Exploring host-immune-microbial interactions during intestinal schistosomiasis

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Abstract

Schistosomes are extraordinarily successful parasites and experts of immune calibration. Like other helminths, schistosomes have evolved sophisticated mechanisms to circumvent and modulate immune responses, ultimately permitting their long-term persistence within the host. This recalibration reflects the spectrum of immunomodulatory molecules produced by schistosomes, alongside the host's reparative response to parasite-inflicted damage. Importantly, as schistosome eggs cause considerable destruction to the host as they rupture the intestinal wall, it is possible that intestinally-derived signals, including those from the microbiota, may contribute to the immune responses found during schistosomiasis. In the work detailed in thesis, we attempt to dissect the involvement of parasite, host, and microbial factors in the instruction of schistosome associated Type 2 and Regulatory cell networks. First, we systematically characterise immune profiles across the course of conventional egg producing infections, providing a concise narrative of how schistosomiasis associated immune profiles evolve over time in effector and priming sites. Here, though the depletion of $CD11c^+$ cells at peak stages of disease, we reveal a role for $CD11c^+$ DCs in the maintenance of *S. mansoni* elicited Type 2 immunity. Next, by using a combination of high vs low dose, and egg producing vs non egg producing infections, we show elevated intestinal permeability during chronic and high dose egg producing infections, with hints towards enhanced bacterial translocation. Infection patency evoked a Type 2 dominated immune response in the mesenteric lymph nodes and colon that coincided with significant intestinal microbiome alterations. Significantly, through the use of germ free mice and faecal transplants, we provide evidence that the schistosome infection associated microbiota can influence the character of host Immunity. Moving on from the intestine and Type 2 immunity, we next sought to better define the signals endorsing schistosome elicited Regulatory B cell (Breg) and T cell (Treg) expansion. Through the interrogation of Type-I signalling, we show IFN-I to assist in murine Breg generation an *in vitro* but not *in vivo setting.* Finally, we show chronic egg-producing and non-egg producing *S. mansoni* infections to expand phenotypically distinct Treg and Breg and populations, with microbiotas from these mice capable of modulating the severity of experimental allergy. Together, our data elevates the mechanistic understanding of parasite-host-microbial relations and provides a strong platform for the future study of schistosome or microbial factors in the modulation of inflammatory disease.

Lay Abstract

Schistosomes are parasitic worms that cause the disease schistosomiasis. To survive and thrive within the mammalian host, schistosomes manipulate host immunity in a variety of ways, including the production of certain factors that interact with immune and non-immune cells. In addition, as part of the schistosome lifecycle, schistosome eggs move across the gut wall causing intense damage. This damage might make the gut 'leakier' and allow substances within the gut (including bacteria) to enter other parts of the body and influence the immune system. In this thesis we investigate how factors produced by parasites, the host and our gut bacteria, influence the immune system during schistosomiasis. Firstly, we look broadly at immune responses generated during conventional egg producing *Schistosoma mansoni* infections, and characterise how immune cells respond in the spleen, liver, and mesenteric lymph nodes at different time points of infection. We show that a specific type of innate immune cell called dendritic cells are important for the upkeep certain immune responses during infection, referred to as Type 2 immunity. Next, by infecting mice with egg producing and non-egg producing schistosomes, we show that intestinal leakiness is provoked by the movement of eggs across the gut wall, and that increasing the infection dose makes leakiness occur at earlier stages of infection. We show the movement of eggs to evoke a Type 2 immune response within the intestine and to also disrupt the diversity and abundance of bacteria within the gut. Next by transferring faeces from schistosome infected mice into naïve mice without intestinal bacteria, we show that microbes from schistosome infected mice can promote aspects of the gut immune response found during schistosome infections, even in the absence of parasites. Next, we investigate the role of certain secreted immune proteins, called cytokines, during schistosomiasis. We show that Type-I IFNs (cytokines) can help support a specific adaptive immune cell, the Regulatory B cell (Breg), to produce another cytokine called IL-10. Finally, previous work has shown *S. mansoni* infections to protect against allergy, with evidence that certain immune cells called Regulatory T cells (Treg) and Bregs mediate this effect. We show that both egg producing and non-egg producing infections are capable of triggering expansion of these immune cells and that the gut bacteria from these mice can modulate the severity of allergic disease in mice. Together this work provides new and exciting insights into the factors governing immune responses during schistosomiasis, with strong hints towards bacterial involvement.