homozygous null cells or Tet2-heterogyzous cells or WT cells following lethal irradiation. After 8 weeks of recovery, mice underwent permanent LAD ligation (MI). **b.** Tet2-homozygous null cells or Tet2-heterogyzous bone marrow cells ($Cd45.2^+$) display a competitive advantage over wild type competitor cells ($Cd45.1^+$) in their ability to expand into multiple blood cell lineages *in vivo*. Peripheral blood was obtained 4 weeks and 8 weeks after BMT. Sample sizes were 5 per genotype. Statistical analysis was evaluated by two-way repeated measure ANOVA with Sidak's multiple comparison tests. **c.** Echocardiographic evaluation of the mice 4 weeks after BMT. Sample sizes were 5 per genotype. Statistical significance was evaluated by one-way ANOVA with Tukey's multiple comparison tests. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001; NS: not significant. HSPC: hematopoietic stem progenitor cells, WT: wild type, Het: heterozygote, KO: knockout, BMT: bone marrow transfer, LAD: left anterior ascending artery, MI: myocardial infarction, LV: left ventricle, EF: ejection fraction.



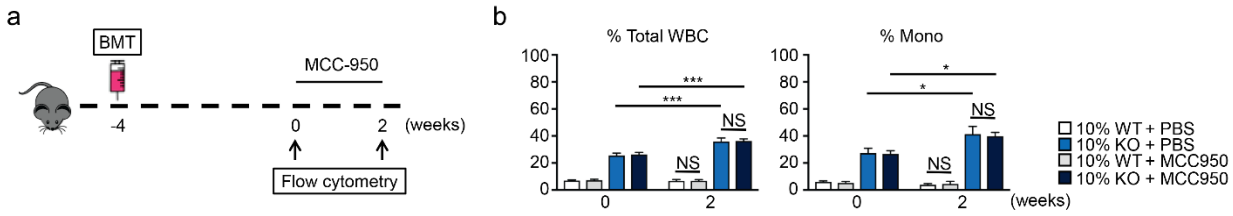

**Online Figure 8. Myeloid-specific Tet2-deficient mice do not show obvious changes in hematological parameters. a.** Absolute numbers of peripheral blood of Hb, WBC, and Plt from Tet2-Myelo-KO mice (n=6) and control mice (n=6) to show there is no significant changes in those hematological parameters. Statistical significance was evaluated by two-tailed unpaired Student's *t* tests or by Mann Whitney U tests for data which failed to pass the Shapiro-Wilk normality test. **b.** Flow cytometry representative data and analysis of peripheral blood from Tet2-Myelo-KO mice (n=6) and control mice (n=6) to show there is no significant changes in lymphoid populations. Statistical significance of difference was evaluated by multiple *t* test. Hb: hemoglobin, WBC: white blood cells, Plt: platelets, B: B cells, T: T cells, NS: not significant.



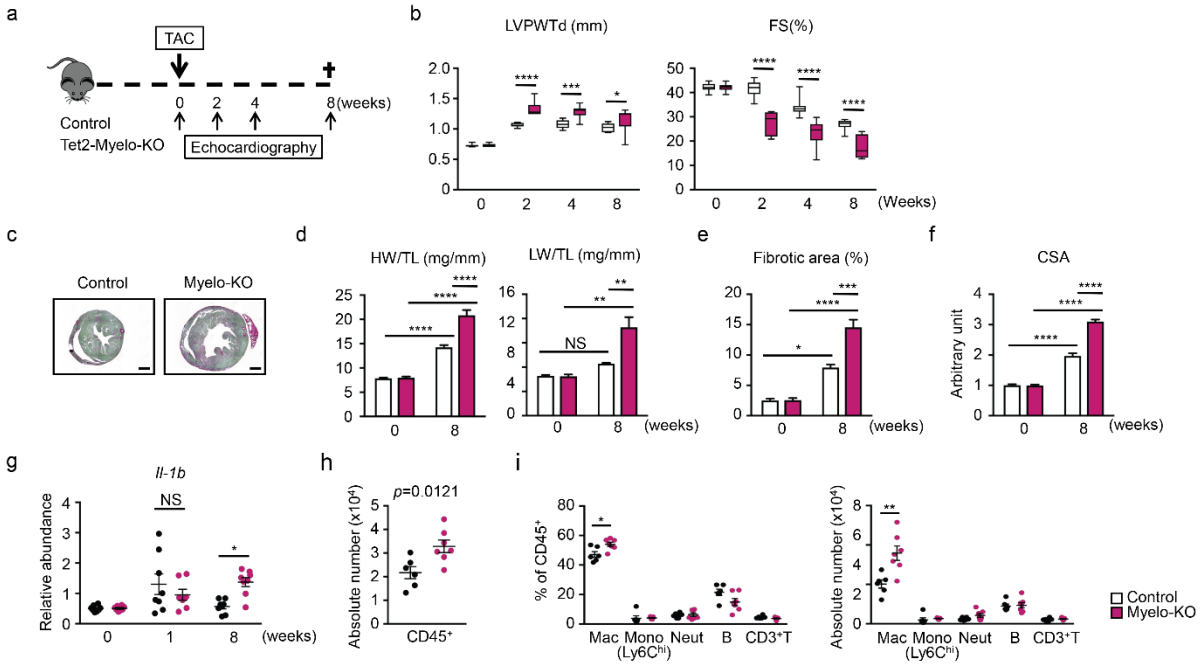

**Online Figure 9. Flow cytometry analysis of cardiac remote area and infarct area in hematopoietic Tet2-deficient mice (related to Figure 3c). a.** Flow cytometry analysis of cardiac remote area from 10% KO-BMT mice (n=7) and 10% WT-BMT (n=7) mice to show the relative proportion of immune cell populations. Statistical analysis was evaluated by multiple *t* tests. **b.** Flow cytometry analysis of cardiac infarct area with marginal zone from the same mice of **a.** to show the absolute number of $CD45^+$ cells (left panel) and macrophages (right panel). Statistical significance of difference was evaluated by two-tailed unpaired Student's *t* test or by Mann Whitney U tests for data which failed to pass the Shapiro-Wilk normality test. *p<0.05, **p<0.01. WT: wild type, Het: heterozygote, KO: knockout, BMT: bone marrow transfer, RM: remote area, IA: infarct area, MZ: marginal zone, Mac: macrophages, Mono: monocytes, Neut: neutrophils, B: B cells, T: T cells.




**Online Figure 10. Hematopoietic Tet2-KO mice do not show obvious change of the macrophages proliferation. a.** Representative data of the Ki67 (green) and Mac3 (red) immunofluorescence staining of the marginal zone from 10% KO-BMT mice (n=6) and 10% WT-BMT (n=6). DAPI is used to detect nuclei (blue). Heart tissue samples are obtained 4 weeks after LAD ligation. Scale bars indicate 20 μm. **b.** The number of $Mac3^+$ cells (left panel) and the ratio of $Ki67^+$ cells over $Mac3^+$ cells (right) are shown. Unpaired two-tailed Student's *t* test was performed for statistical analysis. Scale bar, 100 μm. WT: wild type, KO: knockout, LAD: left anterior ascending artery.




**Online Figure 11. MCC950 does not impact the peripheral blood chimerism. a.** Scheme of the experimental study. Mice underwent partial (10%) bone marrow reconstitution with Tet2-deficient cells or WT cells following lethal irradiation. After 4 weeks of recovery, mice underwent MCC950 or PBS infusion. Blood chimerism was analyzed by flow cytometry at 0 and 2 weeks after infusion. **b.** The percentage of the $CD45.2^{+}$ cells in different peripheral blood lineages before and after MCC950/PBS infusion. Sample sizes were n=3 for 10% WT-BMT/PBS, n=3 for 10% KO-BMT/PBS, n=4 for 10% WT-BMT/MCC950, n=4 for 10% KO-BMT/MCC950. Statistical significance was evaluated by two-way ANOVA with Tukey's multiple comparison tests. *p<0.05, ***p<0.001; NS: not significant. HSPC: hematopoietic stem progenitor cells, WT: wild type, KO: knockout, BMT: bone marrow transfer, PBS: phosphate-buffered saline, WBC: white blood cells, Mono: monocytes.




**Online Figure 12. Conditional myeloid Tet2-deficiency in mice leads worse cardiac remodeling during pressure overloaded hypertrophy. a.** Scheme of the experimental study. Conditional myeloid Tet2-knockout mice and control mice underwent TAC and echocardiography was performed at the indicated time points. **b.** Echocardiographic evaluation shows that mice with conditional Tet2 ablation in myeloid cells (n=9) display worsening cardiac remodeling after TAC surgery compared to control mice (n=9). The echocardiographic measurement time points are indicated. Statistical analysis was evaluated by two-way repeated measure ANOVA with Sidak's multiple comparison tests. **c.** Representative images of Picrosirius Red stained cardiac sections. Hearts from conditional Tet2-KO mice appear larger compared to the hearts from control mice at 8 weeks after TAC. **d.** Measurements of HW and LW normalized to TL. Statistical significance was evaluated by two-way ANOVA with Tukey's multiple comparison tests. Sample sizes were n=3 for control/sham, n=3 for conditional Tet2-KO/sham, n=9 for control/TAC, n=9 for conditional Tet2-KO/TAC. **e.** Quantitative analysis of

cardiac sections stained with Picrosirius red as presented in **Online Figure 6c.** shows that conditional Tet2-KO mice (n=8) exhibit greater cardiac fibrosis after pressure overload then control mice (n=8) 8 weeks after TAC. For the 0 time point, 3 sham-treated mice were also used as used per genotype. The percentage of the fibrotic area was calculated with the image-J software. Statistical analysis was evaluated by two-way ANOVA with Tukey's multiple comparison tests. **f.** WGA staining of the heart sections from hearts from conditional Tet2-KO mice (n=8) and control mice (n=8) isolated at 8 weeks after TAC showing that conditional KO mice display greater hypertrophy of the cardiac myocytes. 3 sham mice were used as used per genotype. Statistical analysis was evaluated by two-way ANOVA with Tukey's multiple comparison tests. **g.** Hearts from conditional myeloid Tet2-deficient mice upregulate of IL-1β transcript after pressure overload. Remodeling heart tissue samples were obtained from control (n=8) mice and conditional KO mice (n=8) and gene expression was analyzed by qPCR analysis. For the 0 time point, sham-treated mice were used (n=8 per genotype). Statistical significance was evaluated by two-way ANOVA with Tukey's multiple comparison tests. **h.** Flow cytometry analysis of hypertrophied myocardium from Tet2-Myelo-KO mice (n=7) and control (n=7) mice to show the absolute number of total $CD45^+$ immune cells are increased in the tissue from Tet2-Myelo-KO mice. Data is expressed as number of cells per 100 mg wet weight. Statistical analysis was evaluated by two-tailed unpaired Student's *t* test. **i.** Flow cytometry analysis of hypertrophied myocardium from Tet2-Myelo-KO mice (n=7) and control (n=7) mice to show the relative proportion (left panel) and absolute number (right panel) of each immune cell populations. Statistical significance of difference was evaluated by multiple *t* tests. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001; NS: not significant. WT: wild type, Myelo-KO: myeloid-specific knockout, TAC: transverse aortic constriction, HW: heart weight, LW: lung weight, TL:

tibia length, LVPWTd: left ventricular posterior wall thickness at end diastole, FS: fractional shortening, qPCR: quantitative polymerase chain reaction, CSA: cross-sectional area of myocytes, Mac: macrophages, Mono: monocytes, Neut: neutrophils, B: B cells, T: T cells.

Online Table

| *Gene name* | *Species* | Forward | Reverse |
|---|---|---|---|
| *Il-1b* | *Mus Musculus* | 5'- TGACAGTGATGAGAATGACCTGTTC -3' | 5'- TTGGAAGCAGCCCTTCATCT -3' |
| *Il-6* | *Mus Musculus* | 5'- GCTACCAAACTGGATATAATCAGGA -3' | 5'- CCAGGTAGCTATGGTACTCCAGAA -3' |
| *Tnf* | *Mus Musculus* | 5'- CGGAGTCCGGGCAGG -3' | 5'- GCTGGGTAGAGAATGGATGAA -3' |
| *Ccl2* | *Mus Musculus* | 5'- CAGCCAGATGCAGTTAACGC -3' | 5'- GCCTACTCATTGGGATCATCTTG -3' |
| *Ccl5* | *Mus Musculus* | 5'- CAGCAGCAAGTGCTCCAATC -3' | 5'- CACACACTTGGCGGTTCCTT -3' |
| *Selp* | *Mus Musculus* | 5'- CATCTGGTTCAGTGCTTTGATCT -3' | 5'- ACCCGTGAGTTATTCCATGAGT -3' |
| *Tet2* | *Mus Musculus* | 5'- ACATCCCTGAGAGCTCTTGC -3' | 5'- AGAGCCTCAAGCAACCAAAA -3' |
| *36b4* | *Mus Musculus* | 5'- GCTCCAAGCAGATGCAGCA -3' | 5'- CCGGATGTGAGGCAGCAG -3' |
| *18S rRNA* | *Mus Musculus* | 5'- AATCAAGAACGAAAGTCGGAGG -3' | 5'- GCGGGTCATGGGAATAACG -3' |