Targeting Epigenetic Regulators to Control Schistosomiasis

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Introduction: Schistosomiasis is a chronic disease that affects 240 million people in the world. The current strategy for the treatment and control of schistosomiasis is the use of Praziquantel, the only available drug. The development of new drugs is therefore mandatory. The new strategy that we have chosen is to target the enzymes involved in epigenetic modifications of the chromatin, such as acetylation and methylation of histones. We have previously shown that acetylation can serve as an effective drug target. In the present work, we show that targeting one major histone demethylase LSD1 from *S. mansoni* is also a valid therapeutic approach.
Objective: Test several LSD1 inhibitors as a new strategy to control Schistosomiasis.
Methodology: Drug screening of *S. mansoni*, by in vitro culture of adult worms or the larval stage of schistosomula; Viability estimation and quantification by ATP measurements; Confocal Laser Scanning Microscopy of the adult worms and quantitative RT-PCR. Western Blot analysis of the methylation status of the Histone H3. Transcriptomic analysis (RNAseq) of treated juvenile and adult schistosomes.
Results: Several compounds that specifically target LSD1 have been tested against schistosomula and adult worms. We have identified a potent compound showing high toxicity leading to complete mortality of the immature forms of the parasite, after 48h at a dosage of 10-25 uM. Adult worms were also sensitive to the same compounds, but after longer period (72h) of incubation. Egg laying by adult female schistosomes was significantly affected by the LSD1 inhibitors. The LSD1 compounds showed specificity, as measured by the increase of H3K4(2met) levels in the treated parasites. Importantly, several genes were differentially expressed in both juvenile and adult schistosomes upon LSD1 inhibition.
Conclusions: So far, we have validated LSD1 inhibitors as a novel and promising strategy to control schistosomiasis. Their molecular mechanisms of action have also been pursued.

Key Words: Epigenetics, *Schistosoma mansoni* and Lysine demethylation, Chromatin, Therapeutics.
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