Mapping the immune response in schistosomiasis – insights from controlled human infection models.

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Infection with the parasitic worm *Schistosoma mansoni* causes considerable global morbidity, affecting over 200 million people, particularly in sub-Saharan Africa. Due to difficulties with diagnosing and tracking early infections, often asymptomatic in endemic individuals, prior studies have not been able to precisely define immune responses in the initial weeks of schistosome infection. Here, we have utilised a pioneering controlled human schistosome infection model to investigate the early immune responses to single-sex male or female schistosomes. At 2 weeks post infection, we used flow cytometry to reveal a change in the myeloid compartment, with an increase in pulmonary dendritic cells during schistosome lung migration. Next, and coinciding with the first moderate or severe clinical manifestations of acute schistosomiasis syndrome, at week 4 post infection we saw evidence of an inflammatory immune response. Proteomic assessment of the serum revealed increases in type-1 messengers such as IFNγ and CXCL10, as well as activation of monocytes and $CD4^+$ effector memory T cells seen by mass cytometry (CyTOF). This inflammatory response had lessened by week 8, when we saw evidence of regulation, with intracellular cytokine staining showing an increase in IL-10 expressing $CD4^-CD8^-$ T cells, and a reduction in expression of the pro-inflammatory cytokine TNFα by T and B cells. Alterations in the B cell compartment at week 8 with an increase in $CD11c^+$ atypical memory B cells, observed by CyTOF, coincided with the appearance of anti-schistosome antibodies in the circulation, measured by antigen-specific ELISA. Notably, initial cytokine and antibody results suggest broad similarity in the clinical and immunological profiles of infection with single-sex male or female cercariae. Current and future work will use refined techniques (CyTOF, RNA-seq) to better understand responses post infection with female cercariae, to compare to the male infection model. This novel data elevates fundamental understanding of the development of immune responses during *S. mansoni* infection, providing clinically relevant insight into the pathology of acute schistosomiasis, and setting an immunological baseline to assess changes in future vaccine studies.