**Title:**

CD4-CD8- T cells, B cells and Complement are Critical for Resolution of Babesia microti Infection in the Absence of CD4

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**Abstract:**

Babesiosis caused by the protozoan parasite Babesia microti is an emerging infectious disease in the United States. In patients who are immunocompromised, particularly those treated with the B cell depleting antibody rituximab, babesiosis is severe and persistent. To understand how the immunocompromised host clears B. microti, we developed a mouse model. In athymic mice, parasitemia was intense and persisted. In cd4-/- mice, however, parasitemia was intense and resolved. In the spleens of the latter, the populations of CD8+ T cells, CD4-CD8- (DN) T cells, and B cells expanded. Parasitemia resolved in cd4-/- cd8-/- mice, but persisted in cd4-/- igh6-/- mice. In cd4-/- mice, the rise in circulating Babesia specific IgGs was delayed but concomitant with resolution of parasitemia. All IgG subisotypes were produced. Fcg receptors were dispensable for resolution of parasitemia, but complement factor C3 was required. DN T cells that produce both IL-21 and IFN-g expanded in cd4-/- mice, but not as fast as CD4+ T cells producing both cytokines in wild-type mice. In contrast, DN T cells producing IFN-g in the absence of IL-21 expanded as fast as their CD4+ T cell counterparts. DN T cells failed to produce IL-21 alone whereas CD4+ T cells producing IL-21 alone quickly expanded. In cd4-/- mice, resolution of infection was not affected by neutralization of IFN-g or IL-21 but was delayed by blockade of both cytokines. Our studies indicate that DN T cells and B cells are key for resolution of B. microti infection in the absence of CD4. Despite the production of IgGs, resolution of infection requires complement activation, but not Fc receptors.