Macrophages Are Critical for Cross-Protective Immunity Conferred by Babesia microti against Babesia rodhaini Infection in Mice

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Abstract

Although primary infection of mice with Babesia microti has been shown to protect mice against subsequent lethal infection by Babesia rodhaini, the mechanism behind the cross-protection is unknown. To unravel this mechanism, we investigated the influence of primary infection of mice with non-lethal B. microti in different time courses on the outcome of subsequent lethal B. rodhaini infection. Simultaneous infections of mice with these parasites resulted in rapid increases in parasitemia, with 100% mortality in BALB/c mice, as observed with control mice infected with B. rodhaini one. In contrast, mice with acute, resolving, and chronic-phase B. microti infections were completely protected against B. rodhaini, resulting in low parasitemia and no mortalities. Mice immunized with dead B. microti were not protected from B. rodhaini infection, although high antibody responses were induced. Interestingly, the protected mice had significantly decreased levels of antibody response, cytokines (including gamma interferon (IFN-γ), interleukin-2 (IL-2), IL-8, IL-10, and IL-12), and nitric oxide levels after infection with B. rodhaini. SCID mice and IFN-γ-deficient mice with chronic B. microti infections demonstrated protective responses comparable to those of immunocompetent mice. Likewise, in vivo NK cell depletion did not significantly impair the protective responses. Conversely, macrophage depletion resulted in increased susceptibility to B. rodhaini infection associated with changes in the immune body and cytokines profiles, indicating that macrophages contribute to the protection against this challenge infection. We conclude that future development of vaccines against Babesia should include a strategy that enhances the appropriate activation of macrophages.