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TITLE

FUNCTIONAL ROLES OF THE SCHISTOSOMA MANSONI TYROSINE KINASES SMABL1 AND SMABL2 IN A MURINE MODEL OF INFECTION

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ABSTRACT

Protein kinases (PKs) regulate complex cellular processes such as metabolism, cell cycle progression, apoptosis, cytoskeleton modifications, and differentiation. Previous studies showed that some PKs in *S. mansoni* may represent potential targets for anti-Schistosoma drug development, with PK inhibitors, such as Imatinib, affecting the reproductive biology as well as gut integrity of the adult parasite. Specifically, it has been reported that two Abl-kinases (SmABL1/SmABL2) in *S. mansoni* are targets for Imatinib. To better understand the roles of SmABLs, expression profiling through in situ-hybridization analyses showed that both proteins are expressed around the ootype, ovaries, and vitellaria in female worms, in the testes of males, and weakly in some parenchyma cells and the gastrodermis. In this study, we present an in silico analysis of Smabl1 and Smabl2 expression levels at different *S. mansoni* life stages, using RNA-seq data available on the tool <https://lifecycle.schisto.xyz/>. This analysis revealed that both genes are more highly expressed in the adult worm stage. To evaluate the function of SmABL1 and SmABL2 during *S. mansoni* infection in the mammalian host, we first synthesized specific dsRNA and exposed, by soaking, newly transformed schistosomula to 200 nM Smabl1-dsRNA or electroporated them with Smabl2-dsRNA. The schistosomula were then maintained in culture, and transcript levels were assessed. The highest inhibition was observed after two and three days for Smabl1 and Smabl2, respectively. Knockdown levels were measured by RT-qPCR, showing a reduction in transcript levels of 98% for Smabl1 and 80% for Smabl2. Next, mice were infected with 350 knocked-down schistosomula and kept for 45 days after which they were perfused for worm recovery. Liver and intestine of each mouse were removed, weighed, and digested to determine the number of eggs. To assess egg maturation, slides were prepared with segments of the ileum. The level of egg maturation in the ileum of animals infected with Smabl1-knocked-down schistosomula showed a 2.5x increase in the percentage of immature and dead eggs, whereas 1.64x decrease in mature eggs was found when compared to the ileum of negative control group. However, there were no significant differences in adult worm recovery, female fecundity, or the total number of eggs in the liver and intestine in the Smabl1-knocked-down group. Conversely, in the Smabl2-knocked-down group, no differences were observed in adult worm recovery, female fecundity, total number of eggs, or egg maturation. In summary, our preliminary results indicate that Smabl1 is associated with egg maturation and may be involved in female reproduction during murine infection.

KEYWORDS

Schistosoma mansoni; SmABL 1; SmABL 2; RNA Interference; Protein Kinase

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