Editorial

γδ T cells and immunity to human malaria in endemic regions

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Malaria, caused by the mosquito borne parasite *Plasmodium spp* is responsible for around 200 million cases each year, resulting in over 600,000 deaths, with nearly half of the world population at risk (1). The lack of our proper understanding of the immunology of clinical malaria has been damaging to the attempts to make reliable vaccines against this disease. Severe clinical manifestations of malaria are often observed in young children or adults experiencing their first exposure to the malaria parasite. In endemic areas, antibody mediated protection from clinical malaria (but not sterile immunity against infection) is acquired only after repeated exposures to the parasite over many years. Though various components of the innate and adaptive immune system likely contribute, the core mechanisms behind development of clinical immunity to severe malaria still remain unknown.

The significance and role of γδ T cells in clinical immunity to malaria has been a controversial subject in the field. In a primary *P. falciparum* and *P. vivax* infection of humans, a subset of γδ T cells ($V\gamma9^+V\delta2^+$) sense parasite-derived (non-peptide) phospho-antigens (2,3) without an antigen presenting cell mediator, to undergo a polyclonal expansion (4,5) with the help of monocytes (2), $CD4^+$ αβ T cells (6), or exogenous cytokines (7). The $V\delta2^+$ γδ T cells are thought to aid in controlling primary plasmodium infection by bridging the innate and adaptive arms of the immune system, through production of pro-inflammatory cytokines and mediators like interferon (IFN)γ, tumor necrosis factor (TNF)α and granzyme B (8), in addition to killing the blood stage merozoites directly (4,9,10). It is noteworthy that in human malaria $V\delta2^+$ γδ T cells expand in number following acute, primary infections only (11,12). Expansion in number of $V\delta2^+$ γδ T cells is not observed in subsequent exposures, despite evidence for reactivation of these cells (13) in patients living in endemic regions. Hence the contribution of this T cell subset to immunity in malaria where people are frequently re-exposed to plasmodia has been contentious.

Of note, primary exposures to plasmodia also cause a more severe clinical disease in humans, compared to re-exposures in an endemic setting. Although a progressively more efficient recall response and control of parasites by the adaptive immune system may be the most apparent reason for this, in a recent issue of *Science Translational Medicine*, Jagannathan and coworkers (14) associate reduction of severe clinical disease with a loss of the $V\delta2^+$ γδ T cell responses. They propose that downregulation of the $V\delta2^+$ γδ T cell responses in repeated exposures to plasmodia may be contributing to a better tolerance to clinical malaria. This suggestion is buttressed by past observations that γδ T cells along with $CD14^+$ monocytes may be responsible for the production of cytokines and chemokines linked to severe clinical malaria (15).

In this study, Jagannathan and coworkers set the stage by confirming that $V\delta2^+$ γδ T cells are lost from peripheral circulation with increasing incidence of malaria in a cohort of Ugandan children. Longitudinal studies of humans provide a powerful approach to address the impact of repeated malaria infections on host immunity (16,17). Jagannathatn *et al*. make the observation that $V\delta2^+$ γδ T cell function, as defined by their ability to produce IFN γ, TNFα and interleukin (IL)-2; as well as proliferate upon *in vitro* re-stimulation with infected RBCs, deteriorated with prior incidence of malaria. Using relevant gene transcriptional changes as a metric, they show that $V\delta2^+$ γδ T cells from children with higher incidence of malaria demonstrated a general unresponsiveness to antigen re-exposure, with induction of immuno-regulatory

pathways that would dampen the overall immune response. This however contradicted an earlier observation describing an apparent lack of anergy in γδ T cell from adult patients living in another malaria endemic region (13). Studies to determine the impact of age and/or many years of recurring plasmodium infections on immune function may be required to resolve this discrepancy.

In this work, Jagannathan and coworkers associate the loss and dysfunction of peripheral Vδ2$^+$ γδ T cells to higher parasitemias and lower probability of exhibiting the clinical symptoms of malaria, dubbed as clinical immunity in subsequent infections. One critical question here is whether γδ T cells contribute to protective immunity, or are merely pathogenic in the context of repeated exposures. Jagannathan *et al*. propose that though clinical immunity develops through the progressive loss of malaria responsive Vδ2$^+$ γδ T cells in repeated natural challenges with *P. falciparum*, they did not protect against the infection itself. However children with lower percentages of circulating, cytokine-producing γδ T cells had a higher risk of parasitemia though with better clinical outcomes and vice versa in re-exposed individuals. This result may suggest that γδ T cells have a role in protection from *P. falciparum* infection in a high transmission, endemic setting. Further studies to understand the mechanisms underlying γδ T cell dysfunction, the resultant clinical immunity as well as its role in controlling the parasites in repeated challenges will be necessary to resolve this issue. This knowledge might help in determining whether therapies [like immune check-point blockade (17)] to enhance responsiveness and/or numbers of γδ T cell subsets would enhance protection or exacerbate disease in people living in endemic areas.

This study is an important step towards understanding the role of γδ T cells in the pathogenesis and control of *P. falciparum* infection in an endemic area, where the disease burden is more severe and requires immediate interventions. Though sterile immunity to plasmodium may be the ideal goal of vaccination strategies, a more practical (both scientifically and economically), achievable goal in the short term may be therapies to facilitate clinical tolerance to malaria. Though it is unclear if the observed correlative loss of Vδ2$^+$ γδ T cell responses in subjects experiencing high incidence of plasmodium infections is a product or cause of the pathogen burden, Jagannathan and colleagues provide an intriguing data set suggesting the relevance of a γδ T cell subset that can play an important role in enhancing strategies towards malaria control in endemic regions.

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