Supporting Information

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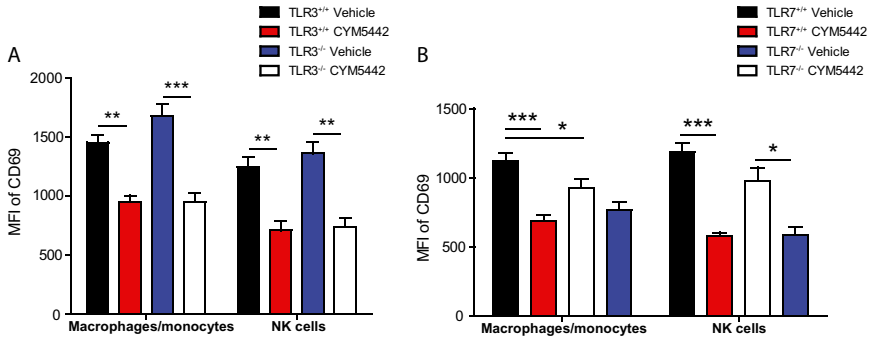

Fig. S1. Sphingosine-1-phosphate-1 receptor ($S1P_1R$) agonist therapy suppresses innate immune cell recruitment and activation independent of Toll-like receptor (TLR)3 or TLR7 signaling. $TLR3^{-/-}$ (*A*) or $TLR7^{-/-}$ (*B*) mice were infected with 1×10^4 PFU WSN influenza virus and either vehicle (water) or CYM5442 (2 mg/kg) were administered intratracheally to mice. (*A* and *B*) Level of expression of the early activation marker CD69 on macrophages and NK cells from collagenase-digested lungs at 48 h postinfection. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.005$. Results are representative of two independent experiments and five mice per group.

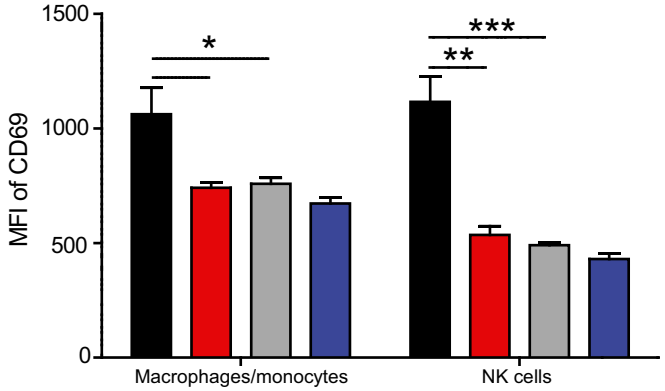

Fig. S2. $S1P_1R$ agonist therapy suppresses innate immune cell activation independent of endosomal TLR signaling. Expression levels of the early activation marker CD69 on macrophages and NK cells from collagenase-digested lungs at 48 h postinfection in 3d mice. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.005$. Results are representative of two independent experiments and five mice per group.

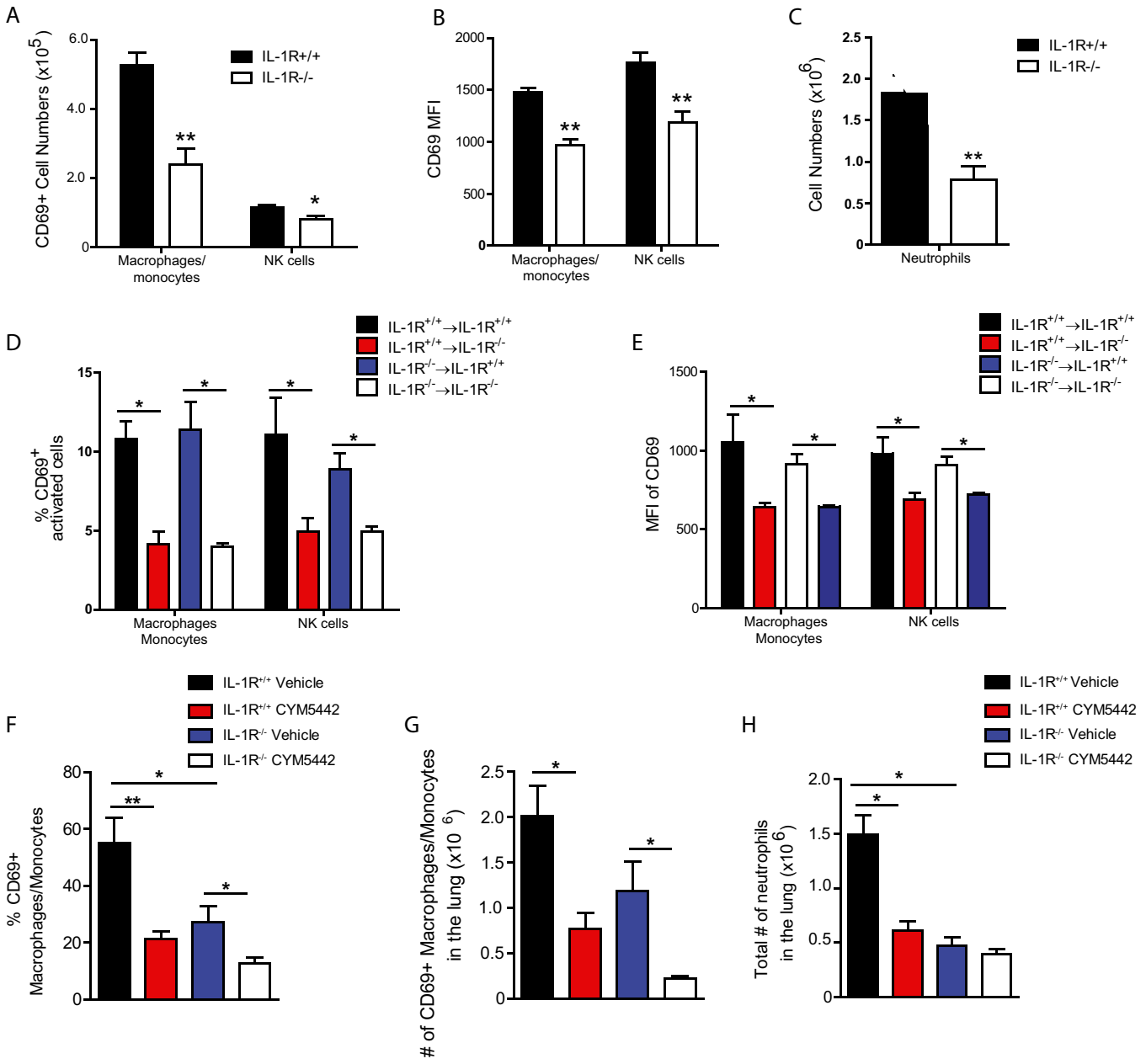

Fig. S3. IL-1R signaling is required for innate cellular activation and recruitment following influenza virus infection. (*A–C*) IL-1R$^{-/-}$ or IL-1R$^{+/+}$ control mice were infected with 1 × 10^4 PFU WSN influenza virus and recruitment of activated macrophages/monocytes and NK cells (*A*), expression levels of the early activation marker CD69 (*B*), and total numbers of neutrophils (*C*) were quantified 48 h postinfection in collagenase digested lungs. (*D* and *E*) Bone marrow chimeras between IL-1R$^{+/+}$ and IL-1R$^{-/-}$ mice by injection of either IL-1R$^{+/+}$ bone marrow cells into lethally irradiated IL-1R$^{-/-}$ mice or vice versa. IL-1R$^{+/+}$ bone marrow cells injected into irradiated IL-1R$^{+/+}$ mice and IL-1R$^{-/-}$ bone marrow cells into irradiated IL-1R$^{-/-}$ mice as controls. Chimeric mice were infected with 1 × 10^4 PFU WSN influenza virus percentages (*D*) and expression levels (*E*) of CD69$^+$ on macrophages and NK cells from collagenase-digested lungs at 48 h postinfection in 3d mice. (*F–H*) IL-1R$^{-/-}$ or IL-1R$^{+/+}$ control mice were infected with 1 × 10^4 PFU WSN influenza virus and either vehicle (water) or CYM5442 (2 mg/kg) were administered intratracheally to mice. Percentage (*F*) and total numbers (*G*) of macrophages/monocytes were quantified 48 h postinfection in collagenase-digested lungs. (*H*) Total numbers of neutrophils in the lungs of IL-1R$^{+/+}$ or IL-1R-1$^{-/-}$ mice 48 h postinfluenza virus infection.*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$. Results are representative of two to three independent experiments and five mice per group.

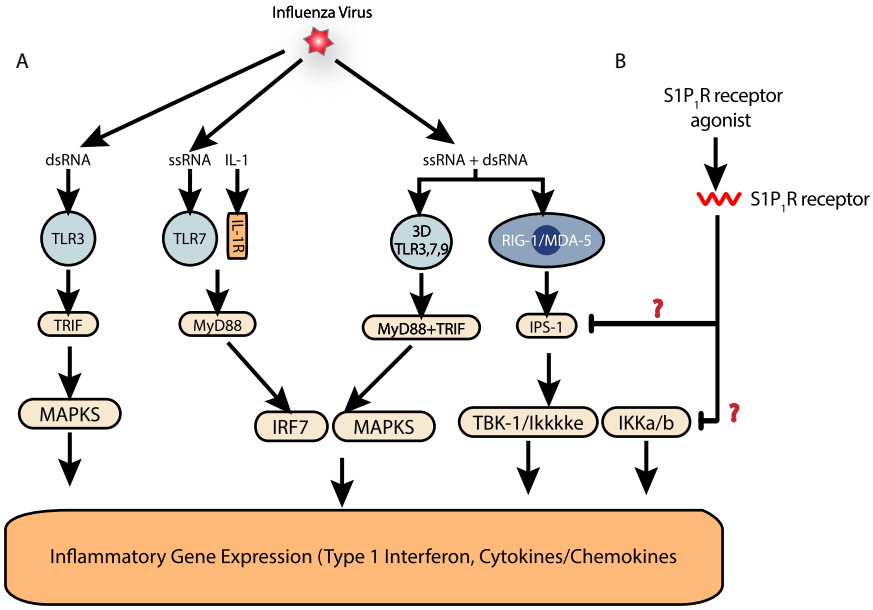

Fig. S4. $S1P_1R$ agonist treatment globally blunts innate immune signaling converging downstream of multiple innate sensing pathways. The figure depicts (*A*) redundant innate signaling pathways triggered by influenza virus infection that induce the expression of inflammatory genes. (*B*) $S1P_1R$ agonist signaling through an unidentified mechanism results in the suppression of inflammatory gene expression at a point common to multiple signaling pathways. Based on our data presented in this study, we postulate that $S1P_1R$ agonist inhibition occurs at one or more of the indicated points depicted in the figure. IPS-1, IFN-β promoter stimulator-1; MDA-5, melanoma differentiation-associated-5; MyD88, myeloid differentiation primary response gene 88; RIG-I, retinoic acid-inducible gene.