Sustained PD-1 Upregulation and Functional Suppression of T Cells Following *Plasmodium berghei* ANKA Infection

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Infection by *Plasmodium* spp. can trigger intense and sustained immune activation, which can favor the development of T-cell exhaustion. This state is characterized by functional hyporesponsiveness and increased expression of inhibitory receptors, such as TIM-3, LAG-3, PD-1, and PD-L1. It is also characterized by reduced cytokine production and proliferative capacity. This dysfunction compromises the effectiveness of the immune response and may impair the control of subsequent infections. This study aimed to evaluate the expression of inhibitory molecules during experimental infection with *Plasmodium berghei* ANKA and after antimalarial treatment. C57BL/6 mice were infected and treated with chloroquine from days four to ten post-infection. We assessed clinical parameters, splenic cellularity, and inhibitory receptor expression on T cells. We observed a significant increase in the number of total CD4 and CD8 T cells in the spleen of infected animals, and this increase persisted even after treatment without evidence of parasite recrudescence. On day four post-infection, the proportion of T cells expressing PD-1 was elevated, and notably remained high even after chloroquine treatment and parasite clearance. This sustained expression suggests the establishment of an exhaustion-like phenotype since PD-1 upregulation persisted despite the absence of antigenic stimulation. Furthermore, T cells from previously infected mice reduced the proliferation of naïve T cells in co-culture assays, indicating regulatory activity associated with the exhausted state. These findings suggest that malaria impacts subsequent immune dysfunction and contribute to the understanding of post-infection immunocompromise mechanisms.

Keywords: Cerebral malaria; T cells; PD-1; Exhaustion; *Plasmodium berghei* ANKA.