Supporting Information

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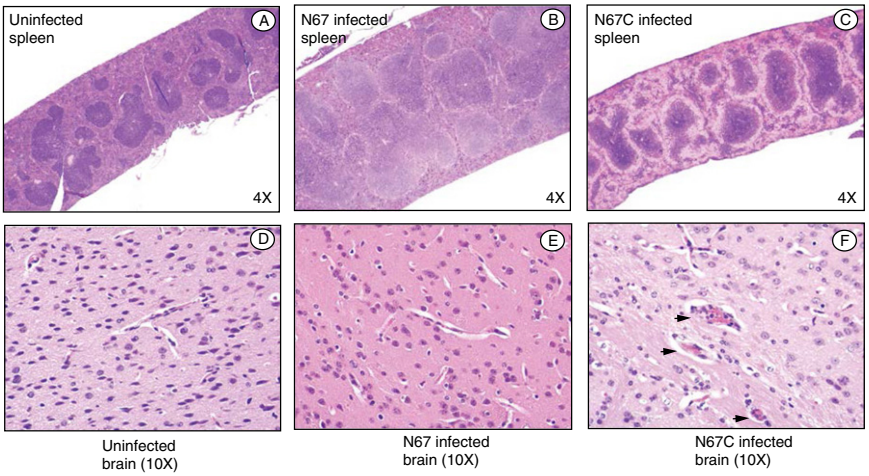

Fig. S1. Images of spleens from uninfected, N67-, or N67C-infected mice of the same age, stained with hematoxylin and eosin (H&E). (*A*–*C*), spleen sections at 4× magnification; (*D*–*F*), brain sections at 10× magnification.

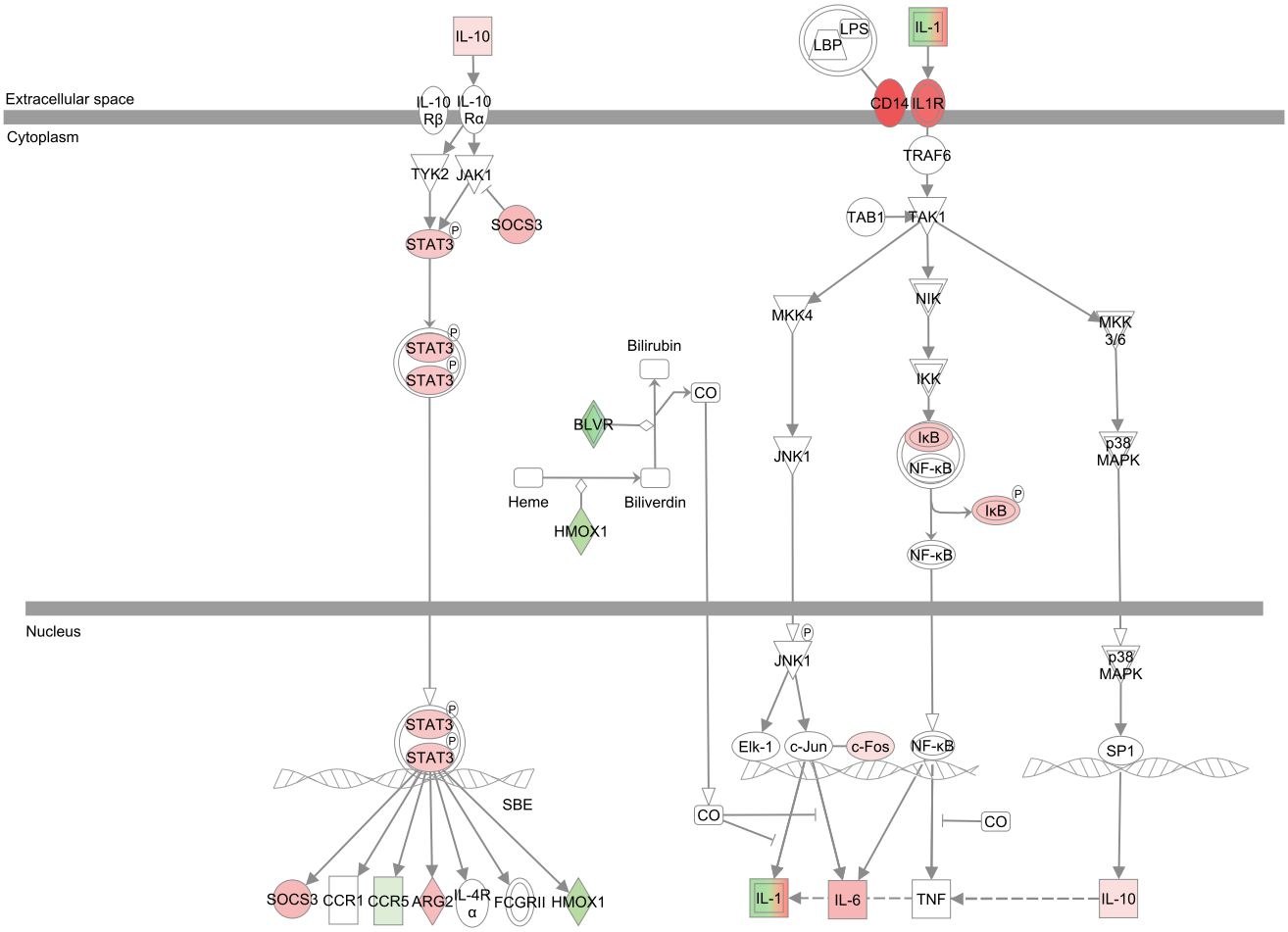

Fig. S2. Comparison of putative inflammatory pathways showing key genes up-regulated in infected mice. The pathways were generated using Ingenuity Systems Pathway Analysis. Molecules in red were expressed at higher levels in N67C-infected mice, whereas those in green were expressed at higher level in N67-infected mice. Darker colors represent larger differences in gene expression between the two parasites.

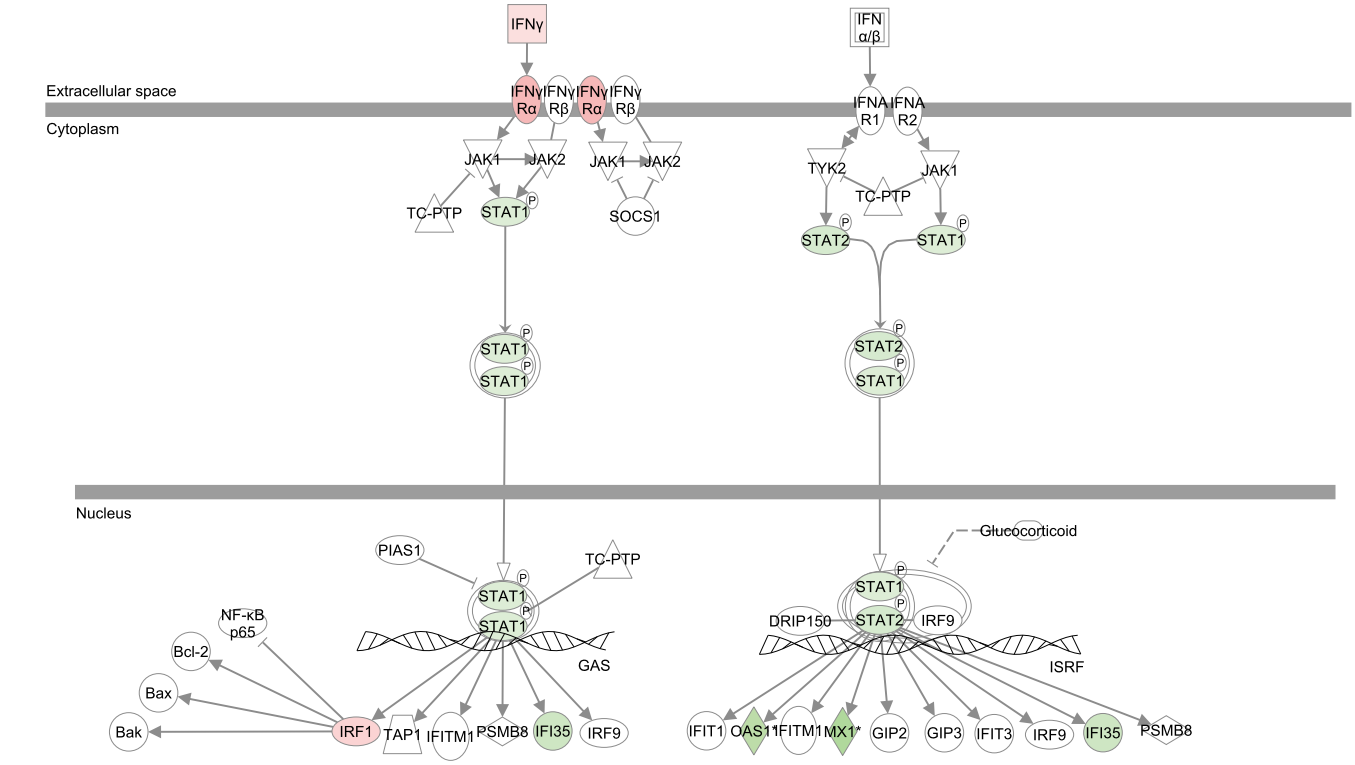

Fig. S3. Comparison of type I and II IFN pathways for differentially regulated components in mice infected with N67 or N67C. The pathways were generated using Ingenuity Systems Pathway Analysis. Molecules in green are expressed at higher levels in the N67-infected mice, whereas those in pink were expressed at higher levels in N67C-infected mice.

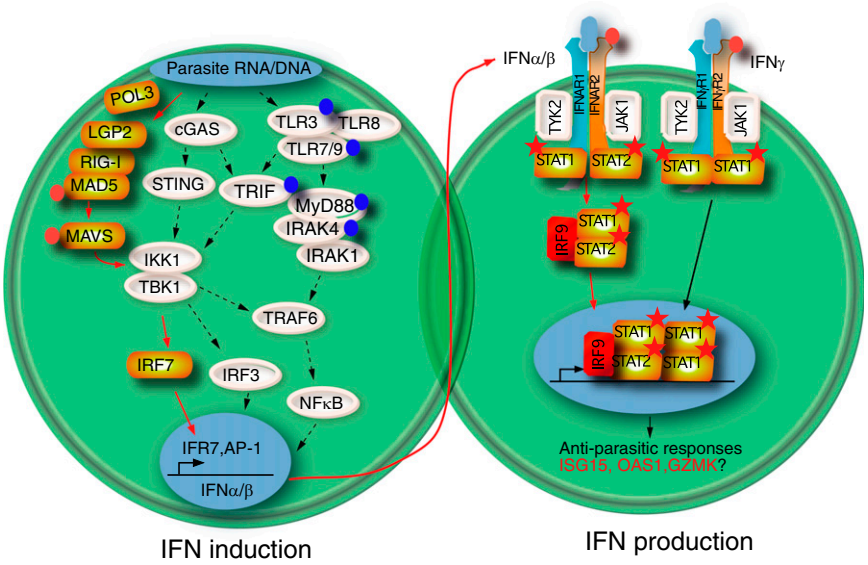

Fig. S4. Molecules involved in type I IFN (IFN-I) response to infection of N67 parasite. Putative IFN-I signaling pathways that may play a role in controlling early parasitemia in mice infected with N67 are marked with red arrows. Red stars indicate high levels of phosphorylation in the N67-infected mice. Red dots indicate key molecules in which significant changes in parasitemia were observed in N67-infected mice when they were disrupted, whereas no significant changes were seen when the molecules with blue dots were disrupted. Dashed arrows suggest pathways that may not play an important role (or not investigated) in the decline of parasitemia in N67-infected mice. POL3, RNA polymerase III; LGP2, probable ATP-dependent RNA helicase; RIG-I, retinoic acid-inducible gene 1; MDA5, melanoma differentiation-associated protein 5; MAVS, mitochondrial antiviral-signaling protein (also IPS-1); cGAS, cGMP-AMP synthase; STING, stimulator of IFN genes; IKK1, IκB kinase 1; TBK1, TANK-binding kinase 1; IRF7(3,9), IFN regulatory factor 7(3,9); TLR, Toll-like receptors; TRIF, TIR-domain-containing adapter-inducing IFN-TB; MyD88, myeloid differentiation primary response gene 88; IRAK4, interleukin-1 receptor-associated kinase 4(1); TRAF6, TNF receptor-associated factor 6; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; AP-1, activator protein 1; IFNα/β, IFN alpha/beta; IFNA1/2, IFN-alpha/beta receptor alpha chain; TYK2, tyrosine-protein kinase 2; JAK1, Janus kinase 1; STAT1/2, signal transducer and activator of transcription 1 and 2; ISG15, IFN-induced 17-kDa protein; OAS1, 2′–5′ oligoadenylate synthetase 1; GZMK, granzyme K.

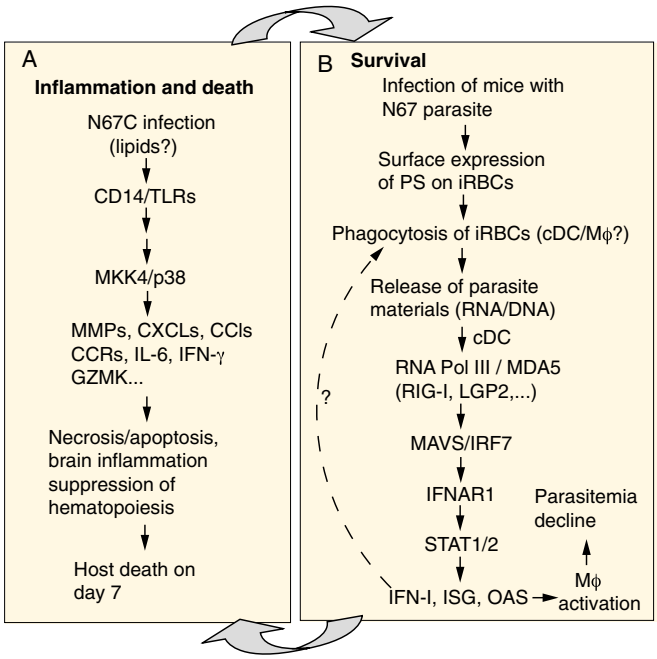

Fig. S5. Differential responses to N67 and N67C infection that can determine host survival or death in early infection. (*A*) Putative proinflammatory responses induced by N67C infection. Binding of unknown parasite ligands, likely parasite lipids, to CD14/TLRs/integrin, activated signaling cascades involving activation of kinases MKK4 and p38 and production of proinflammatory cytokines/chemokines such as CCL2 and IFN-γ and matrix metalloproteinases (MMP-3 and MMP-10), leading to enhanced chemotaxis and migration of neutrophils and monocytes to sites of inflammation such as the brain and spleen. Inflammation of these organs, along with activation of enzymes such as MMP and granzyme K (GZMK), eventually results in tissue necrosis, apoptosis, and host death. (*B*) Putative signaling pathways leading to suppression of parasitemia in N67-infected mice. Infection with N67 induces unique modification of RBC membrane, exposing phosphatidylserines (PSs) that are normally located within RBCs. Surface expression of PS may trigger active phagocytosis of infected RBCs (iRBCs) by macrophages and DC cells, which may release parasite DNA/RNA and other materials. Parasite DNA can be converted into 5′ ppp RNA by RNA Pol III, and the 5′ ppp RNA are recognized by melanoma differentiation-associated protein 5 (MDA5), possibly retinoic acid-inducible 1 (RIG-I), that trigger signaling events leading to production of type I IFN (IFN-I), IFN-inducible proteins (ISGs), and 2′–5′ oligoadenylate synthases (OASs). Other DNA/RNA sensors can also be involved, although we do not have data to confirm their involvement. Active phagocytosis can directly reduce parasitemia, which also results in splenomegaly. Although the increased PS level on N67-infected red blood cells and more active phagocytosis suggested a possibility of higher PS level triggering more active phagocytosis, further studies are necessary to establish a firm causal relationship between the surface PS level, phagocytosis, and IFN-I production. The dashed line represents potential interactions that still lack experimental evidence.

Dataset S1. Histological observations of mouse organs infected with N67 and N67C parasites

Dataset S1

Dataset S2. Gene annotation terms enriched in up- or down-regulated genes in response to infection of *Plasmodium yoelii*

Dataset S2

Dataset S3. Primers used in quantitative PCR to detect gene expression both in mouse spleen and in vitro transfected cells

Dataset S3