Activation of TCR Vδ1+ and Vδ1-Vδ2- $\gamma\delta$ T cells upon controlled infection with Plasmodium falciparum in Tanzanian volunteers

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Our understanding of the human immune response to malaria remains incomplete. Clinical trials using whole-sporozoite-based vaccination approaches such as the Sanaria PfSPZ Vaccine, followed by controlled human malaria infection (CHMI) to assess vaccine efficacy offer a unique opportunity to study the immune response during Plasmodium falciparum infection. Diverse populations of T cells that are not restricted to classical HLA (unconventional T cells) participate in the host response during Plasmodium infection. Although several populations of unconventional T cells exist, the majority of studies focused on TCR Vgamma9Vdelta2 cells, the most abundant TCR gammadelta cell population in peripheral blood. In this study, we dissected the response of three TCR gammadelta cell subsets and mucosal-associated invariant T cells in healthy volunteers immunized with PfSPZ Vaccine and challenged by CHMI using Sanaria PfSPZ Challenge. Using a flow cytometry-based unbiased analysis followed by T cell cloning, several findings were made. Whereas major ex vivo alterations were not detectable after immunization with PfSPZ Vaccine, TCR Vdelta2, and mucosal-associated invariant T cells expanded after asexual blood-stage parasitemia induced by CHMI. CHMI, but not vaccination, also induced the activation of TCR Vdelta1 and Vdelta1(-)Vdelta2(-) gammadelta T cells. The activated TCR Vdelta1 cells were oligoclonal, suggesting clonal expansion, and upon repeated CHMI, showed diminished response, indicating long-term alterations induced by blood-stage parasitemia. Some TCR Vdelta1 clones recognized target cells in the absence of parasite-derived Ags, thus suggesting recognition of self-molecules. These findings reveal the articulate participation of different populations of unconventional T cells to P. falciparum infection.

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