SUPPLEMENTAL METHODS

Human Ischemic Cardiomyopathy Specimens: This study was approved by the Institutional Review Board at Northwestern University (#STU00012288) and performed in accordance with the Helsinki Doctrine on Human Experimentation. Written consent was obtained from all study participants. Cardiac tissue specimens were obtained from the explanted hearts of adult patients with ischemic cardiomyopathy undergoing cardiac transplantation at Northwestern Memorial Hospital. Explanted hearts were immediately immersed and rinsed with cold cardioplegia solution. Tissue specimens from infarct-scar or viable remote (absence of fibrosis) myocardium were obtained from the lateral wall of the left ventricle. Specimens were maintained in cold cardioplegia solution to preserve tissue integrity. Within 1 hour of procurement, specimens were digested with collagenase type II (600U/ml, Worthington) and DNase I (0.1mg/ml) in HBSS at 37°C for 30 minutes with agitation. Specimens were subsequently triturated through a 40μm cell strainer to prepare a single cell suspension for analyses by flow cytometry.

Human ST-segment elevation MI Plasma Specimens: This study was approved by the Institutional Review Board at Northwestern University (#STU00075325) and performed in accordance with the Helsinki Doctrine on Human Experimentation. Written consent was obtained from all study participation and subjects were excluded from the study if they were pregnant or unable to consent. Human peripheral blood was collected in BD Vacutainer EDTA-coated tubes (lavender top) from healthy controls or patients diagnosed with ST-segment elevation MI via electrocardiography within 24 hours of being admitted to the cardiac care unit at Northwestern Memorial Hospital. Blood was centrifuged at 5,000 rpm for 15 minutes 4°C to remove cells and platelets and plasma was stored at -80°C until analyses. Levels of soluble AXL in diluted plasma (1:100) were measured by ELISA according to the manufacturer's instructions. Absorbances were read at 450 nm on an iMark Microplate Reader (BIO-RAD).

Mice: *C57BL/6J* mice were bred in our animal facility prior to use as wild-type controls. *MerKD* (referred to herein as *Mertk-/-*), cleavage-resistant MerTK (*MertkCR/CR*), and *Axl-/-* mice have been previously described (1-3) and were backcrossed to *BL/6J* for ten generations. *Mertk-/-* and *Axl-/-* mice were crossed to generate mice double-deficient in *Mertk* and *Axl* (*Axl-/-Mertk-/-*). *LysM-Cre* (B6.129P2-Lyz2$^{tm1(cre)Ifo}$/J, Stock No: 004781), αMHC-mCherry (Tg(Myh6*-mCherry)2Mik, Stock No: 021577), and *Stat1-/-* (B6.129S(Cg)-Stat1^{tm1Dlv}/J, Stock No: 012606) mice were purchased from Jackson Laboratories. *Axl^{flox}* mice were generated in *BL/6J* background as previously described (4) and provided by Dr. Carla Rothlin (Yale University). *Axl^{flox}* mice were crossed with mice expressing *LysM-Cre* to generate mice with specific deletion of *Axl* in myeloid cells (*LysM-Cre^{+}Axl^{flox}* mice). *Axl^{flox}* littermates without *LysM-Cre* were used as controls in experiments with *LysM-Cre^{+}Axl^{flox}* mice. Mice were housed in temperature- and humidity-controlled, pathogen-free environments and kept on a 14:10h day/night cycle with access to standard mouse chow and water *ad libitum*. Two- to four-month old female or male mice were used for experiments. Animal studies were conducted in accordance with guidelines using a protocol approved by the Institutional Animal Care and Use Committee at Northwestern University.

AXL cleavage resistant mice: Cleavage resistant AXL protein, expressed from recombinant cDNA clones, were initially screened in vitro. CRISPR-Cas9 targeted mutagenesis and deletion of CCC CCA CCT CGC GCC TTC between exons 10 and 11 of murine *Axl* into the *C57BL/*6J background was performed in collaboration with the Transgenic and Targeted Mutagenesis Laboratory at Feinberg School of Medicine at Northwestern University with Dr. Lynn Doglio, Dr. Rajeshwar Awatramani, and Dr. Pei-Ken Hsu. This specifically deleted a 6 amino acid region within a 14 amino acid stalk region proximal to the transmembrane domain of AXL to generate cleavage-resistant AXL mice (*AxlCR/CR*). The male founder Axl-Del2 #6598 was born on 07/18/17 and genotyping confirmed the presence of the correct allele. PCR genotyping primer oligonucleotides

for *AxlCR/CR* genotyping are as follows: Axl-saF: ACT CAC TGG TCA TTC CAC ACC and Axl-saR: CCA TGA CTT CAG CTT CCC CG. For genotyping, a 1 mm piece of tail was digested in Lysis Buffer (100 mM Tris pH 8.0, 5 mM EDTA, 0.2% SDS, 0.2 M NaCl) with 0.2 mg/ml Proteinase K at 55°C overnight. After removing debris by centrifugation, DNA was precipitated using isopropanol and pelleted by centrifugation. After washing with 70% ethanol, DNA was again pelleted by centrifugation before being resuspended in 80 μL DNase-free water and incubated at 55°C for 10 minutes. For DNA amplification, each reaction mixture contained 3 μL 10X Taq buffer, 0.4 μL 10mM dNTP, 1.8 μL 25 mM $MgCl_2$, 1 μL Axl-saF (10 μM), 1 μL Axl-saR (10 μM), 21.5 μL dH_2O, and 1 μL genomic DNA for a total reaction volume of 30 μL. DNA was amplified using a standard Taq-man protocol which consisted of the following steps: (1) 95°C for 1 min; (2) 95°C for 30 sec; (3) 60°C for 30 sec; (4) 72°C for 1 min; (5) Go to 2-4 for 35X; (6) 72°C for 7 min, and (7) 10°C temperature hold. Following amplification, the PCR product was digested using TfiI or BstUI restriction enzymes from New England BioLabs and according to New England BioLabs protocols. Each reaction required 10 μL of PCR product for each enzyme (in separate reactions) with digestions carried out at 62.5°C for 30 min. Digested PCR products were then separated on a 2% agarose gel with expected PCR product sizes of 427 bp for wild-type and 409 bp for *AxlCR/CR*. Supplemental Figure 11D has a representative image of expected genotyping results.

Myocardial Reperfused Infarction: Surgeries were performed on female mice aged 2-4 months of age. Mice were anesthetized with avertin (2,2,2-Tribromoethanol, 99%, 0.1 mg/kg i.p.) and received sustained-release buprenorphine (0.1 mg/kg s.c.) prior to the first incision. Puralube Vet Ointment (Dechra) was applied to the eyes and mice were secured in a supine position and endotracheal-intubated to an Inspira Advanced Safety Single Animal Pressure/Volume Controlled Ventilator (Harvard Apparatus). Animals were maintained at 37°C using a far infrared warming

pad (Kent Scientific) and animal temperature was monitored throughout surgery by a rectal probe using a MircoTherma 2 meter (ThermoWorks). Using a Leica S4E dissecting microscope and ACE Light Source (Schott), a left thoracotomy was performed with the aid of a Geiger Thermal Cautery Unit (Delasco) to maintain normal hemostasis. The left ventricle was visualized and the proximal left anterior descending (LAD) coronary artery was temporarily ligated with Surgipro II 7-0 monofilament polypropylene sutures (Covidien) approximately 2 mm distal to the site of its emergence from under the left atrium. Flexible plastic tubing (Tygon) was used during ligation to preserve the integrity of the vessel. Blanching/pale discoloration and hypokinesis of the anterior wall verified ligation. During ischemia, animal anesthesia was continuously monitored and additional avertin was administered following a positive toe pinch response. Following 45 minutes of ischemia, the ligature was reopened to allow for reperfusion. The reopened ligature was left in place to aid future analyses of infarct tissue. Reperfusion was confirmed by restoration of blood flow in the LAD and return of color to the left ventricle. Using Surgipro II 6-0 monofilament polypropylene sutures (Covidien), the surgical site was closed in layers starting with the chest wall followed by the pectoral muscle and finally skin and subcutaneous tissue. Animals were allowed to recover on a heating pad (Sunbeam) prior to being returned to cages. Mice dying within 48 hours of surgery were treated as technical errors and excluded from analyses.

Left Ventricular Infarct and Area-at-Risk (AAR) Measurements: Mice were anesthetized with avertin (0.1mg/kg i.p.), secured in a supine position, endotracheal-intubated, and ventilated with an Inspira Advanced Safety Single Animal Pressure/Volume Controlled Ventilator (Harvard Apparatus). With the aid of a dissecting microscope, the thoracic cavity was carefully opened to maintain normal hemostasis and expose the heart. The ligature was re-ligated and 100μl of FluoSpheres Polystyrene Microspheres (10 μm, red fluorescent 580/605) were injected into the left ventricle using an insulin syringe with 30G needle. Hearts were excised 1 minute later and

sectioned into 1 mm coronal slices using a Mouse Heart Slicer Matrix (Zivic Instruments). Infarct and viable myocardium were visualized by staining the slices in 1.5 ml microfuge tubes with 1% 2,3,5-Triphenyltetrazolium chloride in saline for 5 minutes at 37°C and then fixing in 10% buffered formalin phosphate for 1 hour at 4°C. Slices were placed directly on an Epson Perfection V600 Photo scanner and scanned to generate digital infarct images. Brightness and contrast were equally adjusted on all images using Adobe Photoshop CC 2018 to aid infarct visualization. AAR was visualized by placing the slices under an Olympus IX51 fluorescent scope and imaging the slices with Olympus cellSens Imaging Software. Both infarct and AAR were measured as a percentage of the left ventricle using ImageJ (NIH). Infarct size, expressed as a percentage of AAR, was calculated by dividing the sum of infarct areas from all sections by the sum of AAR from all sections and multiplying by 100.

Echocardiography: Cardiac function was assessed by transthoracic echocardiography on mice anesthetized with isoflurane before and 3-4 weeks after myocardial ischemia-reperfusion injury using a Vevo 770 equipped with a 25-MHZ probe (VisualSonics) as previously described (5). Heart rate was maintained above 400 beats/min to ensure physiologically relevant measurements in all anesthetized animals. Parasternal short-axis images were acquired using M-mode 1 mm before, at, and after the papillary muscles. Image analysis was performed using Vevo LAB software (VisualSonics). Measurements of LV internal dimension at both end-systole and end-diastole were made in 3 consecutive cardiac cycles and averaged for analysis.

Tissue Isolation: For peripheral blood collection, mice were anesthetized with avertin (0.1 mg/kg i.p.) and whole blood was collected into an EDTA-coated 1.5 ml microfuge tube by retroorbital bleeding with a heparinized capillary tube (Fisherbrand). Peripheral blood cells were collected by centrifuging at 1500 rpm for 5 min at 4°C followed by red blood cell lysis (BioLegend), and resuspension in FACS buffer (1x PBS supplemented with 2% FBS and 2mM EDTA). For

organ harvest, mice were euthanized by carbon dioxide asphyxiation and hearts were extensively flushed through the left ventricle with a volume of 20 ml ice-cold PBS to remove peripheral cells. For bone marrow, the tibia was harvested and cut at both ends at the metaphysis and cells were flushed from the bone with a volume of 5 ml ice-cold PBS. Bone marrow cells were centrifuged at 1500 rpm for 5 min at 4°C, red blood cells lysed (BioLegend), and resuspended in FACS buffer. Whole spleens were harvested and subsequently triturated through a 40 μm cell strainer (Fisherbrand) to prepare a single cell suspension. Splenocytes were centrifuged at 1500 rpm for 5 min at 4°C, red blood cells lysed (BioLegend), and resuspended in FACS buffer. For hearts, infarcted myocardium distal to the ligature was excised, weighed, and transferred to a 1.5 ml microfuge tube. Heart tissue was then minced in 1 ml of DMEM with 450 U/ml Collagenase I, 60 U/ml hyaluronidase, and 60 U/ml DNase I and rotated on a LabQuake rotiessere shaker (ThermoFisher) at 37°C for 30 minutes. After digestion, the sample was pipetted 5 times with a P1000 pipette to disrupt any remaining tissue and transferred through a 40 μm cell strainer. Cardiac cells were collected by centrifuging at 2000 rpm for 5 min at 4°C followed by red blood cell lysis (BioLegend), and resuspension in FACS buffer. Viable cells were counted on a hemocytometer with trypan blue exclusion to determine the total number of viable cells for blood (cells/ml), bone marrow (cells/femur), spleen (cells), and heart (cells/mg). To survey tissue macrophages, mice were euthanized and peripheral cells were flushed by injecting 20 ml ice-cold PBS through the left ventricle followed by injection of 10 ml of digestion solution (450 U/ml Collagenase I, 60 U/ml DNase I) in HBSS. Tissue was recovered from liver, kidney, spleen, pancreas, thymus, salivary gland, and further minced and digested at 37°C for 30 minutes. Samples were transferred through a 40 μm cell strainer followed by red blood cell lysis. Separately, bronchoalveolar macrophages were recovered by cannulating the trachea and lavaging the airways with 1 ml of ice-cold PBS and peritoneal macrophages were recovered from

the peritoneal cavity by lavage with 5 ml of ice-cold PBS. Tissues recovered from *Axl-/-* mice served as a staining control for AXL expression on tissue resident macrophages.

Flow Cytometry: Single cells were resuspended in a volume of 200 μl FACS buffer. Dead cells were labeled by incubating samples with Zombie Aqua Fixable Dye (1:1000) in PBS for 15 minutes at room temperature in the dark. Cells were washed in FACS Buffer and then Fc receptors were blocked using TruStain FcX antibody (1:100) in FACS buffer for 15 minutes on ice. Cells were incubated with primary antibodies (all 1:200) in FACS buffer for 20 minutes on ice in the dark. For secondary antibody staining of AXL and MerTK, cells were first labeled with biotin-conjugated primary antibodies, washed in FACS buffer, and then incubated with Alexa 647 streptavidin (1:200) in FACS buffer for 20 minutes on ice in the dark. For intracellular antibody staining, cells were first incubated with TruStain FcX antibody and cell surface antibodies before fixation and permeabilization using the BD Cytofix/Cytoperm Fixation/Permeabilization Kit (BD Biosciences). After fixation/permeabilization, cells were incubated with antibodies in BD Perm/Wash buffer for 30 minutes on ice. All flow cytometric analyses were performed on either a FACS Canto II or LSRFortessa X-20 Cell Analyzer (BD Biosciences). BD Compbeads (BD Biosciences) were used to optimize fluorescence compensation settings to enable multicolor flow cytometric analyses. All cells were pre-gated on live (live-dead exclusion), single cells (FSC-A vs FSC-H and SSC-A vs SSC-W). Data were analyzed on FlowJo software (Tree Star). Full gating strategies for myeloid cells in the heart are shown for mouse in Supplemental Figure 1A and for human in Supplemental Figure 2B-2D.

Serum levels of soluble proteins: On the days indicated after myocardial ischemia-reperfusion injury, mice were anesthetized with avertin (0.1 mg/kg i.p.) and whole blood was collected into 1.5 ml microfuge tubes by retroorbital bleeding with a heparinized capillary tube (Fisherbrand). Blood was allowed to clot at room temperature for 15 minutes and the clot was removed by

centrifuging at 5,000 rpm for 15 minutes at 4°C. Serum was stored at -80°C until analyses. Levels of IL-1β, TNF-α, or IL-10 in undiluted serum and levels of soluble AXL in diluted serum (1:100) were measured by ELISA according to the manufacturer's instructions. Absorbances were read at 450 nm on an iMark Microplate Reader (BIO-RAD).

In vivo Efferocytosis Assay: Four- to six-week-old αMHC-mCherry recipient mice, which specifically express mCherry protein in cardiomyocytes, were lethally irradiated with 1000 rads from a cesium source before transplantation. A total of $5x10^6$ bone marrow cells from *Axl+/+* or *Axl-/-* mice were injected into irradiated recipients by tail vein injection. After bone marrow transplantation, mice were maintained on acidified drinking water containing neomycin. Six weeks after transplantation, mice were subjected to myocardial ischemia-reperfusion injury surgery. Heart tissue and cells were processed 4 hours after injury as described above and flow cytometric analyses were performed to identify $CD64^+$ macrophages that were also positive for cardiomyocyte-derived mCherry protein.

AXL Inhibition: To test the therapeutic potential of transient AXL inhibition after myocardial ischemia-reperfusion injury, mice were treated with the selective and specific AXL inhibitor, R428 (25 mg/kg s.c.), or vehicle control daily on days 0, 1, 2, and 3 after injury.

Peritonitis Model: Peritonitis was induced by i.p. injection of 1 ml sterile Brewer's thioglycollate medium. On day 3 post-injection, mice were euthanized by carbon dioxide asphyxiation, and macrophages were collected from the peritoneal cavity by lavage with 5 ml of ice-cold PBS and assessed for MHCII expression by flow cytometry.

Bone Marrow-Derived Macrophages: Bone marrow cells were harvested from the tibia and femurs of *Axl+/+*, *Axl-/-*, *AxlCR/CR*, or *Stat1-/-* mice and cultured in petri dishes (Fisherbrand) for 7 days with DMEM containing 20% L929-cell conditioned media, 10% fetal bovine serum, 1% penicillin-streptomycin, 1% sodium pyruvate, and 1% L-glutamine. For primary macrophage experiments, cells were seeded in a 24-well plate (Falcon), at a density of $5x10^5$ cells per well in 500 μl of DMEM containing 10% fetal bovine serum, 1% penicillin-streptomycin and allowed to adhere overnight. For TLR4 stimulation, macrophages were treated with lipopolysaccharide (10ng/ml) for the indicated periods of time. In some experiments, macrophages were serum-starved and treated with lipopolysaccharide (10ng/ml) and AXL-specific agonists, Gas6 (50nM) or anti-mouse AXL agonizing antibody (5μg/ml). Levels of TNF-α or IL-10 in treated culture media were measured by ELISA according to the manufacturer's instructions. Absorbances were read at 450 nm on an iMark Microplate Reader (BIO-RAD).

Inflammasome Activation: Bone marrow-derived macrophages were plated at a density of $5x10^5$ cells/well in a 24-well plate in 500μl of DMEM with 10% FBS, 1% penicillin/streptomycin and primed with lipopolysaccharide (LPS, 100ng/ml) for 40 minutes. Biotin-Caspase-1 inhibitor II (10μM) was added to the culture media for the final 30 minutes of priming with LPS. To activate the inflammasome, primed cells were treated with ATP (5mM) for 20 minutes. Culture media was collected and IL-1β levels were measured by ELISA according to the manufacturer's instructions. Plates were placed on ice and cells were washed with a volume of cold PBS and removed by gentle pipetting. Activated Caspase-1 levels were measured by intracellular staining using Alexa Fluor 647 Streptavidin followed by flow cytometric analyses.

Glycolytic Metabolism Measurements: To measure extracellular acidification rate (ECAR), bone marrow-derived macrophages were plated at a density of $5x10^4$ cells/well in an XFe96 cell culture

microplate (Agilent) and allowed to adhere overnight. Macrophages were treated with LPS (10ng/ml), anti-mouse AXL agonizing antibody or isotype control (5μg/ml), or cobalt chloride (100μM cobalt chloride) for 3 hours in DMEM with 10% FBS, 1% penicillin/streptomycin. After stimulation, the media was removed and experiments were conducted in pre-warmed glycolytic stress test media containing DMEM without phenol red and 2mM L-Glutamine, pH 7.4 and analyzed using a Seahorse XFe96 analyzer (Agilent). After baseline measurements in triplicate, the following chemicals (all from Sigma) were injected in this order: (1) glucose (250mM), (2) oligomycin (10μM), and (3) 2-deoxyglucose (500mM). Measurements were taken in triplicate after the addition of each chemical. ECAR analyses were generated by using Wave software (Agilent).

Immunoblots: To measure proteins, bone marrow-derived macrophages ($5x10^5$ cells/well) in a 24-well plate were treated as described in figure legends. Cells were lysed with 250μl ice-cold cell lysis buffer with protease and phosphatase inhibitor cocktails. Protein concentrations were measured using a Micro BCA Protein Assay Kit. Equal amounts of protein were boiled in 3X Blue Loading Buffer with 2-mercaptoethanol (1:1000) for 5 minutes. SDS-PAGE was performed by resolving proteins on an 8% polyacrylamide gel in Tris-HEPES SDS Buffer in a Mini-Protean Tetra Vertical Electrophoresis Cell (BIO-RAD) at 120V for 1 hour. Precision Plus Protein Dual Color Standard was used to monitor electrophoresis and transfer efficiency. Proteins were transferred to an Immobilon PVDF membrane (0.45 μm Amersham Hybond, GE Healthcare) in Pierce Western Blot Transfer Buffer at 100V for 1 hour. Membranes were blocked in 5% BSA in PBS-Tween (0.2%) with gentle rocking for 1 hour at room temperature. Primary antibodies were also diluted in 5% BSA in PBS-Tween (0.2%) and incubated with membranes with gentle rocking at 4°C overnight. Membranes were then washed and incubated with secondary antibodies diluted in 5% BSA in PBS-Tween (0.2%) with gentle rocking for 1 hour at room temperature. Following

antibody incubations, membranes were washed and incubated with SuperSignal West Pico Plus Chemiluminescent Substrate for 1 minute at room temperature. Proteins were visualized by exposing membranes to HyBlot CL autoradiography film (LabForce, Thomas Scientific) and developing films in a Konica Medical Film Processor (SRX-101A). Films were placed directly on an Epson Perfection V600 Photo scanner and scanned to generate digital immunoblot images. Brightness and contrast were equally adjusted on all images using Adobe Photoshop CC 2018 to aid immunoblot measurements. Relative band density was measured using ImageJ (NIH) and normalized to loading controls.

Axl Cleavage Assay: Bone marrow-derived macrophages from *Axl+/+* or *AxlCR/*CR mice were plated at a density of $5x10^5$ cells/well in a 24-well plate in 500μl of DMEM with 10% FBS, 1% penicillin/streptomycin. To induce AXL cleavage, macrophages were treated with lipopolysaccharide (100ng/ml) for 1 hour. Culture media was collected to assay for soluble AXL by ELISA and cells were harvested for AXL cell-surface expression analysis by flow cytometry. Alternatively, macrophages were stimulated with lipopolysaccharide (100ng/ml) in serum-free DMEM for 12 hours. Culture media was collected and protein content precipitated by trichloroacetic acid (TCA)/acetone extraction, then resuspended in 50 μL 2xSDS loading dye. Adherent cells were washed with cold PBS and then lysed in RIPA buffer (150 mM sodium chloride, 1.0% Triton X-100, 0.5% sodium deoxycholate, 0.1% SDS) with protease inhibitor cocktail. For Western blots, lysate protein concentration was determined using a BCA Kit (Pierce), and equal amounts of total protein were loaded per lane. Cell-associated and soluble AXL were detected using a goat anti-mouse AXL primary antibody followed by a donkey anti-goat antibody conjugated to horseradish peroxidase.

Quantitative PCR: RNA was extracted from cardiac extracts or primary macrophages using TRIzol (Invitrogen) according to the manufacturer's instructions. mRNA was transcribed to cDNA using

the iScript cDNA Synthesis Kit (Bio-Rad). Quantitative PCR was performed using SYBR Green Master Mix (Bio-Rad) on a QuantStudio 3 Real-Time PCR System (Applied Biosystems). Results are expressed as delta-delta Ct values normalized to β2m. Primers used for semiquantitative/real-time PCR are listed in the table below.

Proximity Ligation Assay: Axl+/+ or *Axl-/-* bone marrow-derived macrophages plated at a density of $1x10^5$ cells/well in a 24-well plate were stimulated with lipopolysaccharide (10ng/ml) for 1 hour. Cells were washed twice with ice-cold PBS, fixed in 2% paraformaldehyde in PBS for 20 minutes on ice, and processed according to the Duolink PLA Flow Cytometry Protocol. In brief, cells were washed and incubated in blocking solution for 1 hour at 37°C. Cells were then stained using primary antibodies for anti-AXL (1 µg/ml, source: goat) and anti-TLR4 (1 µg/ml, source: rabbit) in Duolink Antibody Diluent for 30 minutes on ice. Cells were washed and incubated with Duolink In Situ PLA Probes Anti-Goat PLUS and Anti-Rabbit MINUS for 1 hour at 37°C. Ligation was performed for 30 minutes at 37°C followed by amplification overnight at 37°C. Detection was performed for 30 minutes at 37°C. After final washes, cells were resuspended in PBS and analyzed by flow cytometry. Fixed cells with no primary antibodies but with PLA probes were used to set the gate for baseline Duolink PLA fluorescence.

Statistics: Analyses were performed with GraphPad Prism 9 software (GraphPad Software). Comparisons between two groups were performed using two-tailed, unpaired t-test with 95% confidence interval. For comparisons of more than two variables, One-Way ANOVA or Two-Way ANOVA was utilized with 95% confidence interval and when necessary, Tukey test was used to correct for multiple comparisons. For in vivo experiments, experimental sample size is depicted in figures and represent pooled data from 2 or more independent experiments. For in vitro experiments, experimental sample size is depicted in figures and represent 2 or more independent experiments. Data are presented as mean ± SEM. Criteria for significant differences

(*p<0.05, **p<0.01, ***p<0.001) are located in figure legends. Analyses labeled ns are not statistically significant.

Study Approval: These studies were approved by the Institutional Review Board at Northwestern University and performed in accordance with the Helsinki Doctrine on Human Experimentation. Written consent was obtained from all study participants. Animal studies were conducted in accordance with guidelines using a protocol approved by the Institutional Animal Care and Use Committee at Northwestern University.

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Alexa Fluor 488 anti-mouse CD284 (TLR)	eBioscience	Cat #: 53-9041-82
Alexa Fluor 647 Donkey anti-rabbit IgG	BioLegend	Cat #: 406414
Alexa Fluor 647 anti-STAT1 Phospho (Ser727)	BioLegend	Cat #: 686411
Alexa Fluor 647 Phospho-Stat1 (Tyr701) Rabbit mAb	Cell Signaling Tech.	Cat #: 8009S
Alexa Fluor 647 Streptavidin	BioLegend	Cat #: 405237
APC anti-human AXL	R&D Systems	Cat #: FAB154A
APC anti-mouse CCR2	R&D Systems	Cat #: FAB5538A
APC anti-mouse CD115	BioLegend	Cat #: 135509
APC anti-mouse Ly6C	BioLegend	Cat #: 128016
APC anti-human MerTK	R&D Systems	Cat #: FAB8912A
APC/Cy7 anti-human/mouse CD11b	BioLegend	Cat #: 101226
APC/Cy7 anti-human HLA-DR	BioLegend	3 Cat #: 07618
APC/Cy7 anti-mouse I-A/I-E	BioLegend	Cat #: 107627
AXL agonizing mouse antibody	R&D Systems	Cat #: AF854
AXL biotinylated mouse antibody	R&D Systems	Cat #: BAF854
BV421 anti-human CD45	BioLegend	Cat #:304031
BV421 anti-mouse CD64	BioLegend	Cat #: 139309
BV421 anti-mouse F4/80	BioLegend	Cat #: 123132
BV605 anti-human/mouse CD11b	BioLegend	Cat #: 101257
BV711 anti-mouse CD64	BioLegend	Cat #: 139311
BV711 anti-mouse Ly6C	BioLegend	Cat #: 128037
Caspase-1 Rabbit mAb	Cell Signaling Tech.	Cat #: 24232S
Direct-Blot HRP anti-β-actin	BioLegend	Cat #: 643807
FITC anti-mouse CCR2	R&D Systems	Cat #: FAB5538F
FITC anti-human CD64	BioLegend	Cat #: 305006
FITC anti-mouse Ly6C	BioLegend	Cat #: 128006
HIF-1 alpha antibody	Novus Biologicals	Cat #: NB100-449
HRP-linked anti-rabbit IgG	Cell Signaling Tech.	Cat #: 7074S
Human TruStain FcX	BioLegend	Cat #: 422302
MerTK biotinylated mouse antibody	R&D Systems	Cat #: BAF591
NF-κB XP Rabbit mAb	Cell Signaling Tech.	Cat #: 8242S
PE anti-human CCR2	BioLegend	Cat #: 357206
PE anti-mouse CCR2	R&D Systems	Cat #: FAB5538P
PE anti-mouse CD115	eBioscience	Cat #: 12-1152-83
PE anti-mouse Ly6G	BioLegend	Cat #: 127608
PE/Cy7 anti-human CD14	BioLegend	Cat #: 301814
PE/Cy7 anti-mouse F4/80	BioLegend	Cat #: 123114
PE/Cy7 anti-mouse Ly6G	BioLegend	Cat #: 127618
PerCP/Cy5.5 anti-human CD16	BioLegend	Cat #: 302027

PerCP/Cy5.5 anti-mouse I-A/I-E	BioLegend	Cat #: 107626
Peroxidase AffiniPure Donkey Anti-Goat IgG (H+L)	Jackson ImmunoResearch	Cat #: 705-035-003
Phospho-NF-κB p65 (Ser536) Rabbit mAb	Cell Signaling Tech.	Cat #: 3033S
Phospho-Stat1 (Tyr701) Rabbit mAb	Cell Signaling Tech.	Cat #: 7649S
Stat1 Rabbit mAb	Cell Signaling Tech.	Cat #: 14994S
Toll-like Receptor 4 Rabbit mAb	Cell Signaling Tech.	Cat #: 14358S
TruStain FcX (anti-mouse CD16/32) antibody	BioLegend	Cat #: 101319
Zombie Aqua Fixable Viability Kit	BioLegend	Cat #: 423101
Chemicals, Peptides, and Recombinant Proteins		
Adenosine 5'-triphosphate (ATP) disodium salt hydrate	Sigma-Aldrich	Cat #: A26209
BD Cytofix/Cytoperm	BD Biosciences	Cat #: 554714
Biotin-Caspase 1 Inhibitor II	Anaspec	Cat #: AS-60841
Blue Loading Buffer Pack	Cell Signaling Tech.	Cat #: 7722S
Brewer Thioglycollate Medium	Sigma-Aldrich	Cat #: B2551
BstUI	New England BioLabs	Cat #: R0518S
Cellstripper	Corning	Cat #: 25-056-CI
Cobalt(II) Chloride hexahydrate	Alfa Aesar	Cat #: 36554
Collagenase I	Sigma-Aldrich	Cat #: C0130
Collagenase, Type 2	Worthington	Cat #: LS004177
Deoxyribonuclease I	Sigma-Aldrich	Cat #: D4513
DMEM	Corning	Cat #: 10-014-CV
dNTP Mix, 10mM	Promega	Cat #: U151B
Duolink flowPLA Detection Kit-Red	Millipore Sigma	Cat #: DUO94001-40TST
Duolink In Situ PLA Probe Anti-Goat PLUS	Millipore Sigma	Cat #: DUO92003-30RXN
Duolink In Situ PLA Probe Anti-Rabbit MINUS	Millipore Sigma	Cat #: DUO92005-30RXN
EDTA	Promega	Cat #: V4231
Fetal Bovine Serum-Premium Select	Atlanta Biological	Cat #: S11550
FluoSpheres Polystyrene Microspheres, 10μm, 580/605	ThermoFisher	Cat #: F8834
Gas6 recombinant mouse protein	R&D Systems	Cat #: 986-GS/CF
Glucose	Sigma-Aldrich	Cat #: 158968
Halt Protease Inhibitor Cocktail (100X)	ThermoFisher	Cat #: 78429
Hyaluronidase	Sigma-Aldrich	Cat #: H3506
L-Glutamine 200mM (100X)	Gibco	Cat #: 25030-081
Lipopolysaccharide from *E. coli* O111:B4	Sigma-Aldrich	Cat #: L4391
$MgCl_2$, 25 mM	ThermoFisher	Cat #: AB0359
Micro BCA Protein Assay Kit	ThermoFisher	Cat #: 23235
Neomycin solution	Sigma-Aldrich	Cat #: N1142
Oligomycin	Sigma-Aldrich	Cat #: 75351-5MG
Penicillin Streptomycin Solution, 100X	Corning	Cat #: 30-002-CI
Phophatase Inhibitor Cocktail (100X)	Bimake	Cat #: B15002

Phosphate Buffered Saline (PBS)	Corning	Cat #: 21-040-CV
Pierce Western Blot Transfer Buffer (10X)	ThermoFisher	Cat #: 35045
Precision Plus Protein Dual Color Standards	BIORAD	Cat #: 1610374
Proteinase K, recombinant, PCR grade	ThermoFisher	Cat #: EO0491
RBC Lysis Buffer (10X)	BioLegend	Cat #: 420301
R428	APExBIO	Cat #: A8329
Sodium pyruvate solution 100mM	Sigma-Aldrich	Cat #: S8636
SuperSignal West Pico Plus Chemiluminescent Substrate	ThermoFisher	Cat #: 34580
Taq DNA Polymerase	New England BioLabs	Cat #: MO273X
TfiI	New England BioLabs	Cat #: R0546S
Tris-HEPES SDS Buffer (20X)	ThermoFisher	Cat #: 28368
Trypan Blue, 0.4% Solution	Lonza	Cat #: 17-942E
10% Buffered Formalin Phosphate	Fisher	Cat #: SF100-4
2-Deoxy-D-glucose	Sigma-Aldrich	Cat #: D8375-5G
2,2,2-Tribromoethanol, 99% (Avertin)	Alfa Aesar	Cat #: A18706
2,3,5-Triphenyltetrazolium chloride	Sigma-Aldrich	Cat #: T8877
Commercial Assays		
Human Axl DuoSet ELISA	R&D Systems	Cat #: DY154
Mouse Axl DuoSet ELISA	R&D Systems	Cat #: DY854
Mouse IL-1β ELISA MAX Deluxe Set	BioLegend	Cat #: 432604
Mouse IL-10 ELISA Set	BD Biosciences	Cat #: 555252
Mouse TNF (Mono/Mono) ELISA Set	BD Biosciences	Cat #: 555268
Seahorse XFe96 Extracellular Flux Assay Kit	Agilent	Cat #: 102601-100
Experimental Models: Organisms/Strains		
Mouse: *Axl-/-*	Dr. Edward Thorp	N/A
Mouse: *Axl-/-Mertk-/-*	Dr. Edward Thorp	N/A
Mouse: *AxlCR/CR*	Dr. Edward Thorp	N/A
Mouse: *Axl^{flox}*	Dr. Carla Rothlin	N/A
Mouse: *C57BL/6J*	Dr. Edward Thorp	N/A
Mouse: *LysM-Cre*	Jackson Labs	JAX: 004781
Mouse: *Mertk-/-*	Dr. Edward Thorp	N/A
Mouse: *MertkCR/CR*	Dr. Edward Thorp	N/A
Mouse: αMHC-mCherry	Jackson Labs	JAX: 021577
Mouse: *Stat1-/-*	Jackson Labs	JAX: 012606
Oligonucleotides		
Aldoa-F: CATGCCCTACCAATATCCAGCA Aldoa-R: GATGCGGTGAGCGATGTCA	Woods, P.S., *et al.*(6)	N/A
Axl-saF: ACT CAC TGG TCA TTC CAC ACC Axl-saR: CCA TGA CTT CAG CTT CCC CG	This paper	N/A
B2m-F: CTG CTA CGT AAC ACA GTT CCA CCC B2m-R: CAT GAT GCT TGA TCA CAT GTC TCG	This paper	N/A

Gapdh-F: AGG ATG CCG TGC TGA ATG Gapdh-R: TAG AAG AGG GGC TCC AGA GG	Woods, P.S., *et al.*(6)	N/A
Hk2-F: TCT GGA GAT TTC TAG GCG GT Hk2-R: TGC TGT AGG GTG TGT GGT AG	Woods, P.S., *et al.*(6)	N/A
Hif1a-F: CTC AAA GTC GGA CAG CCT CA Hif1a-R: CCC TGC AGT AGG TTT CTG CT	This paper	N/A
Il1b-F: TAC GGA CCC CAA AAG ATG A Il1b-R: TGC TGC TGC GAG ATT TGA AG	This paper	N/A
Il6-F: GCC TTC TTG GGA CTG ATG CT Il6-R: TGC CAT TGC ACA ACT CTT TTC	This paper	N/A
Il10-F: ATA ACT GCA CCC ACT TCC CA Il10-R: GGG CAT CAC TTC TAC CAG GT	This paper	N/A
Ldha-F: ACT GTG TAA CTG CGA ACT CCA Ldha-R: AAG ATG TTC ACG TTT CGC TGG	Woods, P.S., *et al.*(6)	N/A
Pfkfb3-F: TCT AGA GGA GGT GAG ATC AG Pfkfb3-R: CCT GCC ACT CTT ATC TTC TG	Woods, P.S., *et al.*(6)	N/A
Pkm2-F: AGG ATG CCG TGC TGA ATG Pkm2-R: TAG AAG AGG GGC TCC AGA GG	Woods, P.S., *et al.*(6)	N/A
Slc2a1-F: CGT GCT TAT GGG TTT CTC CAA A Slc2a1-R: GAC ACC TCC CCC ACA TAC ATG	Woods, P.S., *et al.*(6)	N/A
Tgfb-F: CGC AAC AAC GCC ATC TAT GAG Tgfb-R: CGG GAC AGC AAT GGG GGT TC	This paper	N/A
Tnf-F: ACG GCA TGG ATC TCA AAG AC Tnf-R: AGA TAG CAA ATC GGC TGA CG	This paper	N/A
Software and Algorithms		
cellSens Imaging Sofware	Olympus	http://www.olympus-lifescience.com
FlowJo v10.6.1	FlowJo	http://www.flowjo.com
ImageJ	NIH	http://imagej.nih.gov
Library of icons for enhanced high level diagrams	Reactome	http://reactome.org/icon-lib
Phantasus	Bioconductor	https://artyomovlab.wustl.edu/phantasus
Photoshop CC 2018	Adobe	http://www.adobe.com
Prism 9	GraphPad	http://www.graphpad.com
Smart Servier Medical Art	Servier	http://smart.servier.com

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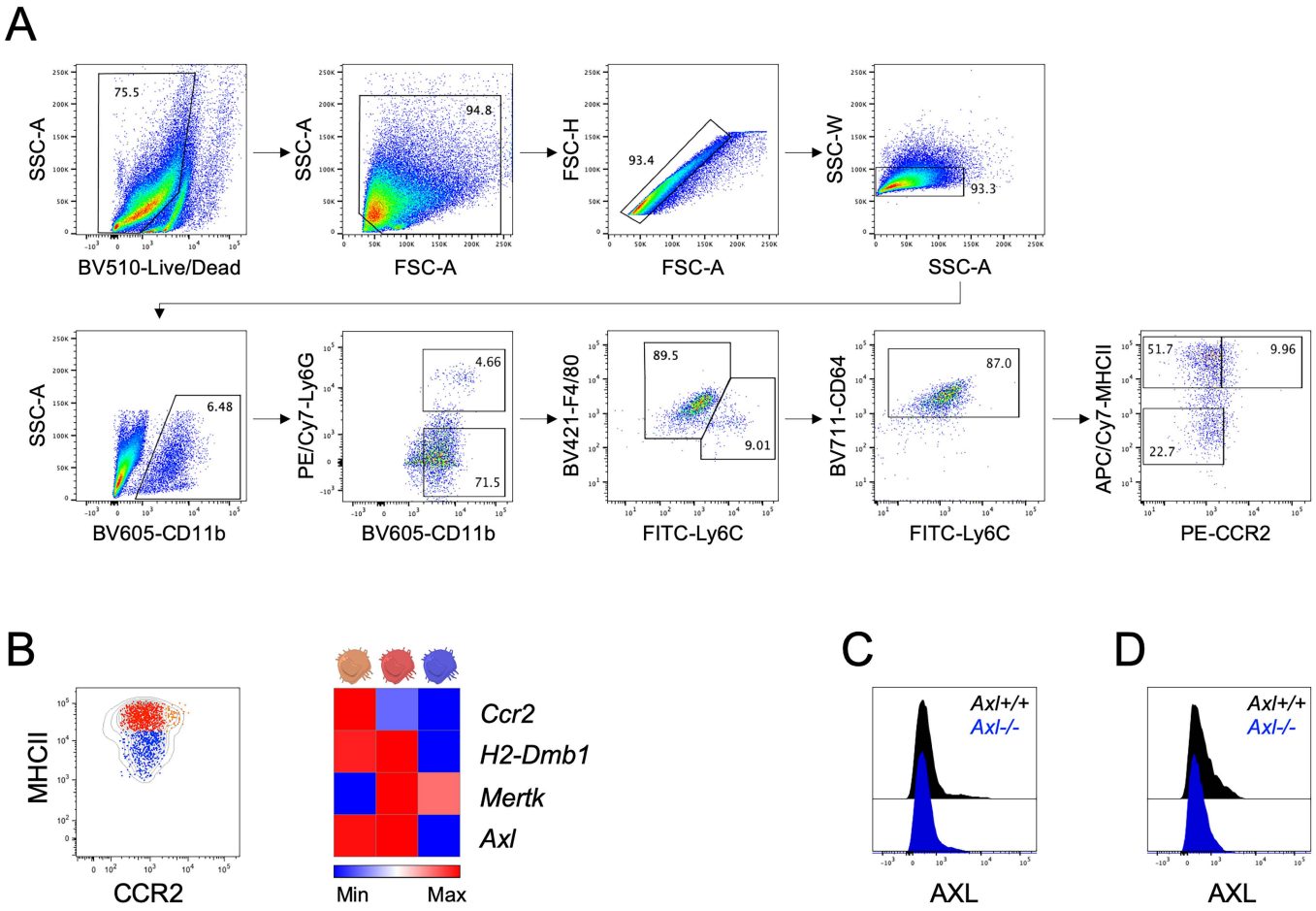
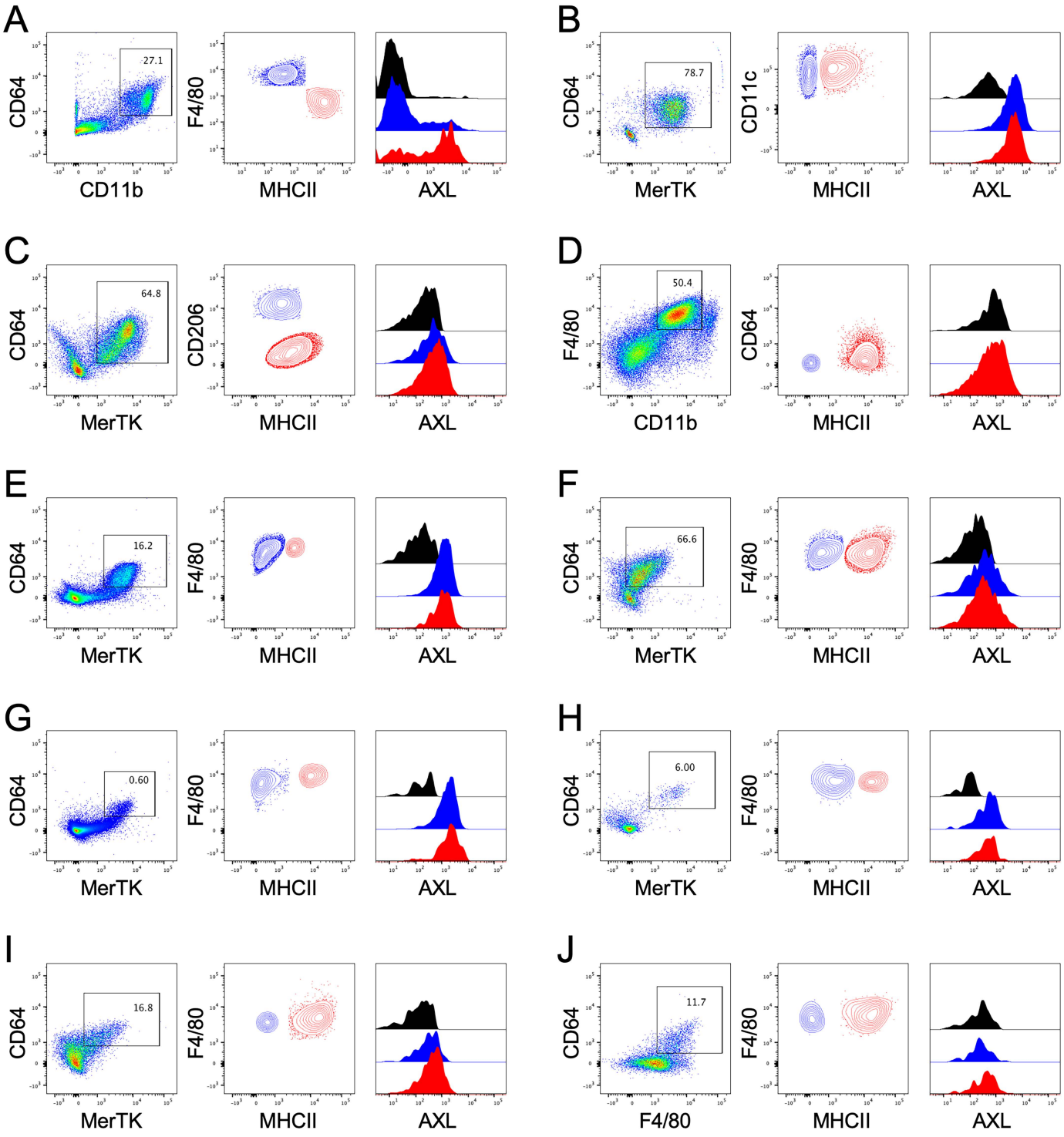
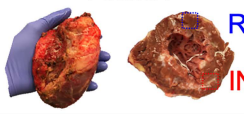
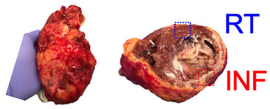
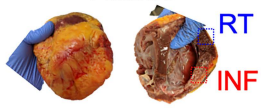


Supplemental Figure 1: Myeloid cell expression of AXL is restricted to MHCII^{HI} cardiac macrophages. **A** Cells were pre-gated on live (BV510-Live/Dead negative), singlets (FSC-A vs FSC-H, SSC-A vs SSC-W). Neutrophils were identified as CD11b^{+}Ly6G^{+}. Ly6C^{hi} monocytes were identified as CD11b^{+}Ly6G^{-}F4/80^{lo}Ly6C^{hi}. Macrophages were identified as CD11b^{+}Ly6G^{-}F4/80^{hi}Ly6C^{lo}CD64^{+} and further distinguished by MHCII and CCR2 expression. Flow plot of PE-CCR2 vs APC/Cy7-MHCII expression on cardiac macrophages is the same plot as shown in Figure 3D, upper left flow plot. **B** Visualization of AXL gene expression in cardiac macrophage subsets from the Gene Expression Omnibus dataset (Accession: GSE53787) using Phantasus software. Flow plot is the same as shown in Figure 1A. Protein expression of AXL on **C** neutrophils (CD11b^{+}Ly6G^{+}) and **D** Ly6C^{hi} monocytes (CD11b^{+}Ly6G^{-}F4/80^{lo}Ly6C^{hi}) as measured by flow cytometry.

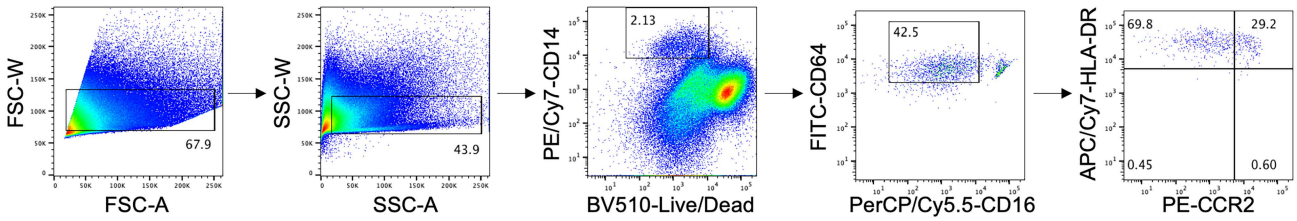


Supplemental Figure 2: AXL expression on tissue resident macrophages. Single cell suspensions were generated from **A** peritoneal lavage, **B** bronchoalveolar lavage, **C** liver, **D** kidney, **E** spleen, **F** pancreas, **G** bone marrow, **H** thymus, **I** salivary gland, and **J** female reproductive tract and analyzed for macrophage expression of AXL by flow cytometry. Cells were pre-gated on live (BV510-Live/Dead negative), singlets (FSC-A vs FSC-H, SSC-A vs SSC-W), lineage (CD3, CD19, Ly6G, NK1.1) negative, and CD45 positive. Most tissue resident macrophages were readily identifiable using CD64 and MerTK expression according to ImmGen guidelines and were further stratified by MHCII expression. Black histogram=*Axl-/-* control, blue histogram=MHCII^{LO} MΦ, and red histogram=MHCII^{HI} MΦ.

A

	Patient 1	Patient 2	Patient 3
Gross Appearance			
Age, yrs	53	69	52
Sex	Female	Male	Female
HF etiology	ICM	ICM	ICM
LVAD	No	Yes	No
HF Duration, yrs	1.3	1.5	0.6

B



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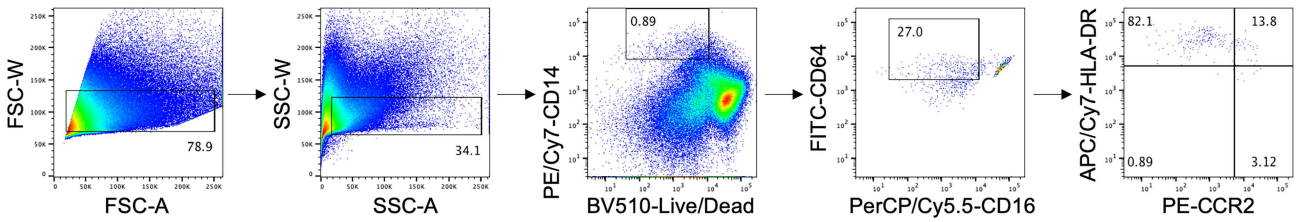

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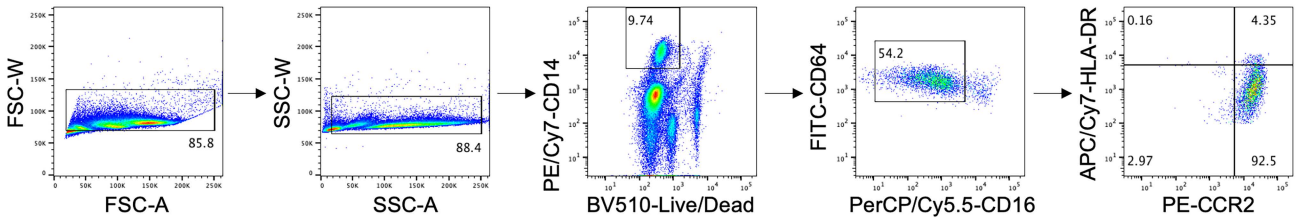
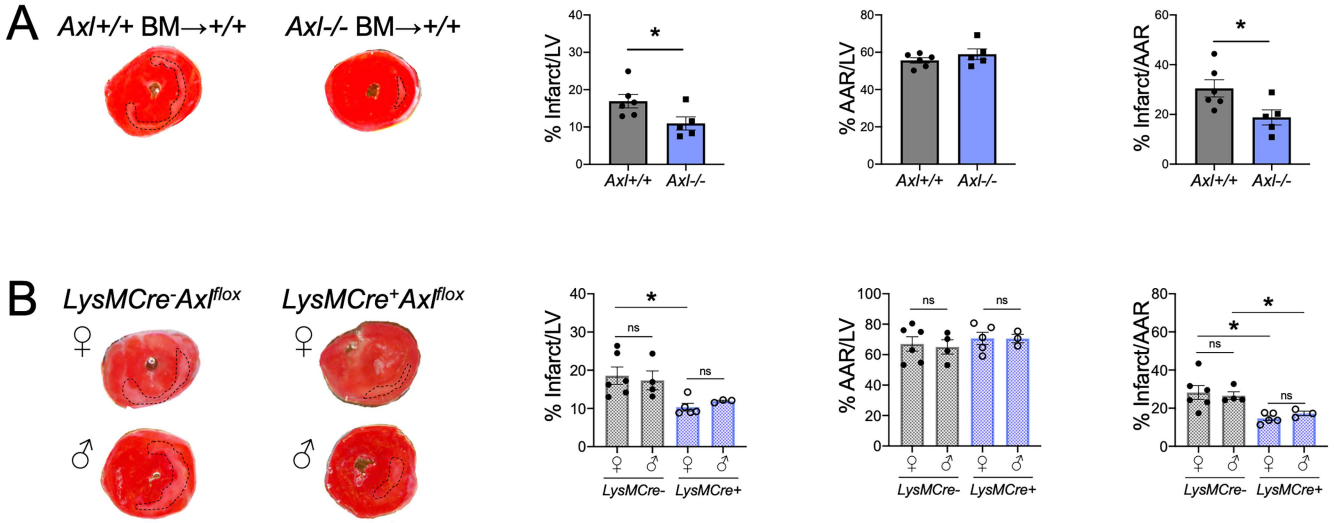
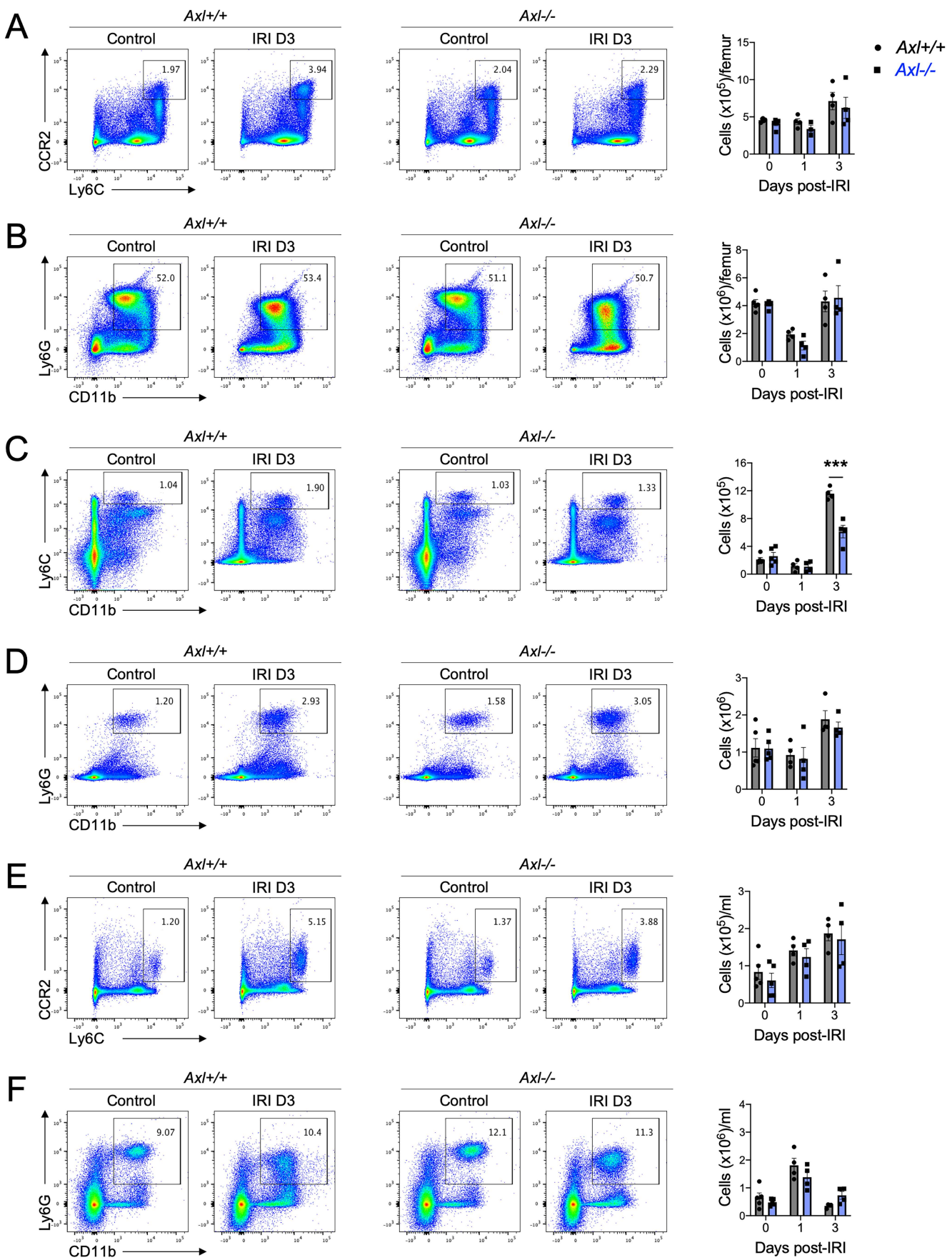


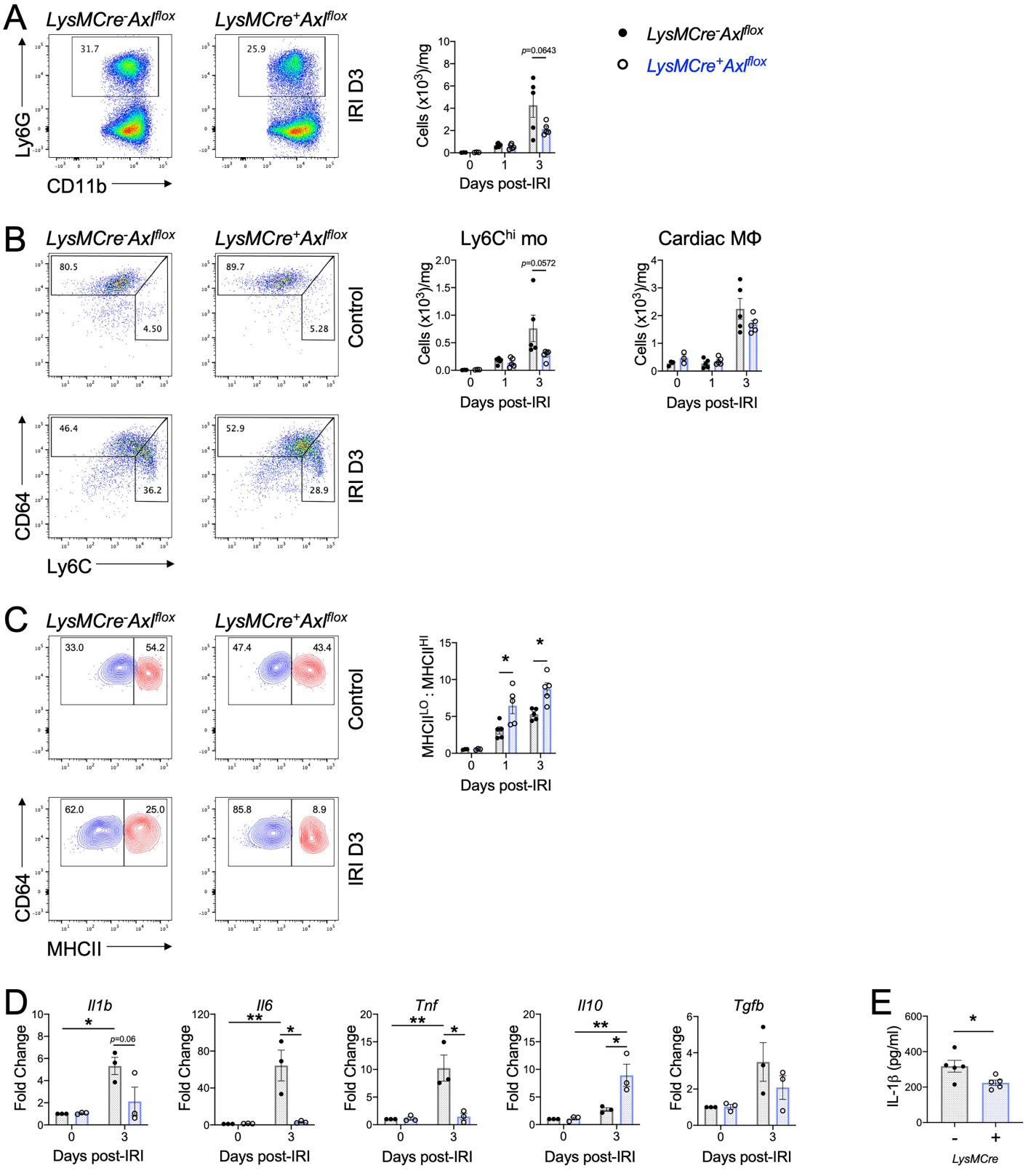
Supplemental Figure 3: AXL is expressed on human cardiac macrophages after myocardial infarction. **A** Clinical Characteristics of ischemic cardiomyopathy patients undergoing heart transplantation. Single cells were isolated from **B** left ventricular myocardium proximal to peri-infarct scar tissue (INF in panel A) or **C** fibrosis-free, remote tissue (RT in panel A) and cardiac macrophages were gated on live, single cells and identified as $CD14^{+}CD64^{+}HLA\text{-}DR^{hi}$. **D** Peripheral blood mononuclear phagocytes collected at the time of heart transplantation but prior to blood transfusion were gated on live, single cells and identified as $CD14^{+}CD64^{+}HLA\text{-}DR^{lo}$ and further distinguished by CCR2 expression.



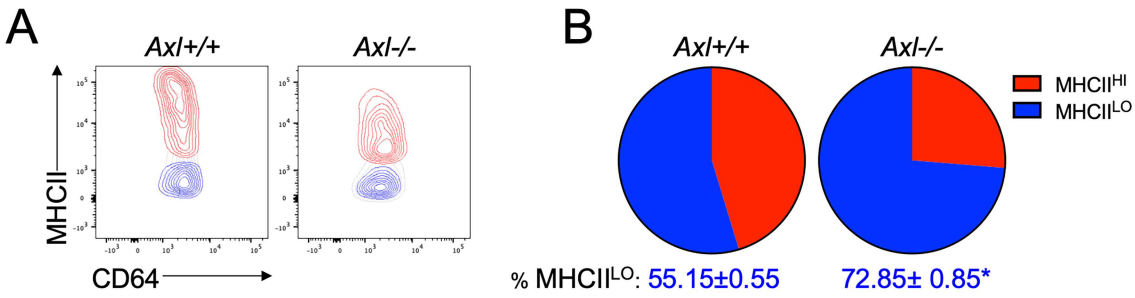
Supplemental Figure 4: Myeloid AXL worsens cardiac repair after myocardial ischemia-reperfused infarction (IRI). A C57BL/6J mice were lethally irradiated with 1000 rads from a cesium source before transplantation. A total of 5x10^6 bone marrow cells from *Axl+/+* or *Axl-/-* mice were injected into irradiated recipients by tail vein injection. After bone marrow transplantation, mice were maintained on acidified drinking water containing neomycin. Six weeks after transplantation, mice were subjected to IRI surgery. Representative triphenyltetrazolium chloride (TTC) stained heart sections 7 days after IRI in bone marrow chimera mice with percent infarct/left ventricle (LV), percent area-at-risk (AAR)/LV, and percent infarct/AAR. Data represent mean ± SEM. n=5-6 mice/group pooled from 2 independent experiments. *p<0.05, 2-tailed unpaired t test. **B** *Axl^{flox}* mice were crossed with mice expressing *LysM-Cre* to generate mice with specific deletion of *Axl* in myeloid cells (*LysMCre^{+}Axl^{flox}* mice). *LysMCre^{-}Axl^{flox}* littermates were used as controls. Representative TTC stained heart sections 7 days after IRI in female (♀) and male (♂) *Cre-flox* mice with percent infarct/LV, percent AAR/LV, and percent infarct/AAR. Representative infarct images and data for female mice is the same as shown in Figure 2D. Data represent mean ± SEM. n=3-6 mice/group pooled from 3 independent experiments. *p<0.05, 2-way ANOVA followed by Tukey's test.



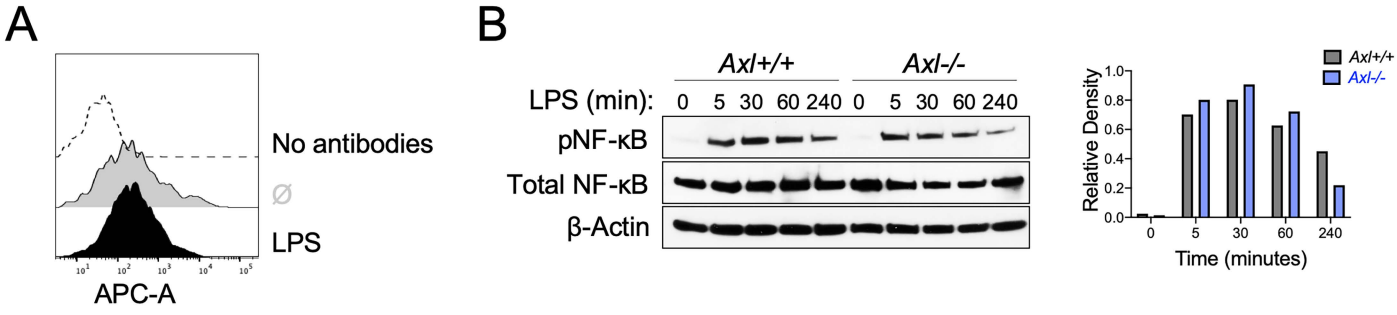
Supplemental Figure 5: Monocyte and neutrophil kinetics in bone marrow, spleen, and peripheral blood after ischemia-reperfused infarction (IRI). Total Ly6C^{hi} monocytes in **A** bone marrow, **C** spleen, and **E** peripheral blood before and after IRI. Total neutrophils in **B** bone marrow, **D** spleen, **F** peripheral blood before and after IRI. Data represent mean ± SEM. n=4-5 mice/group pooled from 2 independent experiments. ***p<0.001, 2-way ANOVA followed by Tukey's test.



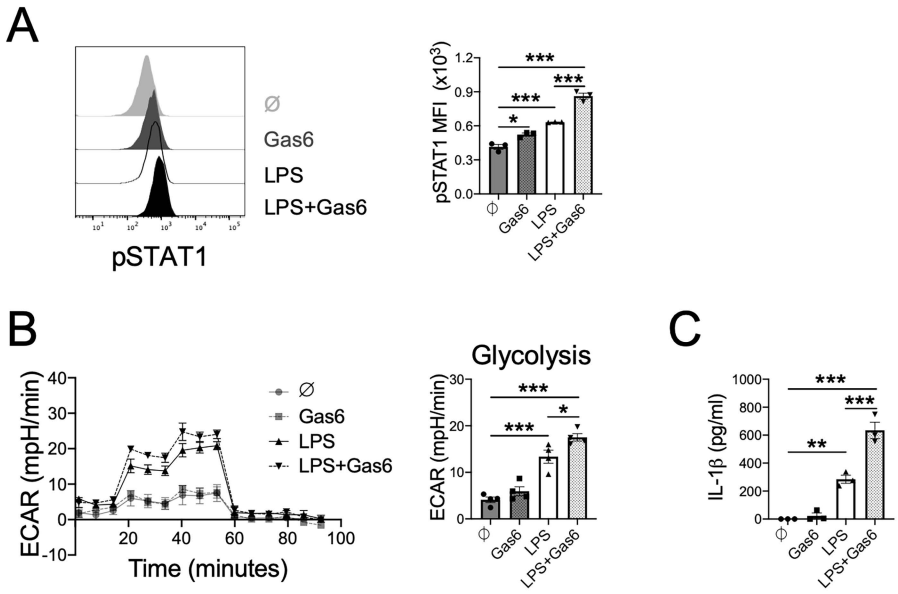
Supplemental Figure 6: Macrophage AXL promotes inflammatory responses after myocardial ischemia-reperfused infarction (IRI). *Axl*^{flox} mice were crossed with mice expressing *LysM-Cre* to generate mice with specific deletion of *Axl* in myeloid cells (*LysMCre*$^{+}$*Axl*^{flox} mice). *LysMCre*$^{-}$*Axl*^{flox} littermates were used as controls. **A** Total number of neutrophils or **B** Ly6C^{hi} monocytes and CD64^{+} macrophages (MΦ) within the infarcted myocardium as measured on the indicated days after IRI. **C** Ratio of MHCII^{LO} to MHCII^{HI} macrophages (MΦ) within the infarcted myocardium as measured on the days indicated after IRI. Data represent mean ± SEM. n=3-5 mice/group pooled from 2 independent experiments. *p<0.05, 2-way ANOVA followed by Tukey's test. **D** Gene expression of pro- and anti-inflammatory mediators in whole infarct extracts. Data represent mean ± SEM. n=3 mice/group pooled from 2 independent experiments. *p<0.05, **p<0.01, 2-way ANOVA followed by Tukey's test. **E** Serum levels of IL-1β as measured 3 days after IRI. Data represent mean ± SEM. n=5 mice/group pooled from 2 independent experiments. *p<0.05, 2-tailed unpaired t test.



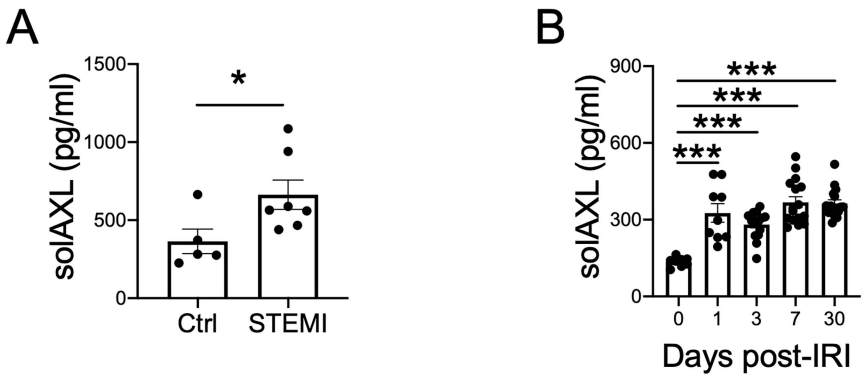
Supplemental Figure 7: AXL promotes inflammatory macrophage accumulation during peritonitis. A MHCII expression on thioglycolate-elicited peritoneal macrophages as measured by flow cytometry. **B** Ratio of MHCII^{HI} to MHCII^{LO} thioglycolate-elicited peritoneal macrophages. Data represent mean ± SEM and are representative of 3 independent experiments. n=3 mice/group. *p<0.05, 2-tailed unpaired t test.



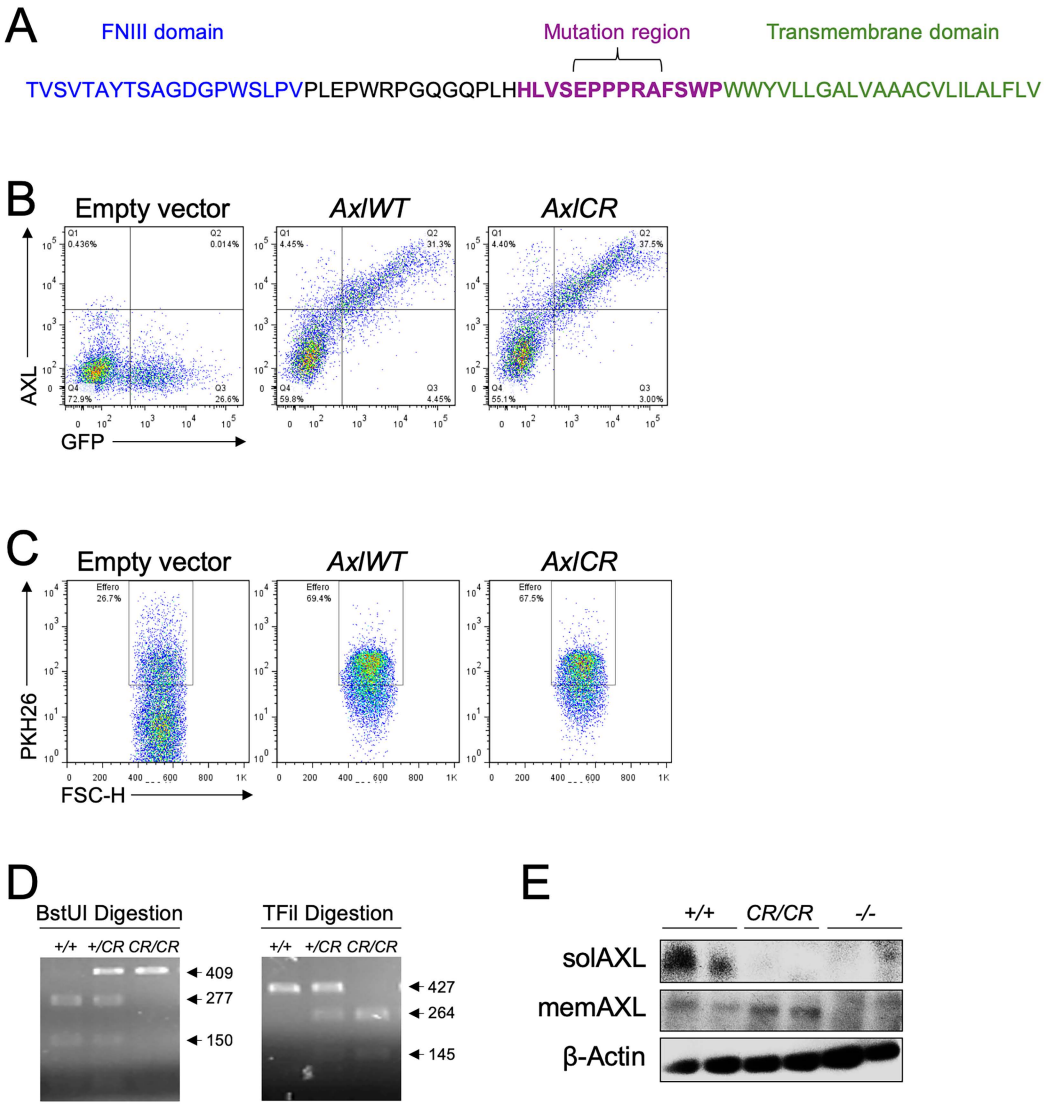
Supplemental Figure 8: AXL does not affect TLR4-induced NF-κB signaling in bone marrow-derived macrophages (BMDMs). A BMDMs were treated with lipopolysaccharide (LPS) for 60 minutes. BMDMs were fixed with 2% paraformaldehyde in PBS and the interaction between AXL and TLR4 was detected by flow cytometry using the Duolink Proximity Ligation Assay. **B** NF-κB phosphorylation in BMDMs treated with LPS. The relative density of phosphorylated to total NF-κB was measured by ImageJ. Data are representative of 2 independent experiments.



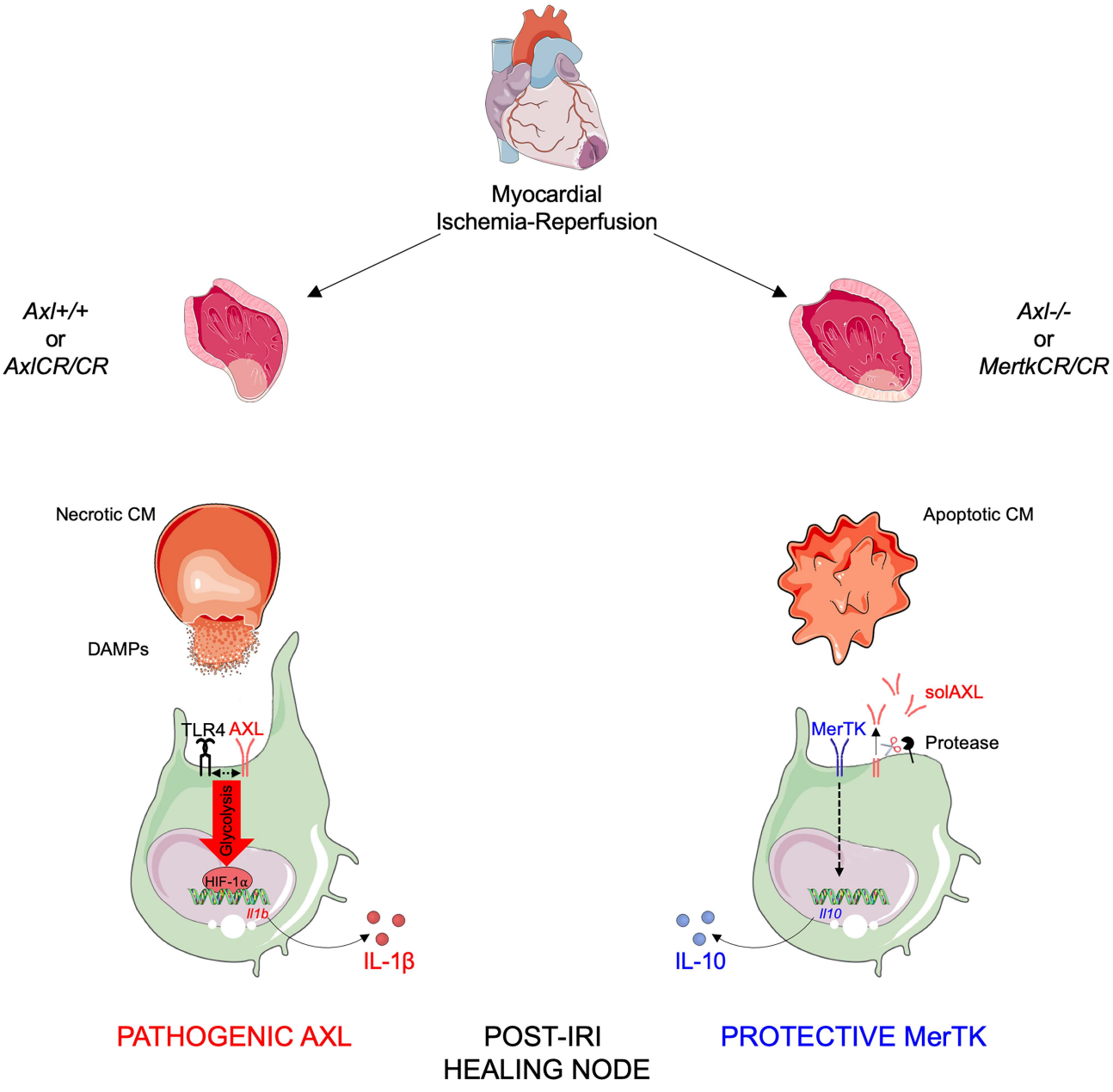
Supplemental Figure 9: Gas6-AXL signaling augments TLR4-induced glycolytic metabolism and proinflammatory responses in macrophages. A Stat1 phosphorylation in bone marrow-derived macrophages (BMDMs) treated with Growth arrest-specific 6 (Gas6), lipopolysaccharide (LPS), or both Gas6 and LPS for 60 minutes. Data represent mean ± SEM and are representative of 3 independent experiments. n=3 sets of cells/group. *p<0.05, ***p<0.001, 1-way ANOVA followed by Tukey's test. **B** Extracellular acidification rate (ECAR) with quantification of glycolysis in BMDMs treated with Gas6, LPS, or both Gas6 and LPS for 3 hours. Data represent mean ± SEM and are representative of 2 independent experiments. n=4 sets of cells/group. *p<0.05, ***p<0.001, 1-way ANOVA followed by Tukey's test. **C** IL-1β production by BMDMs primed with Gas6, LPS, or both Gas6 and LPS for 3 hours followed by activation with ATP for 30 minutes. Data represent mean ± SEM and are representative of 3 independent experiments. n=3 sets of cells/group. **p<0.01, ***p<0.001, 1-way ANOVA followed by Tukey's test.



Supplemental Figure 10: Soluble AXL (solAXL) levels are elevated after myocardial ischemia-reperfused infarction (IRI) in humans and mice. A Serum levels of solAXL in healthy human controls or in ST-segment elevation myocardial infarction (STEMI) patients within 24 hours of percutaneous intervention. Data represent mean ± SEM. n=5-7 patients/group. *p<0.05, 2-tailed unpaired t test. **B** Serum levels of solAXL in mice on days indicated after IRI. Data represent mean ± SEM. n=8-16 mice/group pooled from 3 or more independent experiments. ***p<0.001, 1-way ANOVA followed by Tukey's test.

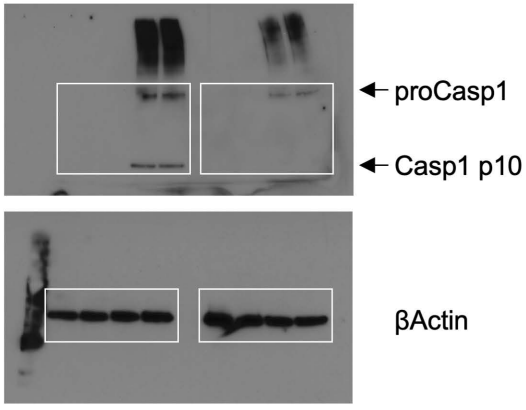


Supplemental Figure 11: Generation of AXL cleavage-resistant mice (*AxlCR/CR*). A Schematic showing region where 6 amino acids were specifically deleted within a 14 amino acid stalk region proximal to the transmembrane domain of AXL to generate a cleavage-resistant AXL protein. **B** HEK293 cells were transfected with indicated plasmids and analyzed for expression of cell surface AXL by flow cytometry. **C** HEK293 cells transfected with indicated plasmids were co-cultured with PKH26-labeled apoptotic splenocytes and efferocytosis was analyzed by flow cytometry. **D** Genotyping of *AxlCR/CR* mice using restriction enzyme digestion of PCR amplification product. The expected band size for uncut *AxlCR/*CR template with BstUI digestion is 409 bp, while the uncut wild-type AXL template with TFil digestion is 427 bp. **E** Bone marrow-derived macrophages (BMDMs) from wild-type (*Axl+/+),* *Axl*-deficient (*Axl-/-*), or AXL cleavage-resistant (*AxlCR/CR*) mice were assayed for membrane or soluble AXL (solAXL) by immunoblot after treatment with lipopolysaccharide.



Supplemental Figure 12: Working Model by which AXL promotes a switch to glycolytic metabolism and inflammatory cytokine production by macrophages to worsen ventricular remodeling and lead to heart failure after myocardial ischemia-reperfused infarction (IRI). Myocardial IRI causes reperfusion-associated cardiomyocyte (CM) death and release of damage associated molecular patterns (DAMP). Recognition of DAMPs by TLR4 induces downstream signaling cascades, which are augmented by AXL activation, promoting HIF-1α stabilization and a switch to glycolytic metabolism. This leads to secretion of proinflammatory IL-1β and culminates in adverse ventricular remodeling and progression to heart failure. In contrast to AXL, MerTK-dependent phagocytic clearance of apoptotic cardiomyocytes leads to cardioprotective IL-10 secretion and preservation of contractile function. Pathogenic AXL functions independently of cardioprotective MerTK to worsen cardiac repair, but like MerTK, is proteolytically cleaved to limit its function. Proteolytic cleavage of AXL results in loss of cell-surface AXL and release of soluble AXL (solAXL), impairing TLR4-mediated proinflammatory reprogramming of macrophages. The molecular mechanisms mediating cross-talk between TLR4 and AXL and potential links between MerTK and metabolic reprogramming of macrophages (dashed lines) will be an important area of future investigation. (*AxlCR/CR*, cleavage-resistant AXL, *MertkCR/CR*, cleavage-resistant MerTK)

Full unedited blot for Figure 4D



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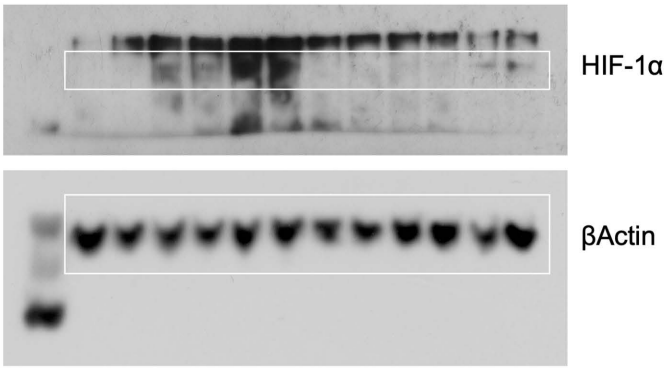

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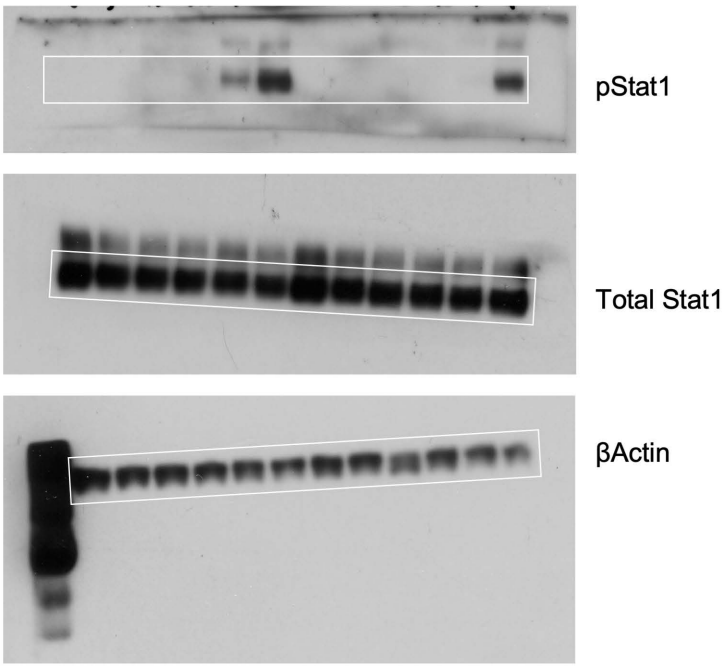

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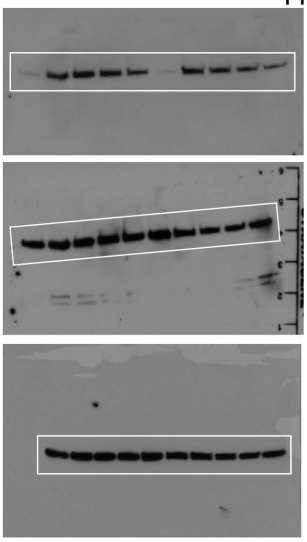
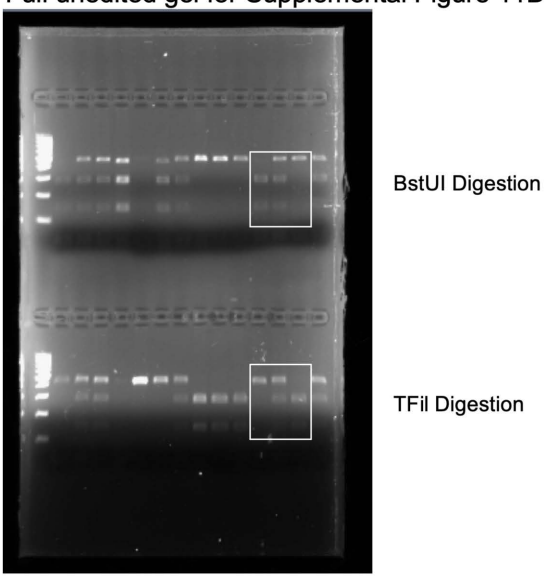


Full unedited gel for Supplemental Figure 11D



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