Immune Signatures Associated with Clinical Outcome in *Plasmodium vivax* Infection

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Individuals may develop the asymptomatic (ASY) form of *Plasmodium vivax* infection. Those individuals typically have very low parasitemia, often undetectable by optical microscopy, serving as parasite reservoirs and sustaining transmission. Evidences indicate that cellular immune responses against *P. vivax* involve complex interactions between conventional and unconventional T cells, including γδ T cells and invariant natural killer T (iNKT) cells, which act at different stages of the parasite life cycle. This project aims to characterize conventional and unconventional T cell populations in ASY and symptomatic (SY) *P. vivax*-infected individuals living in the Brazilian Amazon. Blood samples were analyzed using a 28-parameter flow cytometry panel to profile T cells: conventional ($CD4^+$ and $CD8^+$) and unconventional (TCRγδ and TCRVα24: iNKT), including their differentiation stages (CCR7, CD45RA, CD28, CD95, CD57), their expression of cytokine/chemokine receptors and activation/inhibition markers. Unsupervised analyses revealed distinct immunological profiles between ASY and SY individuals. SY showed a marked expansion of highly activated T follicular helper (Tfh) cells, as well as increased frequencies of $CD4^+$ T effector memory (EM) and activated $CD8^+$ TEM, along with higher frequencies of terminally differentiated (TEMRA) and senescent $CD8^+$ T cells ($CD57^+$ $CD28^{low}$). In contrast, ASY exhibited a predominance of $CD8^+$ TEMRA cells, along with moderate expansion of memory $CD4^+$ T cells, consistant with an efficient and controlled cytotoxic response. These findings indicate that clinical manifestations of malaria are associated with distinct immune profiles, characterized by T helper activation and cytotoxic dysfunction in SY, whereas ASY display a more balanced and potentially protective immune response. These results contribute to a better understanding of the immune mechanisms underlying ASY *P. vivax* infection.

Keywords: Malaria, *Plasmodium vivax*, Asymptomatic, T cells.

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