FIGURE 6

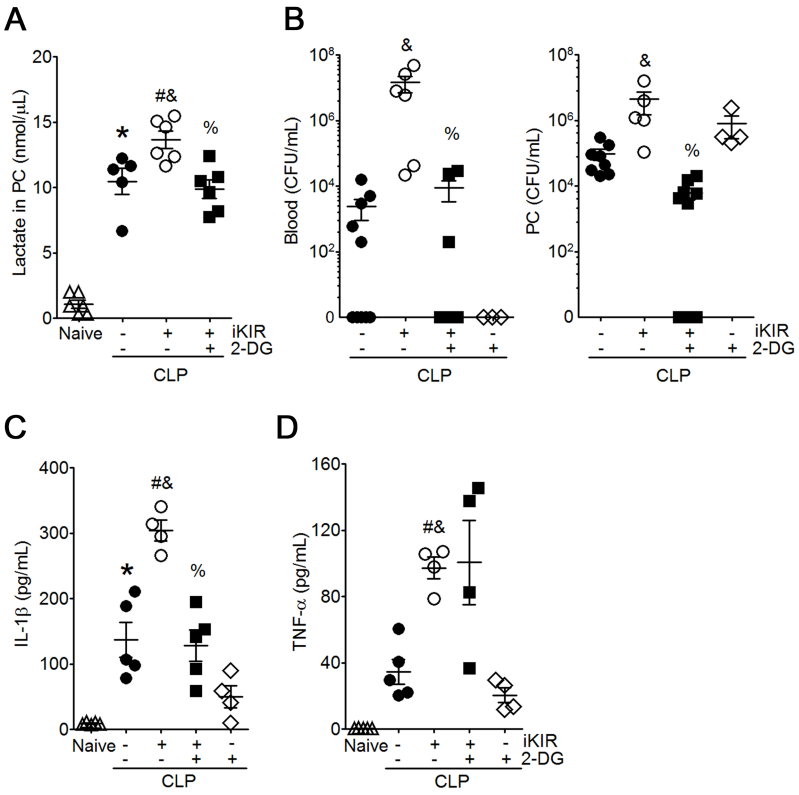
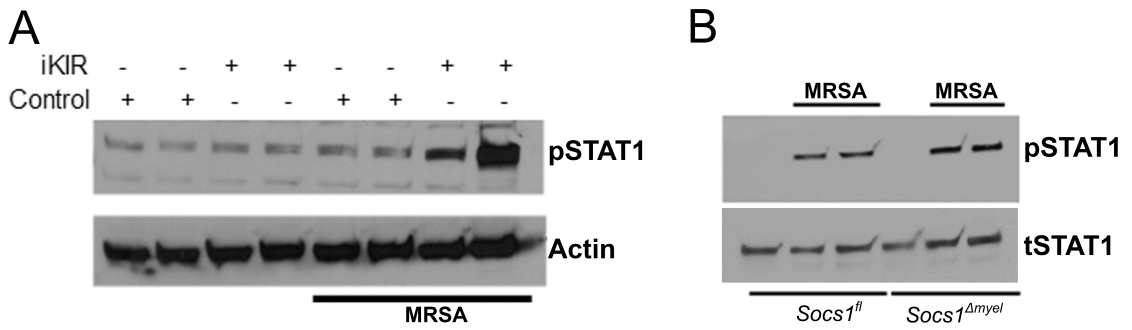


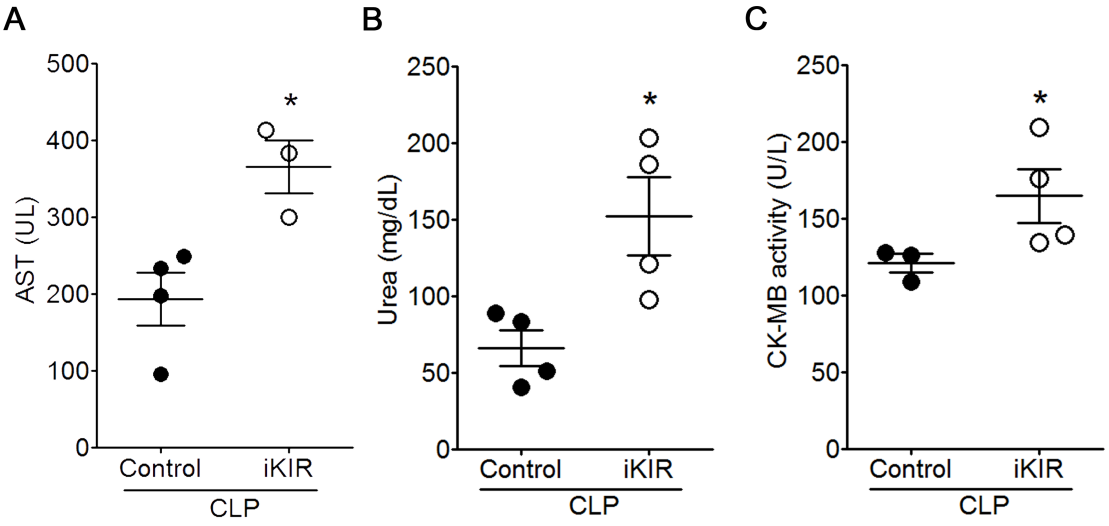
FIGURE 6. Increased glycolysis is responsible for iKIR-mediated animal mortality during sepsis. Mice were treated with competitive hexokinase inhibitor 2-deoxyglucose (2-DG; 0.5 g/Kg, i.p.) daily for 4 days and 1 h before CLP. The animals were also treated with iKIR (inhibitor of the kinase inhibitory region), 24 h and 1 h before surgery. **(A)** Lactate levels in peritoneal exudate (n = 5-7 mice/group, one-way ANOVA, followed by Bonferroni). **(B)** Bacterial loads were determined in blood and peritoneal exudate 18 h after CLP (n = 4-9 mice/group, one-way ANOVA followed by Bonferroni correction). Levels of IL-1β **(C)** and TNFα **(D)** were quantified in peritoneal exudate (n = 4-5 mice/group, one-way ANOVA, followed by Bonferroni). Scatter plot shows individual values, mean, SEM. **P*<0.05, control-treated septic mice vs. naïve; $^{\&}$*P*<0.05, iKIR vs. control-treated septic mice; $^{\%}$*P*<0.05, iKIR and 2-DG vs. iKIR-treated septic mice; $^{\#}$*P*<0.05, iKIR-septic mice vs. naïve mice.

Supplementary Information



Supplementary Figure 1. **Validation of *Socs1*$^{\Delta myel}$ and iKIR in macrophages**. **(A)** Macrophages previously treated with iKIR (inhibitor of the kinase inhibitory region) for 30 min were infected with methicillin-resistant *Staphylococcus aureus* (MRSA) for 1 h, followed by detection of total and phosphorylated STAT1 by immunoblotting. **(B)** *Socs1*^{fl} and *Socs1*$^{\Delta myel}$ macrophages were infected with MRSA for 1 h, and STAT1 phosphorylation was detected by immunoblotting. Data are representative of two independent experiments.

SUPPLEMENTAL FIGURE 2

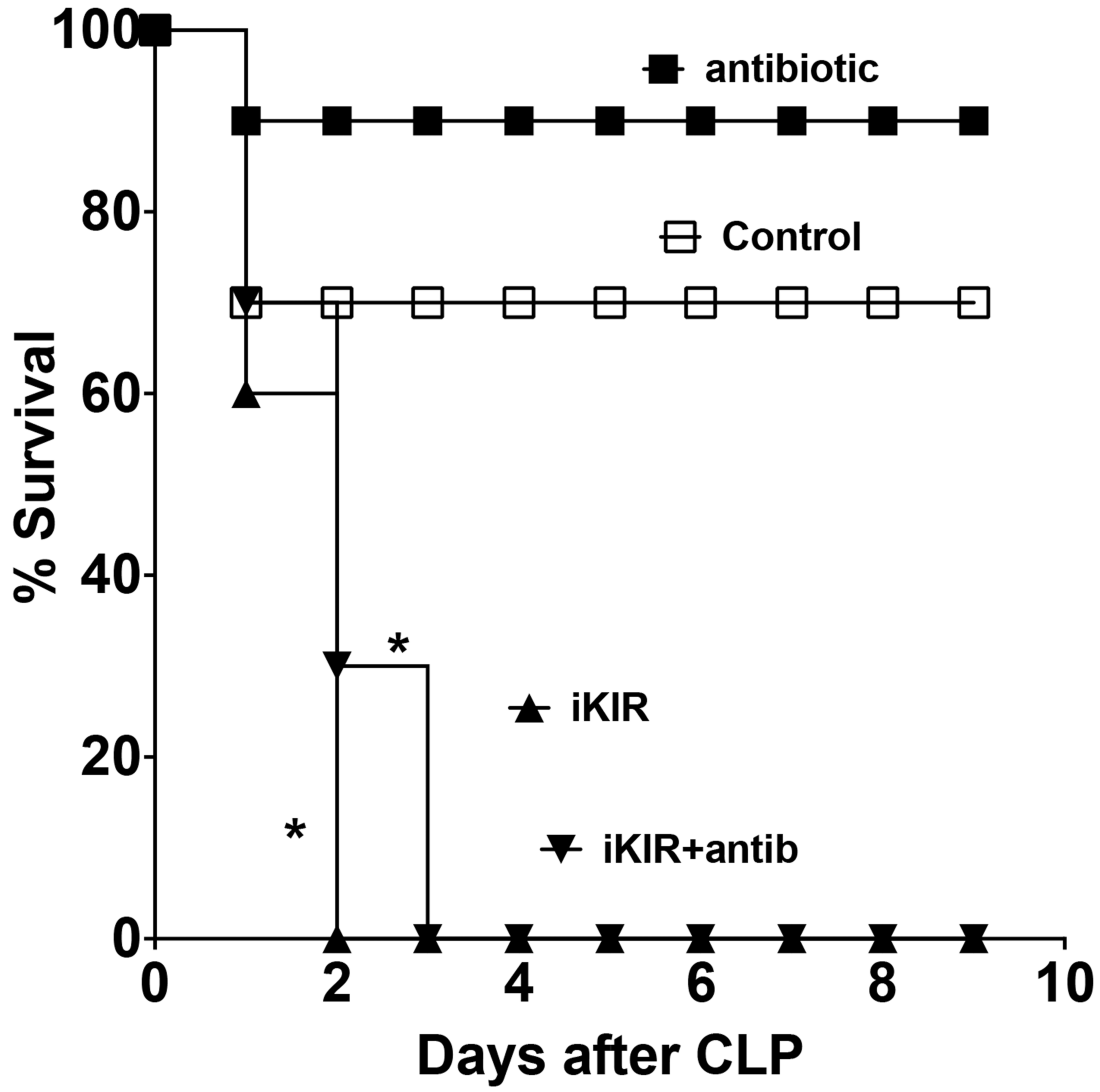


1046

1047 **Supplementary Figure 2. SOCS1 prevents organ damage during sepsis.** Levels of
1048 **(A)** aspartate aminotransferase (AST), **(B)** urea, and **(C)** creatine kinase-MB (CK-MB)
1049 were measured in serum from septic mice 18 h after cecal ligation and puncture (CLP),
1050 as described in the Methods. Scatter plot shows individual values, mean, SEM.
1051 **P*<0.05, (n = 3-4 mice/group, unpaired t-test).

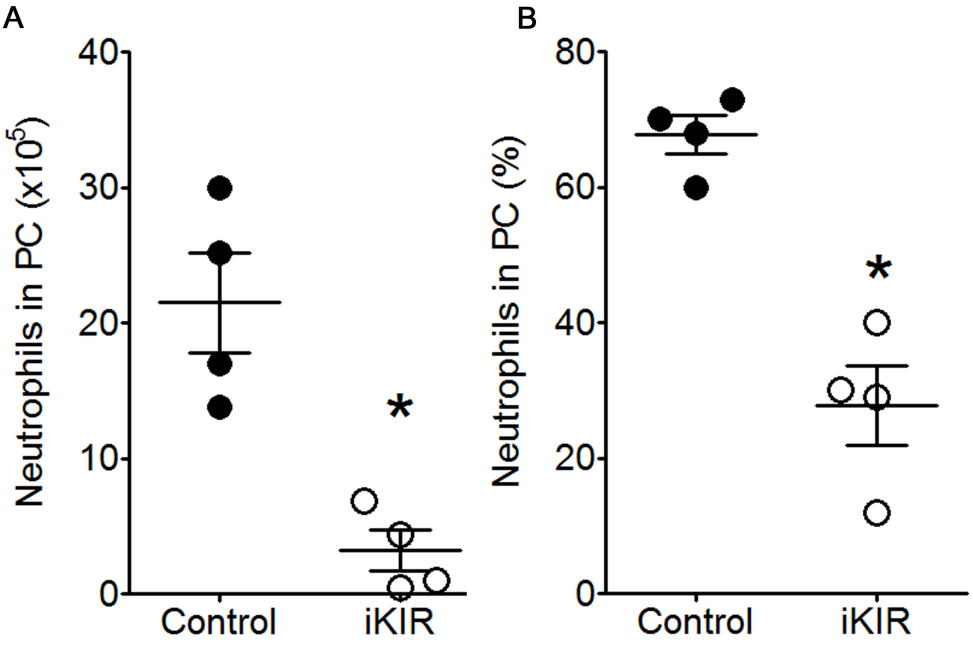
1052

1053

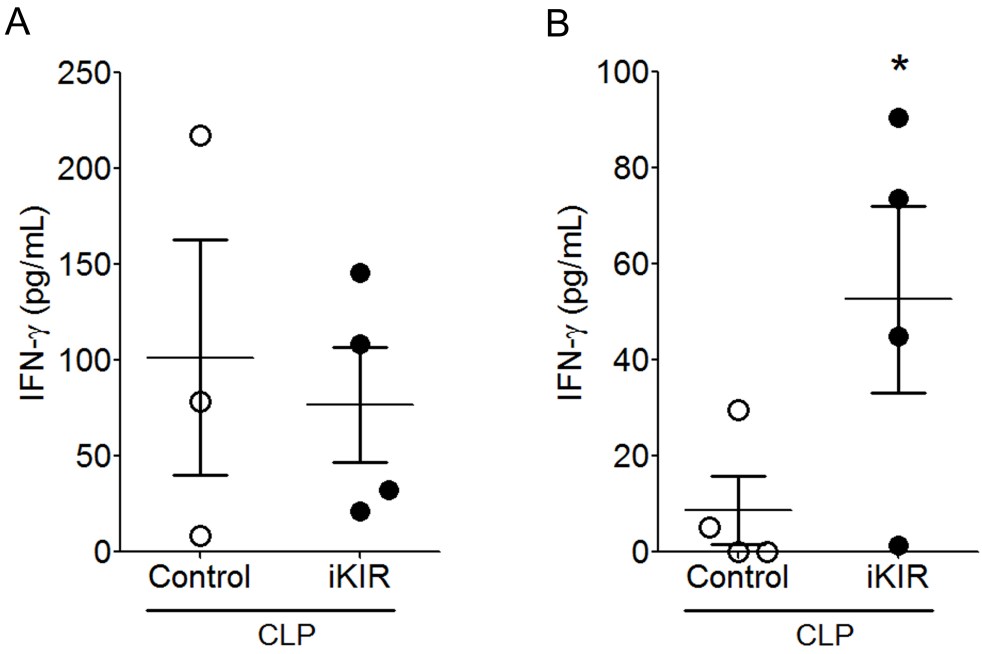


Supplementary Figure 3. Antibiotic treatment does not prevent iKIR-induced animal lethality during sepsis. Survival rates of C57BL/6 mice treated with iKIR (inhibitor of the kinase inhibitory region) or scrambled peptide control prior to receiving moderate CLP. Survival was monitored for 9 days (n = 9 mice/group, log-rank [Mantel-Cox] test).

SUPPLEMENTAL FIGURE 4



Supplementary Figure 4. SOCS1 prevents neutrophil migration to the site of infection during sepsis. Mice previously treated with iKIR (inhibitor of the kinase inhibitory region) were subjected to CLP. Number **(A)** and frequency **(B)** of neutrophils infiltrating peritoneal cavity were quantified 18 h after CLP. Scatter plot shows individual values, mean, SEM. n = 4 mice/group, unpaired t-test. *P<0.05 iKIR-treated vs. control-treated septic mice.



1069

1070 **Supplementary Figure 5. Pharmacological inhibition of SOCS1 increases**
1071 **systemic IFNγ in septic mice.** Quantification of IFNγ in serum **(A)** and peritoneal
1072 cavity **(B)** from mice treated with iKIR (inhibitor of the kinase inhibitory region) or
1073 control peptide. Scatter plot shows individual values, mean, SEM. **P*<0.05 iKIR-treated
1074 septic mice vs. control-treated septic mice (n = 3-4 mice/group, unpaired t-test).

1075