Supplementary Materials and Methods

Mice

The wild type mice were from the Charles River Laboratories. The *Glut1* floxed mice (*Glut1*$^{fl/fl}$) mice in C57/BL6 background were obtained from Dr. Abel's laboratory (University of Iowa). We generated myeloid cell-specific *Glut1* knockout (*LysM-Cre-Glut1*$^{fl/fl}$) mice by crossing *Glut1* floxed mice (*Glut1*$^{fl/fl}$) with LysM-Cre mice in which Cre recombinase is expressed in macrophages. *LysM-Cre-Glut1*$^{fl/fl}$ and the *Glut1*$^{fl/fl}$ mice were genotyped using standard PCR of tail DNA. The *Aim2* deficient mice (*Aim2*$^{-/-}$) in C57/BL6 background were obtained from Jackson Laboratory. The *Nlrp3* knockout mice (*Nlrp3*$^{-/-}$) were obtained from Dr. Richard A. Flavell (Yale University, New Haven, CT) which were backcrossed 10 times against C57BL/6 (43). Upon receipt, mice were handled under identical husbandry conditions and fed certified commercial feed. Body weights were measured daily and mice were humanely euthanized if they lost more than 15% of their starting body weight. All mouse experimental protocols were approved by the Institutional Animal Care and Use Committee of Weill Cornell Medical College (protocol #: 2014-0059 and 2014-0052; Weill Cornell Medical College, New York, New York, USA).

Animal studies

Primary bleomycin instillation: Mice were exposed to PBS or bleomycin (0.01 mg/mouse) via oropharyngeal aspiration. *S. pneumoniae* infection: All mice were anesthetized with isoflurane (5% for induction and 2% for maintenance) prior to intranasal instillation with 1x10^6 CFU of *S. pneumoniae* (ATCC 6303) (50μL volume in PBS). For the *S. pneumoniae* only, the lungs were studied on day 3, whereas for bleomycin only, the lungs were studied on day 17.

Glucose uptake assay

After *S. pneumonia* infection, ^{18}F-FDG was administered intravenously via the tail vein. ^{18}F-FDG injection and PET/CT imaging were performed under 1.5% isoflurane general anesthesia. PET/CT imaging was performed for 20 minutes (10 minutes per bed) using the Siemens Inveon system at CBIC (Citygroup Biomedical Imaging Center, Weill Cornell Medical Center), follow by a CT scan. PET images were corrected for random and scatter coincidence events and reconstructed with the ordered-subsets expectation-maximization algorithm using 16 subsets and 2 iterations. No attenuation correction was applied. SUVs were calculated according to the formula (SUV = a / [A/W]), where a represents the activity concentration in the organ region of interest measured using PET images (Bq/ml), A represents the injected activity (Bq), and W represents the mouse body weight in grams.

Isolation and Culture of Bone Marrow-Derived Macrophages

WT and *Nlrp3*$^{-/-}$ bone marrow cells (BMCs) were prepared from the femurs and tibias of mice as previously described (19, 55). Briefly, bone marrow cells were collected from femur and tibia on day 0 and cultured with 30% L929 media containing DMEM, 10% FBS, and 1X antibiotic/antimycotic solution (catalog # 15240062; ThermoFisher Scientific, Carlsbad CA). On Day 3, media was removed, and cells were cultured in 25% L929 media containing DMEM, 10% FBS, and 1X antibiotic/antimyotic solution. On day 7, macrophages were harvested and replated with 20% L929 media.

Reagents

Bleomycin (CAS 9041-93-4, Cayman Chemical), 2DG (D3875, Sigma-Aldrich), phloretin (CAS 60-82-2, Cayman Chemical), LPS (tlrl-3pelps, Invivogen), poly (dA:dT) (P0883, Sigma).

Transfection of *Glut1* siRNA

Glut1 small interfering RNA (siRNA) (Flexitube GeneSolution siRNA; QIAGEN, Valencia, CA) (15 nmol/sequence) was complexed with GenMute siRNA transfection reagent (SignaGen Laboratories, Ijamsville, MD) for 15 minutes before being added to macrophage cultures. *Glut1* siRNA-transfected cells were cultured for 24 hours before LPS and/or poly (dA:dT) stimulation. *Glut1* silencing was confirmed by Western blot analysis.

Immunoblot Analysis

Immunoblotting was performed as previously described (22). Anti-β-actin (4967), -GLUT1 (12939), –AIM2 (13095) antibodies were obtained from Cell Signaling (Danvers, MA). Anti-GLUT1 (ab40084), -collagen type 1 (ab21286) antibodies were from Abcam (Cambridge, MA). Anti-IL-1β (AF-401-NA) was from R&D Systems (Minneapolis, MN).

Assessment of Fibrosis

Lung tissues were formalin fixed and H&E stained by the Research Pathology Laboratory at Weill Cornell Medical Center. Fibrosis was evaluated histologically using Masson trichrome stains and biochemically using Sircol collagen assay kit (S1000, Biocolor, County Antrim, UK).

Immunohistochemistry

Paraffin-embedded murine lung tissue sections went through antigen retrieval using target retrieval buffer (S1699, Dako). Antibodies included GLUT1 (ab40084, Abcam) and AIM2 (ab93015, Abcam). Secondary antibodies included a biotinylated goat anti-mouse antibody (PK-6102, Vector Laboratories Inc.) and a biotinylated goat anti-rabbit antibody (PK-6101, Vector Laboratories Inc.). Slides were developed using Vector NovoRed (SK-4800, Vector Laboratories Inc.), and counterstained with Gill's hematoxylin (GHS33Z, Sigma-Aldrich).

Glycolytic Function Assay

Primary murine cells were plated on XF96 cell culture microplates (101085-004, Seahorse Bioscience). ECAR as parameters of glycolytic flux, was measured on a Seahorse XF96 bioanalyzer, using the XF Glycolysis Stress Test kit according to the manufacturer's instructions (102194-100, Seahorse Bioscience).

ASC Speck Formation

BMDMs transfected with non-target siRNA (control siRNA) or siRNA for *Glut1* and treated with vehicle or phloretin were seeded on chamber slides. After stimulation, cells were fixed with 4% paraformaldehyde and then incubated with Anti-ASC antibody (AL177, Adipogen) for 16 h followed by DAPI (P36962, ThermoFisher Scientific) staining as described previously (44). ASC specks were analyzed by Zeiss LSM880 laser-scanning confocal microscope and quantified by using ImageJ software. The graph represents the quantification of cells with specks in five distinct areas.

Cytokine analysis

Lung tissues from WT, *LysM-Cre-Glut1*$^{fl/fl}$and *Aim2*$^{-/-}$ mice and supernatants from BMDMs were measured for mouse IL-1β (BMS6002TEN, Invitrogen) and mouse IL-18 (BMS618-3, Invitrogen) according to the manufacturer's instructions.