Title:

Identification of New Therapeutic Targets for Schistosomiasis using RNAi

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Abstract:

Schistosomes are parasitic platyhelminths (blood flukes) that can cause a chronic, often debilitating, disease called schistosomiasis that affects several hundred million people around the world. Infection is water-borne; free-swimming larval forms penetrate the skin and invade the vasculature of their hosts. In the laboratory, we focus on the molecular and cellular biology of the schistosome outer covering (the tegument). This surface constitutes a major site of host-parasite interaction and molecules making up this surface are likely accessible therapeutic targets.

Among the surface molecules identified in the parasite surface membranes are a collection of enzymes which, we hypothesize, act to impair host immune signaling and hemostasis. Using RNA interference (RNAi) to suppress the expression of genes encoding these surface enzymes, we have shown that one, ecto-ATP diphosphohydrolase 1 (SmATPDase1), can cleave the pro-inflammatory DAMP ATP and a second, alkaline phosphatase (SmAP), can generate the potent anti-inflammatory mediator, adenosine. Another host-interactive schistosome tegumental enzyme, the phosphodiesterase SmNPP-5, is rapidly upregulated following invasion of the definitive host. Suppressing the expression of the gene encoding SmNPP-5 greatly impairs the ability of schistosomula to establish infection. Thus SmNPP-5 can be considered a virulence factor for schistosomes.

Other host-interactive enzymes include a carbonic anhydrase (SmCA) which likely functions to regulate pH homeostasis and the transport of CO_2, and an acetylcholinesterase (SmAChE) which may impact host vascular physiology. Suppressing the expression of these genes too impairs parasite infectivity. This work has identified that these are essential molecules for normal parasite development and are therefore important therapeutic targets. We have begun drug screens to identify chemicals that can impede the function of these surface proteins (to mimic the RNAi effect) and debilitate the worms.

In addition our work is designed to generate a comprehensive understanding of the role of these surface proteins in promoting parasite survival by controlling the biochemistry of their immediate external environment.