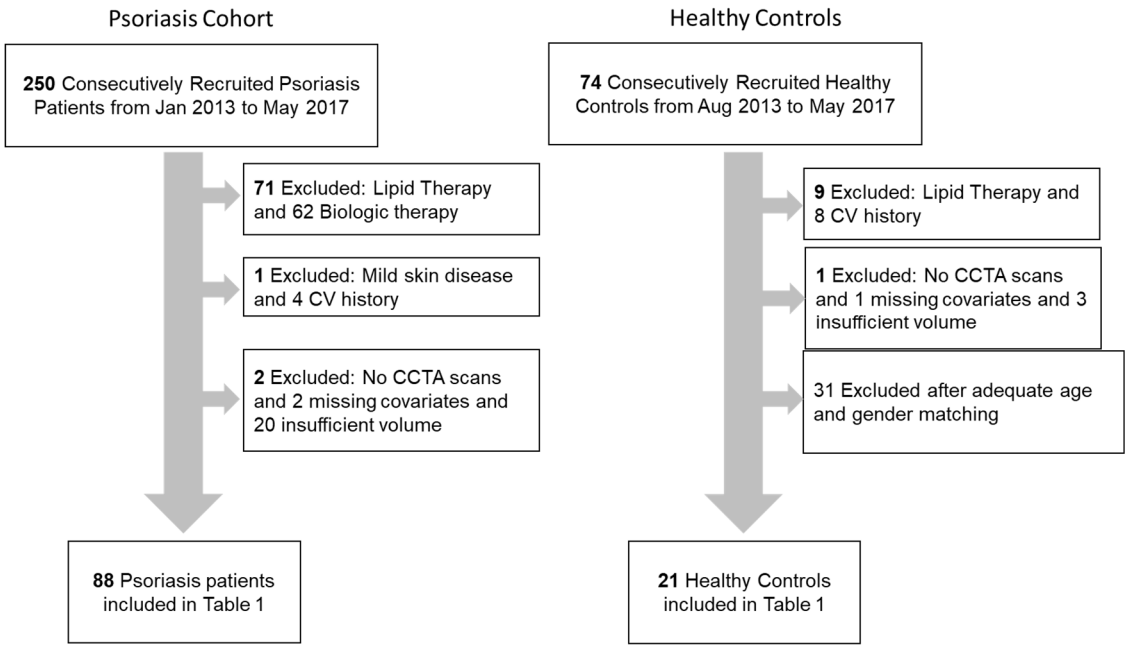
**SUPPLEMENTARY MATERIAL**

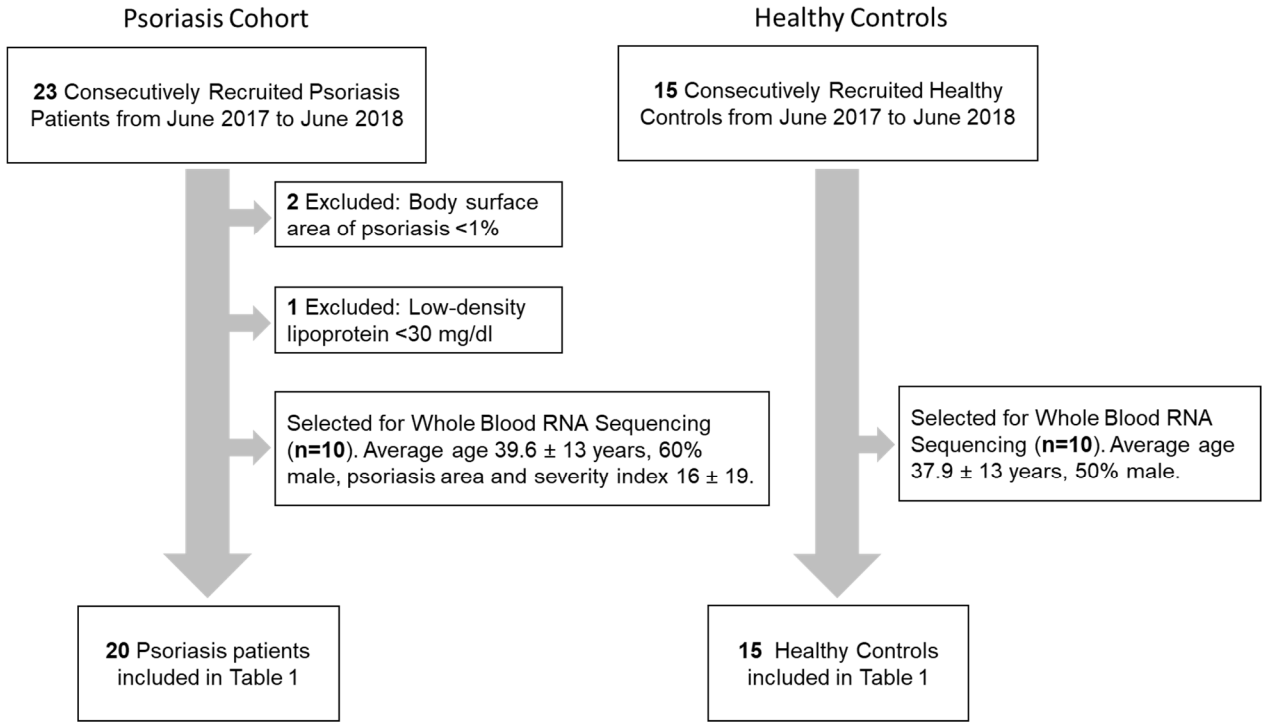
Supplementary Table 1. Correlation between PCSK9 and other pro-inflammatory protein expression in the NYU Langone Health cohort.

| Protein | Correlation Coefficient (*r*) | P-value |
|---|---|---|
| HsCRP | 0.31 | 0.11 |
| IL6 | 0.64 | <0.001 |
| IL17C | 0.35 | <0.05 |
| IL20 | 0.29 | 0.08 |
| KLK6 | 0.59 | <0.01 |
| CCL20 | 0.44 | <0.01 |
| E-Selectin | 0.47 | <0.01 |
| TNFR1 | 0.57 | <0.01 |
| IL8 | 0.45 | <0.01 |
| IL18 | 0.47 | <0.01 |
| IL7 | 0.45 | <0.01 |
| CXCL9 | 0.28 | 0.09 |
| IL1RA | 0.57 | <0.01 |
| IL12 | 0.30 | 0.07 |
| IL17A | 0.53 | <0.01 |
| IL24 | 0.44 | <0.01 |
| TNFα | 0.35 | <0.05 |

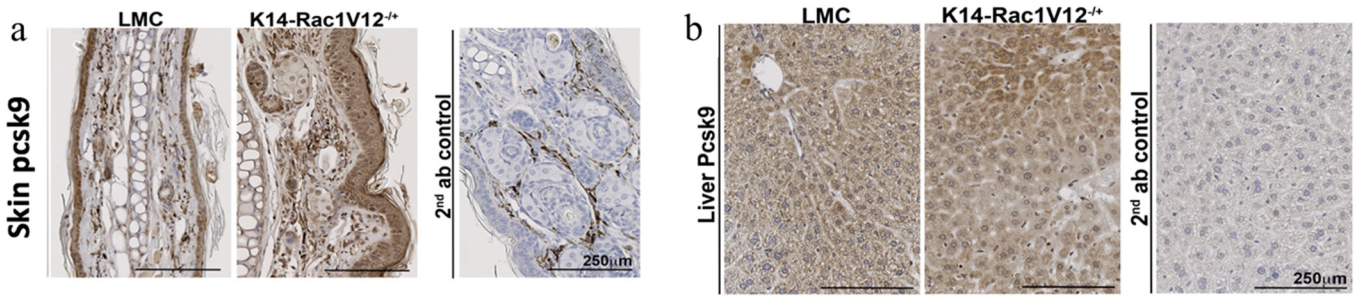
Correlation between serum protein and proprotein convertase subtilisin/kexin type 9 (PCSK9) levels. Hs-CRP, high sensitivity C-reactive protein; IL – Interleukin; KLK6, kallikrein related peptidase 6; TNFR1, tumor necrosis factor receptor 1.



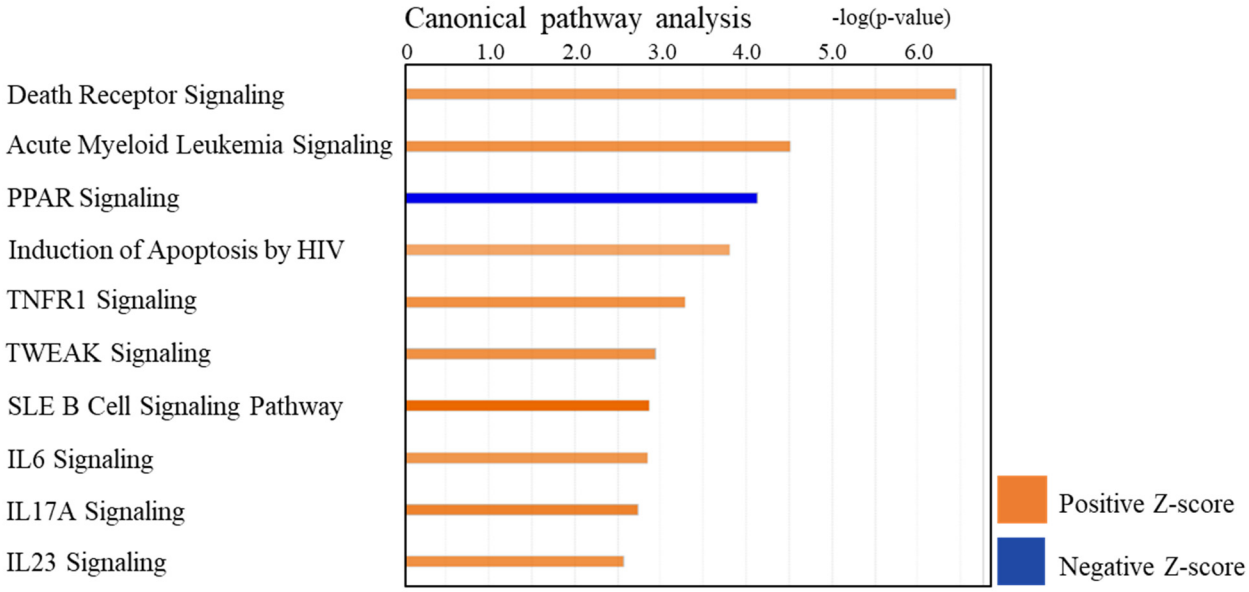

**Supplementary Figure 1. Patient recruitment scheme demonstrating inclusion and exclusion criteria in the National Institutes of Health psoriasis cohort.**




**Supplementary Figure 2. Patient recruitment scheme demonstrating inclusion and exclusion criteria in the NYU Langone Health psoriasis cohort.**




**Supplementary Figure 3: PCSK9 levels are increased in *K14-Rac1V12*$^{-/+}$ psoriatic mice and human skin.** (a) PCSK9 protein expression in psoriatic skin of *K14-Rac1V12*$^{-/+}$ mice and their LMC by histology which includes appropriate secondary antibody. (b) Human biopsy samples subjected to PCSK9 histological staining. LMC, littemate controls; PCSK9, Proprotein convertase subtilisin/kexin type 9.




**Supplementary Figure 4**. **Inflammation in psoriasis associates with circulating PCSK9**. Ingenuity Pathway Analysis of the top 10 upregulated canonical pathways (using an absolute Z-score cut off > 1.5) assessing the association between circulating PCSK9 and blood transcripts in patients with psoriasis (n=10). IL, interleukin; PCSK9, Proprotein convertase subtilisin/kexin type 9; PPAR, Peroxisome proliferator-activated receptor; SLE, Systemic lupus erythematosus.

## Material and Methods

### Study/Ethical Approval – National Institutes of Health

The patient recruitment scheme is displayed in Figure S1 for the National Institutes of Health (NIH) cohort. More detailed information: Patients with plaque psoriasis between the ages of 18-70 were included in the study. Patients were excluded if they were on any systemic/biologic psoriasis treatment or on any lipid therapy at baseline or had mild skin disease. Patients were excluded if they had any comorbid condition known to promote cardiovascular disease or systemic inflammation, such as known cardiovascular disease, uncontrolled hypertension, internal malignancy within 5 years, human immunodeficiency virus, active infection within the past 72 hours of baseline, or major surgery within 3 months. Healthy volunteers were excluded if they were pregnant, breastfeeding or had solid organ/hematologic malignancy, active infection within 3 months, collagen vascular disease, clinical diagnosis of diabetes or cardiovascular disease, liver function tests greater than three times the upper limit of normal, estimated glomerular filtration rate<60 ml/min or body mass index >40 $kg/m^2$.

### Covariates – National Institutes of Health

Relevant medical history including cardiovascular risk factors, hypertension history, diabetes, hyperlipidemia, smoking, alcohol, age, and sex were collected from all study participants enrolled in our protocol. All patients underwent clinical, laboratory, and imaging evaluation. A dedicated study healthcare professional confirmed the onset, duration of psoriasis, and assessed psoriasis severity using the psoriasis area severity index (PASI) score. Psoriasis area severity index score combines the severity of lesions and the area affected into a single score, considering erythema, induration and desquamation within each lesion. All patients underwent blood draws to assess lipid levels including total, HDL, and LDL cholesterol, glucose, insulin, and high-

sensitivity C-reactive protein levels. Patients were asked to complete survey-based questionnaires regarding smoking, previous cardiovascular disease, family history of cardiovascular disease, and previous established diagnoses of hypertension and diabetes. Patient responses were then investigated and confirmed by interview with the physician. Cardiovascular disease included acute coronary syndrome comprising both MI and unstable angina pectoris, angina pectoris, cerebrovascular event, transient ischemic attack, peripheral vascular disease and revascularization procedures that comprised of coronary artery bypass grafting and percutaneous interventional procedures. Diabetes and hypertension were defined either by an established diagnosis or by use of glucose lowering and blood pressure lowering drugs, respectively.

**Study Criteria – New York University Langone Health**

Patients with a diagnosis of psoriasis were recruited from the general dermatology, phototherapy, psoriasis and psoriatic arthritis specialty clinics at New York University Langone Health between June 2017 and June 2018. Study recruitment flow is outlined in Figure S2. Psoriasis patients age 18 - 90 were included if they had a confirmed diagnosis of plaque psoriasis by a board-certified Dermatologist and active psoriatic disease (≥1% body surface area (BSA) of psoriasis or psoriatic arthritis ≥1 swollen/tender joint confirmed by a board-certified Rheumatologist. Exclusion criteria included a recent (~ 1 month) change in biologic, oral or light therapy for psoriasis. To accurately characterize the vasculature, participants were excluded if they took lipid-lowering therapy within the past 6 months, aspirin with the past two weeks and non-steroidal anti-inflammatory therapy <48 hours prior to enrollment. Other exclusion criteria included a history of clinical cardiovascular disease, other autoimmune diseases aside from psoriasis or psoriatic arthritis, active infection within the past month, non-dermatologic malignancy within 10 years, chronic kidney disease defined as creatinine clearance < 30 ml/min, active pregnancy or history

of intravenous drug use. In order to limit significant confounding effects on the endothelium, those with poorly controlled hypertension defined as a systolic blood pressure >160mmHg at the time of study enrollment, requiring treatment with two anti-hypertensive medications and a significant burden of diabetes defined as a hemoglobin A1c >7.0% or requiring insulin therapy were also excluded.

**Control Subject Inclusion/Exclusion Criteria**

In the NHLBI cohort, healthy volunteers recruited through the community were prospectively recruited as part of the healthy volunteer arm of an ongoing protocol studying inflammatory characterization of diabetes, coronary disease and healthy volunteers (NCT01934660). The strategy was to recruit these controls matching by age (within five years) and gender to our psoriasis patients in a prospective fashion in blocks of five patients. For eligibility, exclusions included individuals who were pregnant, breastfeeding, or had solid organ or hematologic malignancy (excluding nonmelanoma skin cancer), active infection within 3 months requiring antibiotics, collagen vascular diseases, clinical diagnosis of diabetes or cardiovascular disease, liver function tests greater than three times the upper limit of normal, estimated glomerular filtration rate40 kg/m2 . Diabetes was defined as fasting glucose of ≥ 125 mg/dL, hemoglobin A1C > 6.5%, or use of diabetic medication. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or use of anti-hypertensive medication. Hyperlipidemia was defined as total cholesterol >200 mg/dL, LDL-C ≥ 160 mg/dL, or HDL-C ≤ 40 mg/dL.

In the NYU, controls were recruited using similar criteria as the NHLBI. Control subjects from the community were recruited sequentially between June 2017 through June 2018. As psoriasis

participant recruitment accrued throughout the year, age and sex of the psoriasis participants were averaged and targeted recruitment used to find appropriately matched controls.

## Study Protocol

Participants presented to the New York University Clinical Translational Science Institute outpatient research center. Participants were asked to fast >4 hours before arrival. A medical history was obtained, physical exam performed by a licensed physician and then participants underwent endothelial harvesting and blood sample collection. Clinical data including age, sex, self-reported medical history (confirmed through review of the New York University Langone Health medical record and ICD-9 coding) were collected at the time of endothelial harvesting. Resting blood pressure before and after endothelial biopsy were obtained using well-established protocols.(Kurtz et al., 2005) Because of potential patient anxiety resulting in artificially elevated blood pressures pre-endothelial harvesting, the lowest recorded blood pressure was noted. Psoriasis diagnosis and severity were confirmed and quantified using BSA by a board-certified Dermatologist and psoriatic arthritis severity using the Classification Criteria for Psoriatic Arthritis (CASPAR) by a board certified Rheumatologist. Psoriasis area and severity index (PASI) was calculated at the time of endothelial harvesting.

## Vascular Endothelial Cell Harvesting

As previously described and published (Jelic et al., 2010) a 20-gauge angiocatheter was inserted into the brachial forearm vein by a trained nurse using sterile protocol. Three J – shaped endovascular guidewires (Teleflex Inc., Reading Pa) were sequentially advanced into the brachial vein up to 10cm. The guidewire tips were removed, washed in endothelial dissociation buffer solution and kept at $4^0$C until endothelial cell isolation occurred.

**Laboratory and Protein Measurements**

Blood collections happened immediately after vascular endothelial cell harvesting. Lipid profiles and high-sensitivity C-reactive protein were performed in the New York University clinical laboratory (Abbott Architect System). As previously described and reported, aliquots of stored samples were analyzed using the OLINK Proseek multiplex assay including assessment for IL17A, IL6, TNFα and proprotein convertase subtilisin/kexin 9.(Kim et al., 2018) Briefly, Oligonucleotide-labeled antibody probes with proximity extension assay technology bind to their designed target. These antibody pairs attach to their designed target to create a new DNA amplicon. The amplicons were quantified using a Fluidigm BioMark HD real-time PCR platform. Data is reported as Normalized Protein eXpression (NPX), a unit of measurement based on a Log2 scale.

**Murine Skin Analysis**

Severity of the psoriasis-like skin lesions was graded through a systematic assessment of skin inflammation to provide correlative data on skin severity and systemic disease. Severity of psoriasis phenotype was based on visible symptoms and determined on a 0–5 scale as:

0 Animal with K14-Rac1V12-/+ genotype but failed to express phenotype

1 Animal with skin lesions on ears or muzzles or tail

2 Animal with skin lesions on ears and/or muzzle and/or tail (2 symptoms must be present)

3 Animal with skin lesions on ears/muzzle/tail and eyes and one of the following: back or head skin or joint swelling

4 Animal with all of the above symptoms

5 Animal from scale 4 with symptoms of fatigue, pain score 3 or lethargy

**Endothelial Harvesting and Isolation**

As previously described,(Emin et al., 2016) brachial vein endothelial cells were collected by centrifugation at $4^0$ C 150g for 6 minutes. Half of this cell pellet was placed in RBC lysis buffer, incubated at $4^0$C for 5 minutes and then fixed with 10% formaldehyde. Fixed cells were plated on slides (Sigma, St. Louis, MO), dried at $37^0$C and stored at -$80^0$C for future analysis. The second half of this cell pellet was suspended in isolation buffer, incubated with biotinylated mouse anti-human monoclonal antibody directed against CD146 (1:200; Millipore MAB16985B) at $4^0$C, then underwent positive extraction with Streptavidin FlowComp Dynabeads (Invitrogen). Isolated endothelial cells were frozen at –$80^0$C until mRNA extraction occurred.

**Endothelial Transcript Analysis**

Extracted endothelial cells underwent mRNA extraction using RNAqueous isolation kit (Invitrogen, Carlsbad CA). Messenger RNA was converted to cDNA using qSCRIPT XLT cDNA SuperMix (Quantbio, Beverly, MA). Preamplification of cDNA occurred using PerfeCta PreAmp SuperMix (Quantabio) all using manufacturer protocols. TaqMan (Life Technologies) primers were used on an Applied Biosystems 7500 Fast Real-Time PCR System (Foster City, CA). Preamplified cDNA (9 uL) was combined with 10 uL of PerfeCta qPCR ToughMix (Quantabio), 1 uL of TaqMan gene with all samples performed in duplicate. Any transcript with a cycle count >34 was considered to be 0 expression. To ensure reproducibility across analysis, results are generated normalized to human acidic ribosomal protein (hARP) for each sample and

gene.(Guttman-Yassky et al., 2008) Samples with an inadequate housekeeping gene expression of either hARP, or beta-actin were excluded from the analysis.

**Coronary Computed Tomography Angiography Image Acquisition**

All patients underwent coronary computed tomography angiography (CCTA) on the same day as blood draw, using the same CT scanner (320-detector row Aquilion ONE ViSION, Toshiba, Japan). Guidelines implemented by the NIH Radiation Exposure Committee were followed. Scans were performed with retrospective gating between 75kV-120kV, tube current of 750-850 mA, with a gantry rotation time of ≤420ms. Image acquisition characteristics included slice thickness of 3-mm and pitch of 0.2-0.4. Images were reconstructed using standard filtered back projection. CAC was evaluated as a part of normal workflow by an experienced cardiologist using semiautomatic software (SmartScore, GE Healthcare). CAC (mean total Agatston scores) was measured using electron beam tomography from 40 continuous 3-mm thick computed tomograms (Imatron, San Francisco, CA). A single, experienced radiological technologist performed scoring, blinded to clinical and laboratory data, using customized software (Imatron). Natural log-transformation of CAC scores, (ln[CAC+1]), were performed to account for the high percentage of CAC scores of 0 in all groups.

**Unbiased RNA Blood Transcriptomic Sequencing**

A subset of psoriasis patients (Figure S2) underwent blood RNA sequencing (10 psoriasis/10 controls, GEO accession number GSE147339. Peripheral blood samples were collected in PAXgene Blood RNA tubes (PreAnalytiX, Qiagen/BD) using manufacture approved protocols, stored at -20$^0$C and then subsequently -80$^0$C until use. Automated RNA extraction was accomplished using a QIAsymphony PAXgene Blood RNA Kit (PreAnalytiX, Qiagen/BD) and

according to manufacture recommended protocols. Prior to RNA sequencing, yield, quantity and quality of the RNA was assessed using a NanoDrop 8000 (Thermo Fisher Scientific, Waltham, MA) and Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). RNA sequencing libraries were generated with the Illumina TruSeq (Sand Diego, CA) stranded mRNA sample kit according to standard Illumina protocol. 200ng total RNA in 50ul was used as starting input concentration per sample. Samples underwent 12 cycles of amplification. Completed libraries were quantitated, normalized, and pooled. Pooled libraries were run on 2 lanes of single read 50 on the Illumina Hiseq 4000 sequencer.

Sequencing reads were mapped to the human reference genome (GRCh37/hg19) using the STAR aligner (v2.5.0c).(Dobin et al., 2013) Alignments were guided by a Gene Transfer Format file (Ensemble GTF version GRCh37.70). The mean read insert sizes and their standard deviations were calculated using Picard tools (v.1.126) (http://broadinstitute.github.io/picard). The read count tables were generated using HTSeq (v0.6.0)(Anders et al., 2015), normalized based on their library size factors using DESeq (v3.7)(Anders and Huber, 2010), and differential expression analysis was performed. The Read Per Million (RPM) normalized BigWig files were generated using BEDTools (v2.17.0)(Quinlan and Hall, 2010) and bedGraphToBigWig tool (v4). Pathway analysis and Gene Set Enrichment Analysis (GSEA) was performed using ClusterProfiler R package (v3.6.0).(Yu et al., 2012) Normalized count values of the genes from the blood transcriptome analysis were generated and the correlation between genes (at a base mean cut off of >30) and protein levels of proprotein convertase subtilisin/kexin 9 were assessed in patients with psoriasis (n=10). All downstream statistical analyses and generating plots were performed in R environment (v3.1.1) (http://www.r-project.org/). To evaluate pathways and differential gene expression a p-value $< 0.05$ was used to determine statistical significance. Genes which were

significantly correlated with PCSK9 were uploaded to Ingenuity Pathway Analysis (Qiagen Bioinformatics, Redwood City, CA) which was used to discover differentially expressed canonical, disease, and upstream pathways.