Senescence-Associated KLRG1^{+} CD8 T Cells Accumulate in the Brain during Experimental Cerebral Malaria

Ana Clara S. Poeys, Mônica L. Ribeiro-Almeida, Vitória Monteiro-Azevedo, Luan Matheus DeAssis, Lucas Freire-Antunes, Uyla Ornellas-Garcia, Cláudio T. Daniel-Ribeiro, Flávia L. Ribeiro-Gomes

E-mail: anaclarapoeys@gmail.com

Laboratório de Pesquisa em Malária, Instituto Oswaldo Cruz (IOC), Fiocruz, Rio de Janeiro, Brasil

Malaria remains a major global public health problem, with high morbidity and mortality, particularly due to cerebral malaria (CM), a severe form caused by protozoan parasites of the *Plasmodium* genus. CM is associated with an intense inflammatory response and the sequestration of erythrocytes and T cells in the cerebral microvasculature. Although CD8 T cells are directly associated with the development of CM, the role of dysfunctional T cells generated during processes of exhaustion and cellular senescence remains poorly understood. T cell senescence is characterized by reduced proliferation, telomere shortening, and the expression of molecules such as NKG2D and KLRG1, in addition to increased secretion of inflammatory cytokines and cytotoxic factors. Immunosenescence, previously associated with aging and neurodegenerative diseases, also occurs in parasitic infections, including malaria. Studies in malaria patients suggest the presence of peripheral CD4 and CD8 T cells expressing senescence markers. Murine models corroborate these observations, indicating that the inflammatory environment generated by infection may induce CD8 T cell senescence in the periphery. In this context, we evaluated whether *Plasmodium berghei* ANKA infection in C57BL/6 mice, an experimental model of CM (eCM), is associated with the presence of CD8 T cells with senescence-related features in the brain. We evaluated the presence and phenotype of these cells during infection. We observed a significant increase in the frequency and absolute number of CD8 T cells in the brains of infected animals compared with controls. Approximately 50% of these cells expressed KLRG1. In addition, most KLRG1^{+} CD8 T cells coexpressed Ly6C, suggesting an activated and potentially cytotoxic phenotype. No significant differences were observed in the expression of CD28 or PD-1 in these cells. These findings suggest that CD8 T cells with senescence-associated features may contribute to the immunopathology of eCM.

Keywords: Cerebral malaria; CD8 T cells; Immunosenescence; *Plasmodium berghei* ANKA; KLRG1.