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TITLE

UNRAVELING THE EXPRESSION AND FUNCTION OF LYSINE SPECIFIC DEMETHYLASES (SMLSDS) IN DIFFERENT LIFE STAGES OF SCHISTOSOMA MANSONI

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ABSTRACT

The complex life cycle of Schistosoma mansoni requires many changes and intense regulation of gene expression, including epigenetic mechanisms. These are also responsible for the rise in phenotypic variation influencing disease establishment. Among them are histone modifications, made by histone-modifying enzymes (HMEs) that alter histone tails. Lysine Specific Demethylases of S. mansoni (SmLSDs) are a group of these HMEs (SmLSD1, 2, and 3) responsible for removing methylation from lysine four on the tail of histone H3. Given the limited effectiveness of praziquantel in immature worms, the disease recurrence, and reported parasite drug resistance, new therapeutic targets are needed. This study aims to elucidate epigenetic control in S. mansoni by identifying SmLSDs regulatory profile, exploring the implications of Smlsds knockdown mediated by RNA interference, and evaluating their expression in different parasite stages and cell types. Schistosomula and adult worms were exposed to specific double-stranded RNA (dsRNAs) for seven and ten days, respectively. Different conditions were evaluated: in schistosomula, addition of dsRNA (1) on day of transformation, (2) on day of transformation and 48 h later, (3) associated with PEI carrier. In adult worms, the dsRNA was associated with PEI (1) after plating and (2) after plating and 48 h later. For both stages, the first condition showed greater knockdown efficacy. In schistosomula, Smlsd1 (86%) and Smlsd3 (92%) knockdown were more significant on day four, while Smlsd2 showed maximum reduction (81%) on day two. In adult worms, the most expressive reduction in Smlsd1 (63%), Smlsd2 (43%), and Smlsd3 (64%) transcripts was observed on day four. Furthermore, reduction in egg-laying was observed in couples exposed to SmLSD2 dsRNA. The motility of adult worms exposed to dsRNAs was assessed using WormAssay. There was difference in motility in females (day 6) and in males (days 3 and 10) for SmLSD1 group, and a reduction in motility in males (day 8) in SmLSD1 and SmLSD3 groups. RT-qPCR was performed to evaluate the expression of SmLSDs in parasite's life stages. Smlsd1 presented higher expression in tree-days-old schistosomula, Smlsd2 in cercariae, and Smlsd3 in females. Furthermore, we also performed searches in public databases containing RNA sequencing and single-cell RNAseq (scRNAseq) data to investigate Smlsds expression in different stages and cell types. In general, Smlsds expression converges between studies showing lower expression in mixed-sex infections and the last days of infection. Also, we observed a low expression of the Smlsds in miracidia, Smlsd1 and 3 in cercariae, and a high expression of all in sporocysts and juveniles. Additionally, from scRNAseq data, no enrichment of Smlsds expression in any cell cluster was observed. Thus, the analyses revealed variations in Smlsds expression in different parasite stages, highlighting their relevance in gene regulation during the parasite's life cycle.

KEYWORDS

Lysine Specific Demethylases; Schistosoma mansoni; Epigenetics; RNA Interference

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