Human immune responses to *Schistosoma mansoni*, lessons from controlled human infection models and natural endemic infection.

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Prior studies have revealed mixed Type-1/Type 2 response in early migrating and maturing *Schistosoma mansoni (Sm)* infection, developing to a Type-2 and regulatory response upon egg production. These findings have been mainly derived from animal (murine) models, as longitudinal assessment of how worm-specific immune responses develop in humans has not been possible. Here, we have used a *Sm* controlled human infection model (*Sm*-CHI) to study immune response development over repeat (3x) male-cercariae exposure (Netherlands, n=24), comparing our findings to natural infection (Uganda, n=30). *Sm*-specific cellular and cytokine responses were assessed via spectral flow cytometry and luminex. Clinically, repeated *Sm*-CHI led to reduced symptoms (when compared to single), but did not result in (sterile) protection. In line with this symptom profile, Type-1 responses (serum CXCL10, activated $CD38^{+}HLADR^{+}$ T cells) peaked post exposure one and two, reducing post exposure three. In contrast, *Sm*-specific regulatory and Th2 responses increased with repeat exposure. Five *Sm*-CHI participants were inadvertently exposed to female (instead of male) cercariae during exposure two. This led to a potential mixed-sex infection and one positive *Sm* faecal PCR post exposure three before praziquantel treatment, indicative of low-level egg production. An elevated Type-2 response was observed in mixed-sex exposed individuals, with eosinophilia and *Sm*-specific Th2 cytokine production. *Sm*-specific Th2 responses in mixed-sex *Sm*-CHI were significantly higher than those observed in endemic natural infection, likely attributable to well-described immunoregulation induced by chronic *Sm* infection. Taken together, this data significantly advances our understanding of human immune response development during schistosome infection.