Distinct cytokine signatures associated with long-term maintenance of humoral responses to multiple *Plasmodium vivax* blood-stage antigens

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The biological complexity of *Plasmodium vivax* (Pv) has driven the development of multi-antigen vaccine strategies, making careful antigen selection essential to their success. Among the Pv blood-stage antigens, Duffy Binding Protein region II (DBPII) is a leading vaccine candidate. However, variations in its B-cell epitopes drive strain-specific immunity. The engineered vaccine DEKnull-2 elicited broadly inhibitory IgG antibodies that block *in vitro* Pv reticulocyte invasion. Because cytokines play key roles in both innate and adaptive immune responses, we hypothesize that a balanced immune signature is essential for maintaining long-lasting antibody responses against blood-stage antigens. In this study, we evaluated cytokine profiles in individuals with persistent antibody responses to DBPII and DEKnull-2 over 15 years in a population from the Brazilian Amazon, as well as IgG reactivity to a panel of 16 Pv blood-stage antigens. Pro-inflammatory and regulatory cytokines were quantified in PBMC supernatants from persistent responders (PR), non-responders (NR), and non-exposed controls (NE) after stimulation with DBPII and DEKnull-2. Distinct cytokine signatures were observed among the groups. PR exhibited a more expanded and balanced Th1, Th2, Th17, and regulatory cytokine profile compared to NR, whereas the NE showed a predominance of pro-inflammatory cytokines. Subsequently, we assessed IgG reactivity against 16 Pv antigens in plasma samples from all groups using an Luminex assay. Consistently, PR maintained broadly and long-lasting IgG responses against multiple Pv antigens, with stable magnitude and seropositivity over time, even in the absence of recent reinfections. Taken together, the findings indicate that a balanced cytokine signature is associated with the persistence of the humoral response to multiple Pv antigens and may contribute to strategies for the development of multi-target vaccines against Pv. (Support: CNPq, CAPES, FAPEMIG, NIH, Fiocruz/ReTMavi).

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