Dysfunctional $\gamma \delta$ T cells: a contributing factor for clinical tolerance to malaria?

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 $\gamma\delta$ T cells are a small subset of T cells that can rapidly recognize and respond to antigen in a non-MHC restricted manner. The importance of $\gamma\delta$ T cells during malaria infection is established by studies in both mouse models and with human cells, where $\gamma\delta$ T cells expand during acute blood stage infections (1,2) and control parasitemia (3). We and others have demonstrated that human $\gamma\delta$ T cells are one of the predominant cytokine producers following stimulation with *Plasmodium*-infected red blood cells *in vitro* (4-6) and following infection (7,8). $\gamma\delta$ T cell cytokine responses are also associated with severe disease (9).

Recently, Jagannathan *et al.* [2014] (10) described compositional modification and presence of dysfunctional $\gamma\delta$ T cells in the periphery of individuals living in malaria hyper endemic areas of Uganda. The study cohort consisted of 78 HIV-uninfected children enrolled before 1 year of age. Routine blood smears were performed monthly on these children until the age of 5 years to obtain a comprehensive clinical record of asymptomatic and symptomatic episodes. Children with episodes of fever (tympanic temperature ≥ 38 °C) were assessed for malaria by thick blood smears and diagnosed malaria was treated with artemisinin-based combination therapy. The peripheral blood mononuclear cell (PBMC) samples used to investigate $\gamma\delta$ T cells were collected at the age of 4 and 5.

The authors found that the incidence of symptomatic malaria for the cohort was 5.4 episodes per person-year (PPY) which declined with age whereas asymptomatic parasitemia increased. Assessment of $\gamma\delta$ T cell subsets V $\delta1$ and V $\delta2$, uncovered a decrease in the frequency of V $\delta2$ + cells relative to prior incidence of malaria. Further investigation of V δ 2+ cells demonstrated a decline in functional capacity including proliferation and cytokine production in response to malaria-specific stimulation, and was negatively associated with increased prior malaria incidence. The authors subsequently investigated whether upregulation of immunoregulatory pathways was a result of repeated infection. Consequently comparison of basal gene expression and malaria antigen-induced gene expression was performed between children with <2 prior episodes PPY and children with ≥ 8 episodes. Basal gene expression identified a higher expression of immunomodulatory genes in highly exposed children whereas mRNA encoding for cytokines were significantly expressed at higher levels in children with <2 prior episodes PPY following stimulation. The frequency and function of V δ 2+ cells was subsequently analysed relative to clinical immunity. The authors found that the frequency of malaria-responsive $V\delta^{2+}$ cells was significantly lower in children who experienced asymptomatic episode compared to children who developed clinical malaria. While lower frequency of cytokine production was associated with higher risk of parasitemia, this conferred lower risk of clinical symptoms in highly exposed children. The authors conclude that $\gamma\delta$ T cells do not protect from infection, but with loss of responsive Vδ2+ cells there is an increased probability of asymptomatic infection.

This study clearly contributes to the current understanding of malaria immunology. The cohort offers good measures of exposure relative to clinical and immunological outcomes. The high rate of exposure (379 infective bites PPY in 2012) (11) and malaria incidence of

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the cohort is likely to resemble chronic infections with other pathogens (e.g., HIV or HCV) in which dysfunctional cells are a well-established occurrence (12). Thus the findings of dysfunctional $\gamma\delta$ T cells in this cohort are consistent with previous reports of dysregulated cells and chronic immune activation. However, the high frequency of infections in the cohort also confers limitations as samples are not necessarily collected during convalescence and this may affect the ability to assess cell functionality and gene expression. In fact 22% of the children were parasitemic at the time of sample collection. Although the authors found no significant difference in the percentage of cytokine producing cells compared to non-parasitemic children, it would have been interesting to take "time lapsed from last infection" into account in the analysis. This would potentially allow separating effects from recent infection such as contraction phase from persistently existing atypical $\gamma\delta$ T cell distribution and function. Although the study indicates that exposure is an important factor for the observations made, it will also be interesting to establish whether similar findings are observed in individuals living in areas of lower endemicity where clinical tolerance is also noted.

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