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Human *Plasmodium falciparum* infection induces a predictable and persistent distortion in transcriptomic landscapes across T cell subsets

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Malaria infection still remains one of the world's most formidable issues across both health and economical systems. Despite the best intervention strategies, over 200 million people are infected annually and mortality rates exceed 400,000 deaths per year. To develop effective therapeutics and vaccines, a better understanding of fundamental human immunology is required. This is particularly true of the contribution of T cells to malaria defence. Research to date comes from field samples which can sometimes be difficult to interpret due to confounding factors including multiple exposures. As such, the underlying immune correlates of an efficient response remain unknown. To investigate the role of T cells in disease, we used a human model of blood stage *Plasmodium falciparum* infection involving the medicines for malaria venture (MMV). We performed high-dimensional phenotyping and T cell receptor (TCR) sequencing of T cell subsets before infection, during infection and during convalescence. *Plasmodium falciparum* infection resulted in marked phenotypic 'scaring' across all T cell subsets and persisted during convalescence. We identified gene modules that correlated with parasitaemia, revealing possible continua between individuals at risk of disease and 'elite controllers'. Remodelling of the TCR repertoire could also be correlated with transcriptomic changes, and gene expression and TCR repertoire metrics could serve as novel proxies of disease burden and assist in identifying pathways for immunotherapies or vaccine activation. Indeed, characterizing the T cell biology of elite controllers opens the possibility of inducing this phenotype for the purposes of rational vaccine design and therapeutic intervention.

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