**Supplemental Digital Content**

**Figure 1**

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**Figure 1.** Blockage of S1PR2 improves survival rates and protects from macrophage pyroptosis during *Escherichia coli* sepsis. WT mice were injected intraperitoneally with 4 mg/kg JTE-013 (a S1PR2 antagonist) or vehicle after *E. coli* (3.5 × 106 colony-forming units [CFU]) infection. (A) Survival rates were monitored for 48 h. n = 22 for vehicle group and n = 24 for JTE-013 group from three independent experiments. Values were analyzed by the Mantel-Cox test. (B) Macrophage pyroptosis was determined by flow cytometry analysis at indicated time points: F4/80+ cells were gated and analyzed for FLICA and PI. Representative images are shown on the left and quantitative analysis of F4/80+ FLICA+PI+ cells are shown on the right (n = 3 for 0 h and n = 4 for 6 h). Data are presented as mean ± SD and were analyzed using two-tailed Student’s *t* test. (C) IL-1β and (D) TNF-α levels from serum (n = 3 for 0 h and n = 4 for 6 h) and PLF (n = 3 for 0 h and n = 4 for 6 h) were detected by enzyme-linked immunosorbent assay. Data are presented as mean ± SD and were analyzed by Student’s *t* test. \*Significant difference was compared with respective WT control mice. \**P* < 0.05. IL-1β = interleukin-1β; TNF-α = tumor necrosis factor-α.

**Figure 2**

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**Figure 2.** S1PR2 deficiency did not affect macrophage apoptosis in *Escherichia coli* sepsis. Wild-type (WT) and *S1pr2* deficient (*S1pr2-/-*) mice were injected intraperitoneally with *E. coli* (3.5 × 106 colony-forming units [CFU]). Macrophage apoptosis was determined by flow cytometry analysis at indicated time points: F4/80+ cells were gated and analyzed for Annexin V and PI. Representative images are shown on the left and quantitative analysis of F4/80+Annexin V+PI- cells are shown on the right (n = 3 at 0 h; n = 7 for WT group and n = 5 for *S1pr2-/-* group at 6 h). Data are presented as mean ± SD and were analyzed using two-tailed Student’s *t* test. S1PR2 = sphingosine 1-phosphate receptor 2.

**Figure 3**

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**Figure 3.** S1PR2 deficiency improves *Escherichia coli* sepsis outcome and decreases macrophage pyroptosis in female mice. Wild-type (WT) and *S1pr2* deficient (*S1pr2-/-*) female mice were injected intraperitoneally with *E. coli* (3.5 × 106 colony-forming units [CFU]). (A) Survival curves of WT and *S1pr2-/-* mice after *E. coli* sepsis. Data consist of three independent experiments (n = 16 per group) and were examined using the Mantel-Cox test. (B) Macrophage pyroptosis was determined by flow cytometry analysis at indicated time points: F4/80+ cells were gated and analyzed for FLICA and PI. Representative images are shown on the left and quantitative analysis of F4/80+ FLICA+PI+ cells are shown on the right (n = 3 for 0 h and n = 4 for 6 h). Data are presented as mean ± SD and were analyzed using two-tailed Student’s t test. (C) IL-1β and (D) TNF-α levels from serum (n = 5) were detected by enzyme-linked immunosorbent assay. Data are presented as mean ± SD and were analyzed by Student’s *t* test or Mann-Whitney test. \*Significant difference was compared with respective WT control mice. \**P* < 0.05. S1PR2 = sphingosine 1-phosphate receptor 2; IL-1β = interleukin-1β; TNF-α = tumor necrosis factor-α.

**Figure 4**

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**Figure 4.** Caspase-11 activation is reduced by RhoA inhibitor in a dose-dependent manner.WT peritoneal macrophages were treated with 5, 10, 30 and 50 μM Y27632 (a RhoA antagonist) or vehicle after *Escherichia coli* stimulation. Caspase-11 activation was determined by western blots. Values are presented as mean ± SD from 3 independent experiments and were analyzed using one-way ANOVA followed by Bonferroni post-test. Representative images are shown on the top and band intensity quantifications are shown on the bottom. \*Significant difference was compared with *E. coli* group. \*\*\**P* < 0.001. Y2 = Y27632; Cont = control.

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