# *Schistosoma mansoni* phenotypic evaluation after aspartyl proteases cathepsin D-like knockdown

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Praziquantel is the only commercially available drug for the treatment of schistosomiasis, although its mechanism of action remains unknown. Studies show the need to search for new targets, including different classes of peptidases that play an important role in the development of the parasite and the success and maintenance of the infection. An aspartyl protease (AP) similar to cathepsin D from *Schistosomamansoni* (SmCD1) has been reported to be involved in the initial breakdown of hemoglobin in the host's erythrocytes, with distinct hemoglobin cleavage points and 51% identity with the human ortholog. Subsequently, other SmAPs were identified (SmCD2 and SmCD3). This work aims to functionally characterize SmCD1 and SmCD2 and to validate these targets as potential therapeutic targets. For this, the RNA interference technique was used, with exposure of schistosomula and adult worms to specific SmCD-dsRNAs. First, by qPCR, it was observed that the targets are more expressed in female adult worms. Significant reductions in target transcripts were observed in schistosomula (~99.9%) on the fifth day of dsRNA exposure. Phenotypic changes were observed in female adult worms recovered by perfusion, with reduced body length and decreased formation of hemozoin pigment in the digestive tract. Confocal microscopy analyzes showed a reduction in the ovary area, absence of eggs in the reproductive tract, and a decrease in mature oocytes, possibly related to sexual immaturity and indicating possible participation of the targets in the worm development. However, no phenotypic changes were observed in males recovered and analyzed so far. Analyzes of adult worms' motility, exposed to dsRNA, showed a decrease in motility of male adult worms on the fifth day for both targets. The evidence presented here suggests that SmCD1 and SmCD2 are promising targets for inhibitor screening in search of a new therapy against schistosomiasis.

Keywords: Schistomiasis, Schistosoma mansoni, RNAi, aspartyl proteases