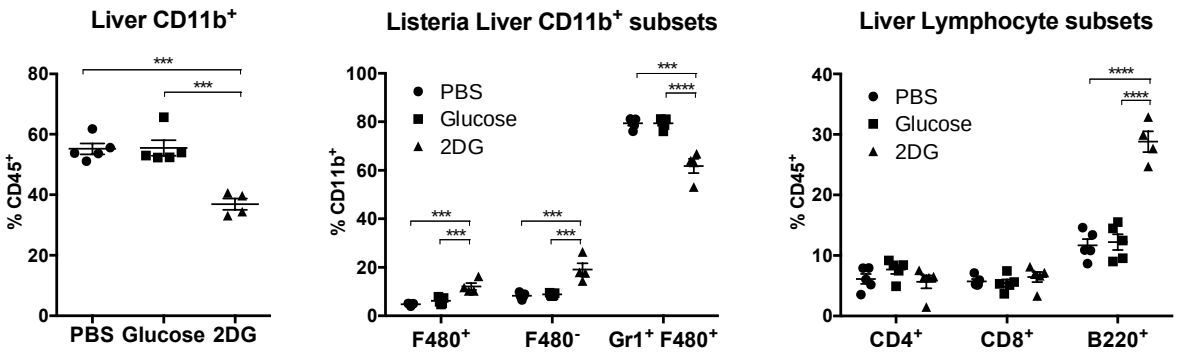

Figure S1. The effect of glucose caloric supplementation or inhibition of glucose utilization on hepatic immune cell infiltration during *L. monocytogenes* infection, Related to Figure 1

Flow cytometry analysis of $CD45^+$ cells within the liver 4 days after *L. monocytogenes* infection and treatment with PBS, glucose, or 2DG.

Data are represented as mean ± SEM. ***p<0.001, ****p<0.0001.

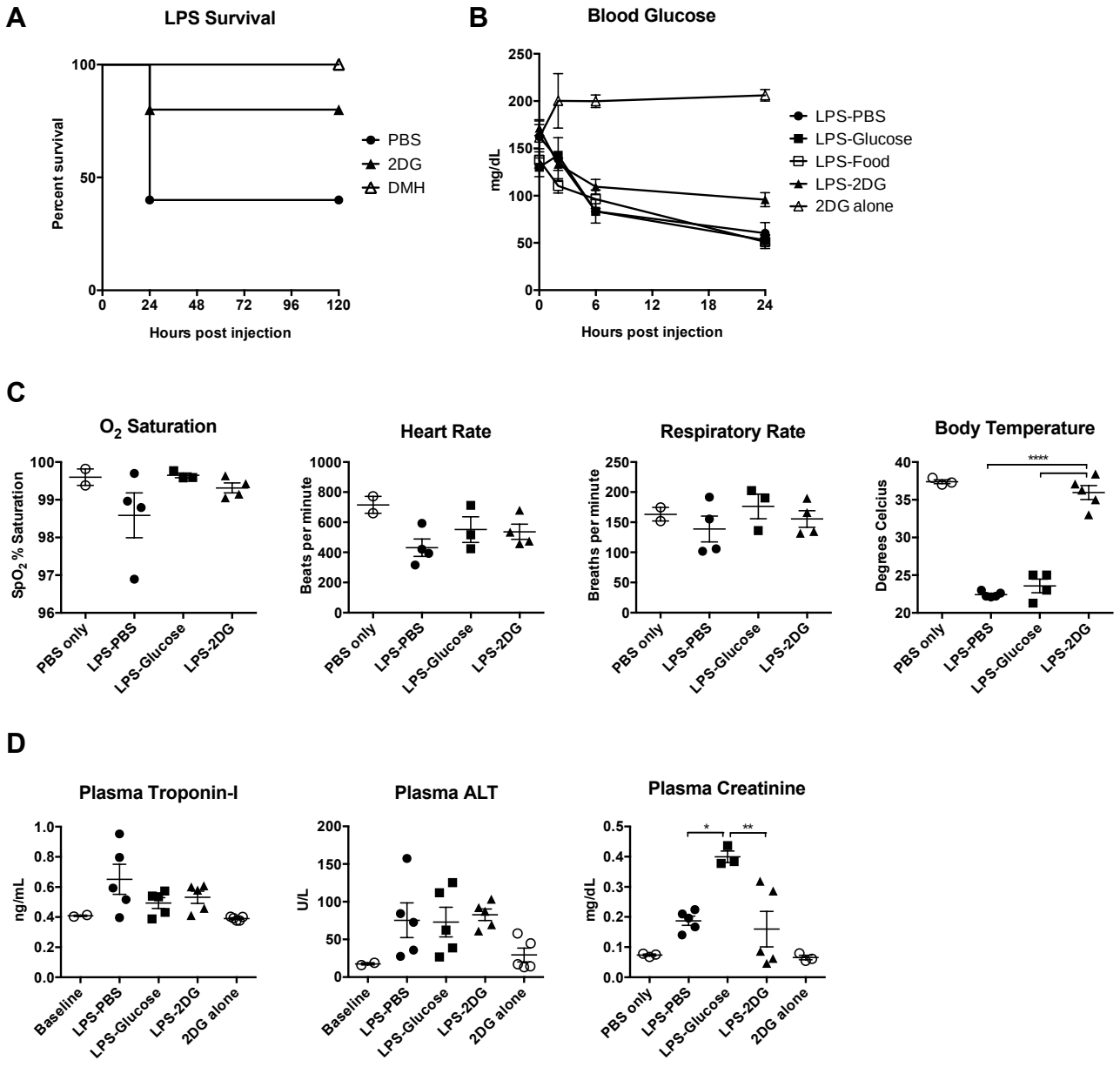

Figure S2. Systemic effects of glucose caloric supplementation or inhibition of glucose utilization during LPS sepsis, **Related to Figure 2**

(A) Mice were given 15 mg/kg IP LPS, then treated with PBS, 5 mg 2DG, 50 mg/kg D-mannoheptulose (DMH) given IP twice a day initiated one hour after LPS administration. n=5/group.

(B) Blood glucose at baseline, 2, 6 and 24 hours after 15 mg/kg IP LPS with PO gavage of PBS vehicle (LPS-PBS), glucose (LPS-Glucose), or Abbott Promote (LPS-Food) BID; or with IP 2DG (LPS-2DG). Blood glucose of mice treated with only 2DG IP are also shown.

(C-D) Mice were given 15 mg/kg IP LPS, then treated with IP PBS, glucose, or 2DG given IP.

(C) O_2 saturation, respiratory rate, heart rate and body temperature 24 hours after LPS.

(D) Plasma troponin-I, ALT, and creatinine levels measured at 24 hours after LPS.

Data are represented as mean ± SEM. *p<0.05, **p<0.01, ****p<0.0001.

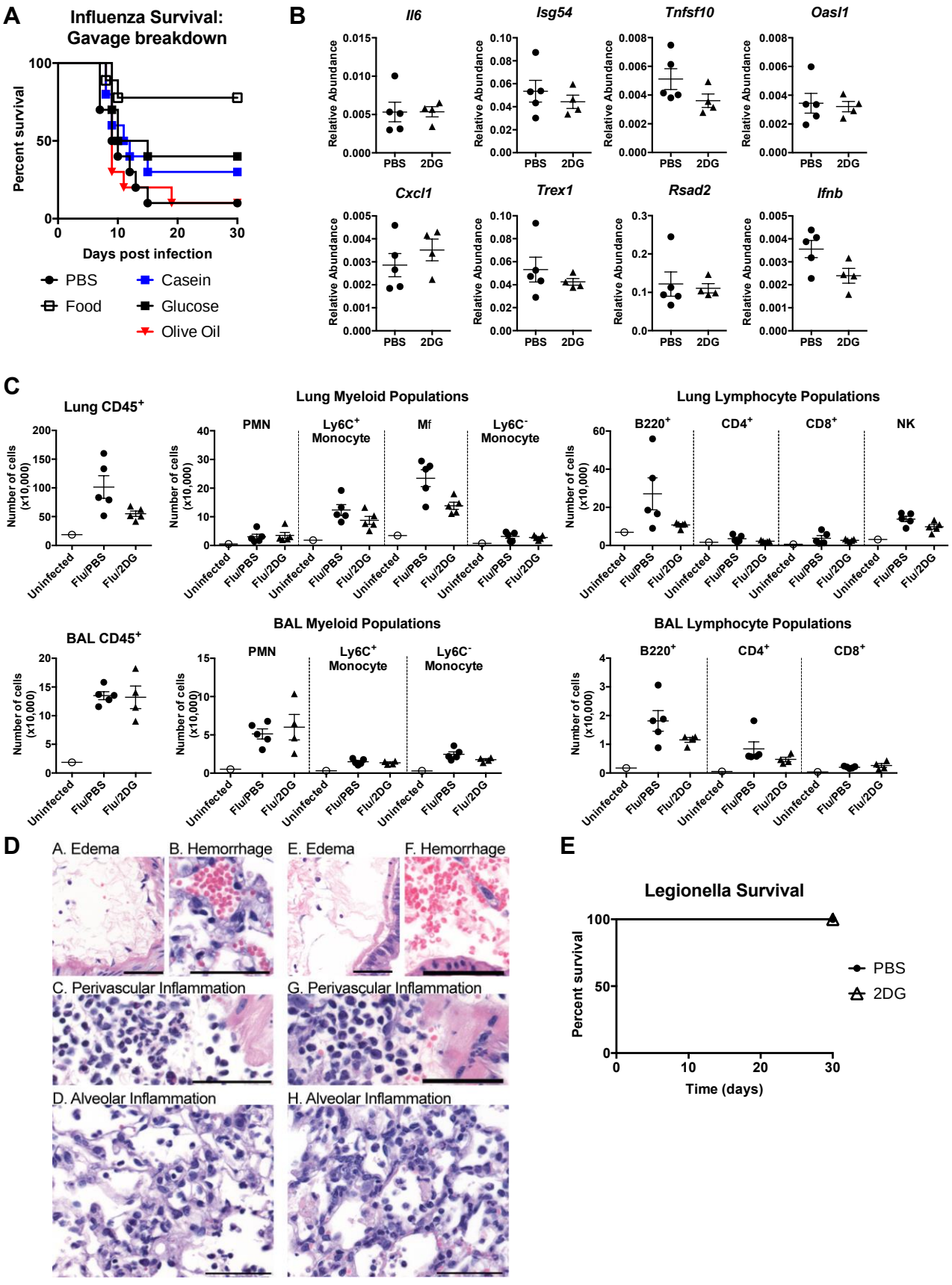

Figure S3. The effect of caloric supplementation or inhibition of glucose utilization on survival and lung inflammation after influenza virus infection, Related to Figure 3.

(A) Survival after infection with 800 PFU of influenza virus. Mice were gavaged with Abbott Promote (Food), casein, olive oil, or PBS vehicle. Figure 3B and 3C are a subset of Figure S3A, separated for clarity (the same PBS-treated and food-treated groups are shown).
(B) mRNA expression of whole lung tissue at day 6 after 375 PFU of influenza virus.
(C) Flow cytometric analysis of lung and BAL on day 6 after 700 PFU of influenza virus.
(D) H&E staining of lung tissue 6 days after influenza virus infection. Letters correspond to areas of the lung annotated in Figure 3. Scale bar = 50 μm.
(E) Survival after infection with $1x10^6$ *L. pneumophila*, and treatment with IP PBS or 2DG. n=5/group. Data are represented as mean ± SEM.

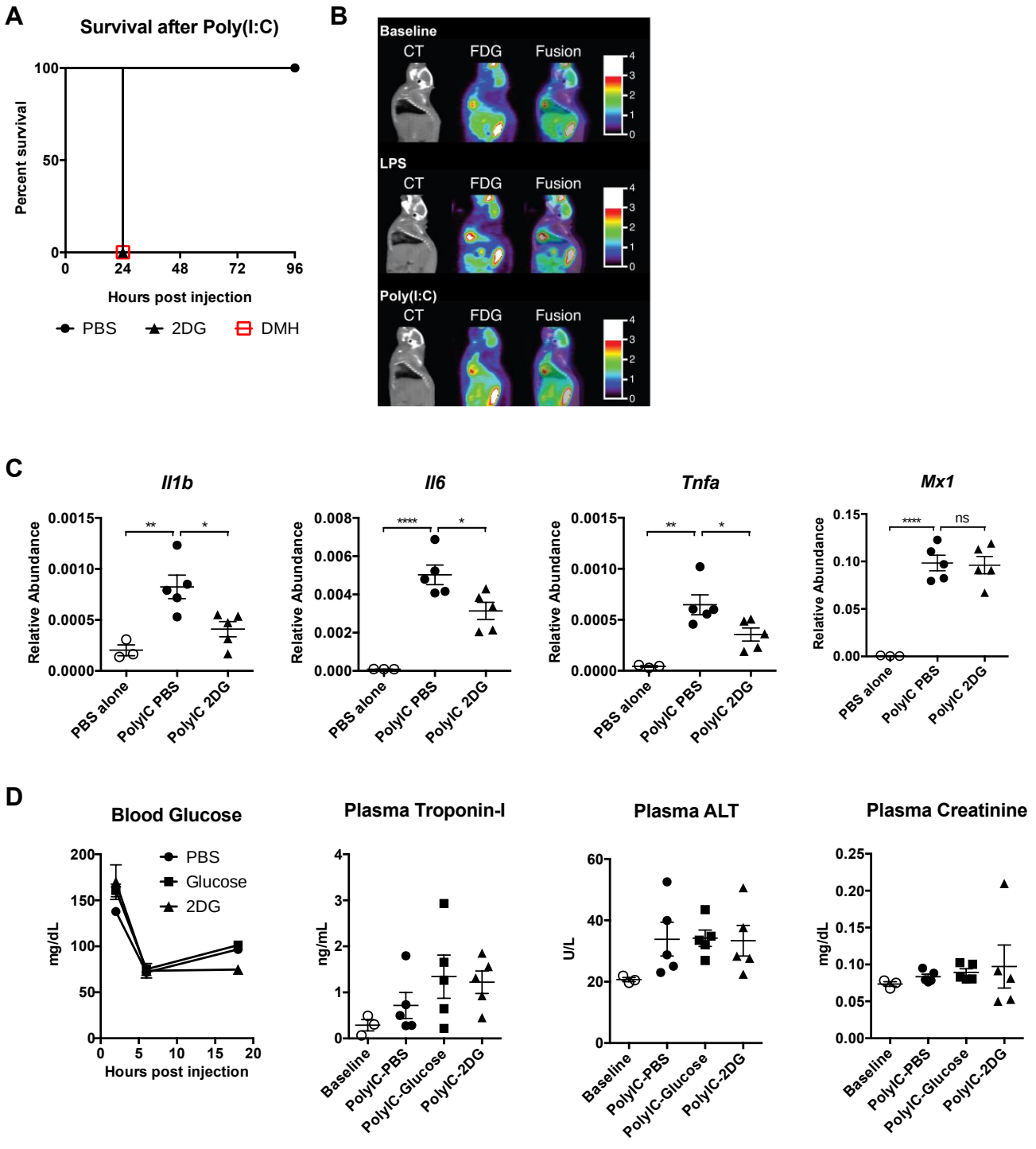

Figure S4. Systemic effects of glucose caloric supplementation or inhibition of glucose utilization during Poly(I:C) sepsis, Related to Figure 4.

(A) Survival of mice after Poly(I:C) challenge and treatment with either IP PBS, 2DG, or DMH.

(B) Averaged sagittal PET images after PBS vehicle (baseline), LPS, and Poly(I:C) administration. CT, computed tomography; FDG, 2-deoxy-2-[^{18}F] fluorodeoxy-D-glucose. n=3/group.

(C-D) Mice were challenged with Poly(I:C), then treated with either IP PBS, glucose, or 2DG.

(C) Hindbrain mRNA expression 4 hours after Poly(I:C) administration and indicated treatments. n=3-5/group.

(D) Blood glucose measured at 2, 6, and 18 hours after Poly(I:C) and indicated treatments. Plasma troponin-I, ALT and creatinine measured at 24 hours after Poly(I:C).

Data are represented as mean ± SEM. *p<0.05,**p<0.01, ****p<0.0001. n.s., not significant.

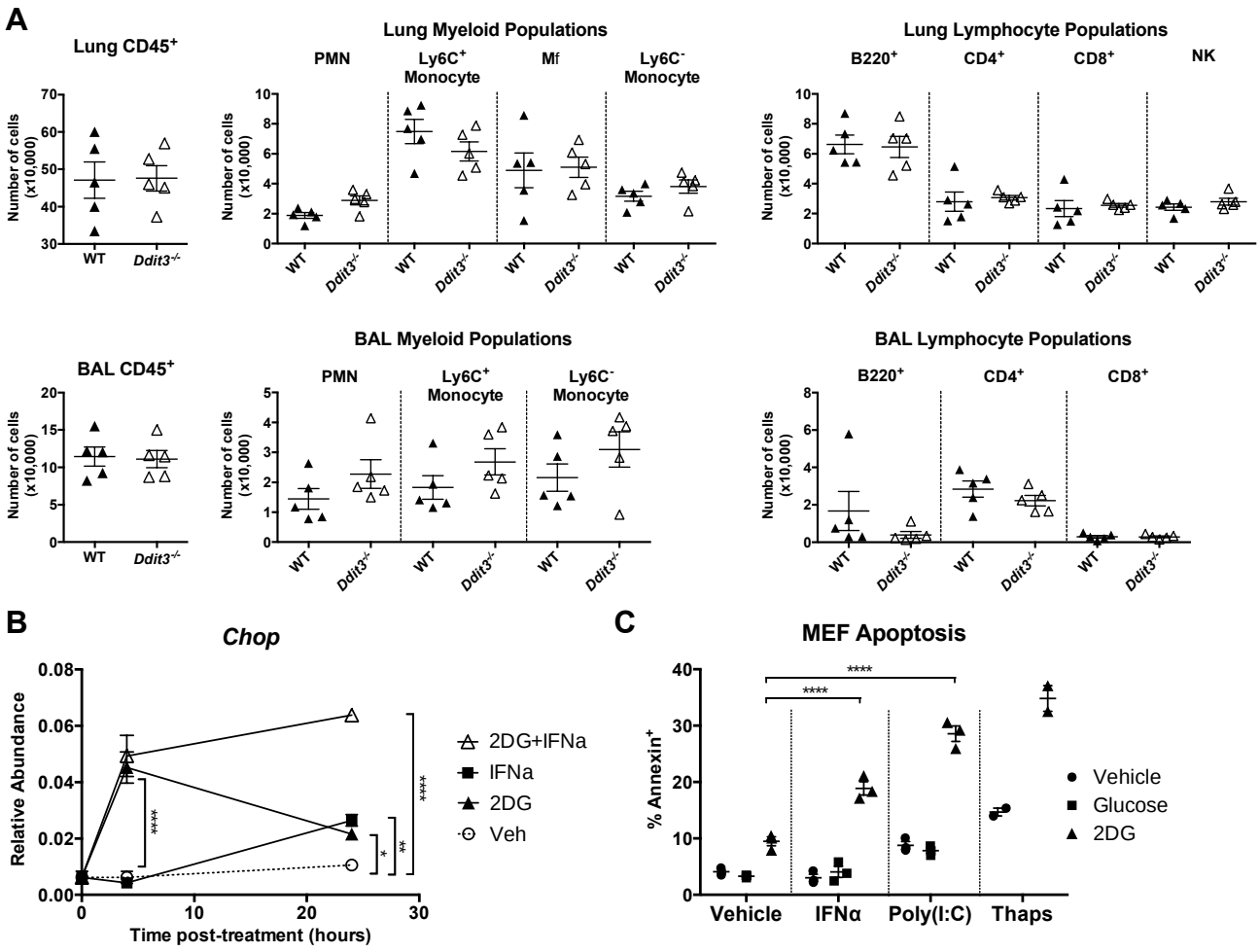

Figure S5. The effect of inhibiting glucose utilization on inflammation and ER stress during viral inflammation, Related to Figure 5.

(A) Flow cytometric analysis of Lung and BAL on day 5 after infection with 700 PFU of influenza virus in B6 WT and *Ddit3*$^{-/-}$ mice.

(B) Mouse embryonic fibroblasts (MEFs) treated with vehicle, IFNα, 2DG, or IFNα and 2DG. mRNA expression at 0, 4, and 24 hours after treatment. n=3 replicates per group. Data representative of two independent experiments.

(C) MEFs treated with vehicle, IFNα, Poly(I:C), and Thapsigargin (Thaps), in the presence of vehicle, glucose or 2DG for 24 hours. Flow cytometric analysis for Annexin V. Two-three replicates per group. Data representative of three independent experiments.

Data are represented as mean ± SEM. *p<0.05,**p<0.01, ****p<0.0001

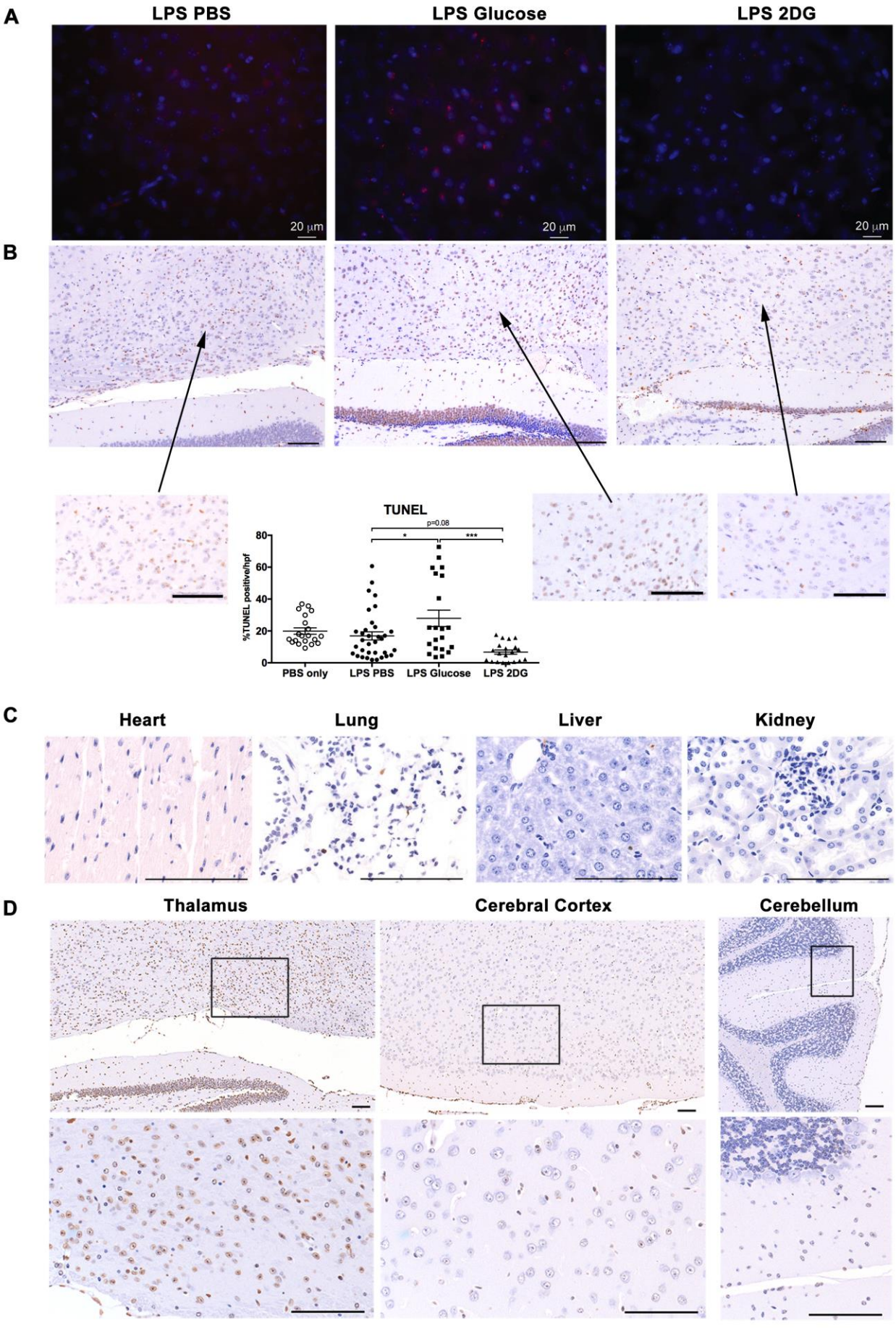
A
LPS PBS
LPS Glucose
LPS 2DG
20 μm
20 μm
20 μm
B
TUNEL
p=0.08
*
***
%TUNEL positive/hpf
80
60
40
20
0
PBS only
LPS PBS
LPS Glucose
LPS 2DG
C
Heart
Lung
Liver
Kidney
D
Thalamus
Cerebral Cortex
Cerebellum

Figure S6. Histopathology of LPS sepsis, Related to Figure 6.
(A) Mice were given IP LPS then initiated with IP PBS, glucose, and 2DG treatment. Dihydroethidium staining of brain 24 hours after LPS.
(B) TUNEL-stained sections of brain 24 hours after LPS and treatment with PBS, glucose, or 2DG. 3,3'-Diaminobenzidine (DAB) hematoxylin, scale bars = 100 mm. Quantification of TUNEL positive cells per 400x power field. n=3/group.
(C) Representative images of TUNEL-stained sections of heart, lung, liver, and kidney 24 hours post-LPS. DAB Hematoxylin, scale bars = 100 mm.
(D) Representative sections of TUNEL-stained thalamus, cerebral cortex, and cerebellum 24 hours post-LPS in WT mice. DAB Hematoxylin, scale bars = 100 mm.
Data are represented as mean ± SEM.

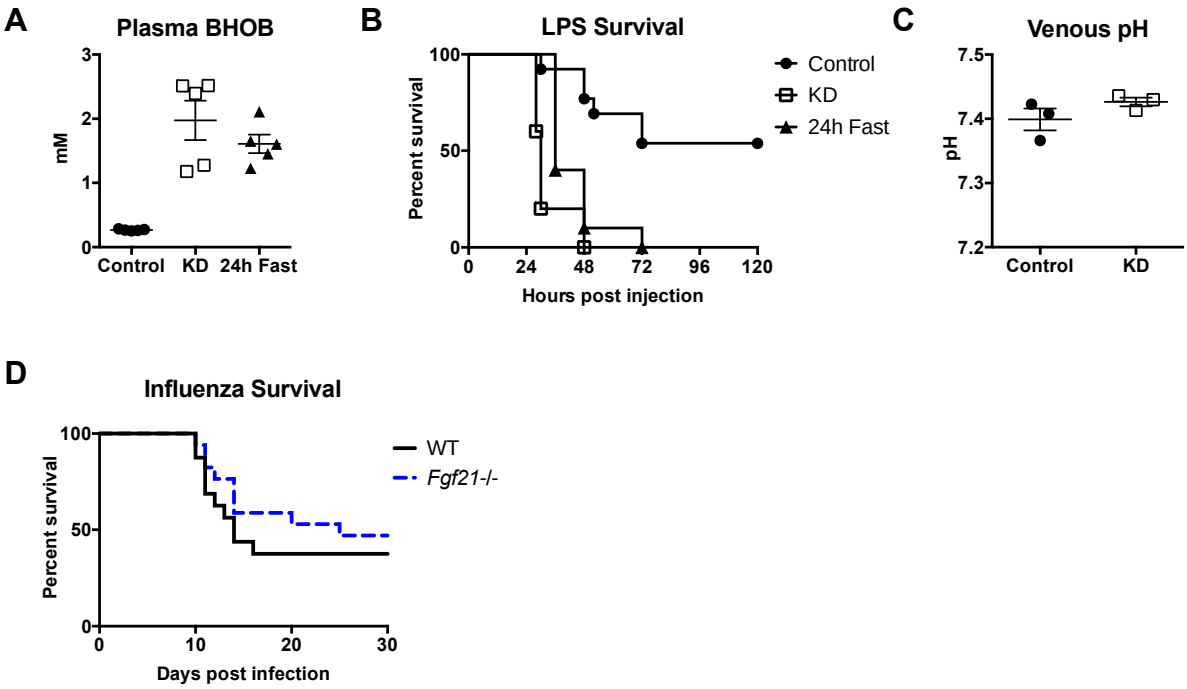

Figure S7. Investigation of the ketogenic program in bacterial and viral inflammation, Related to Figure 6.

(A) Plasma BHOB levels after 3 days of ketogenic diet (KD) and 24 hours of fasting compared to control fed mice. Control vs KD diet p=0.0001; Control vs 24h Fast p=0.0011. n=5/group.
(B) Survival after 10 mg/kg IP LPS in mice on control diet, after 3 days of ketogenic diet (KD), and after 24 hours of fasting. Control vs KD p=0.0002; Control vs 24h Fast p=0.0007.
(C) Venous blood gas measured in mice on control diet and 3 days after ketogenic diet (KD).
(D) Survival after 375 PFU influenza in WT and *Fgf21*$^{-/-}$ mice.
Data are represented as mean ± SEM.