Inhibitors of schistosome histone modifying enzymes: effects on large-scale gene expression

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Epigenetic mechanisms play a central role in regulation of gene expression by changes in histones and chromatin remodelling, and it is known that inhibition of *Schistosoma mansoni* histone deacetylase (HDAC) induces schistosomula apoptosis. In this context, histone modifying enzymes (HMEs) are promising targets for schistosomiasis therapy. In order to identify the mechanisms of drug action on the parasite, we measured large-scale gene expression under the effect of three HME inhibitors: two HDAC inhibitors (Trichostatin-A and one novel inhibitor), and one novel histone methyltransferase (HMT) inhibitor. We employed expression microarrays as well as RNA-Seq, using RNA samples from worms treated in vitro with sub-lethal doses of the inhibitors or with vehicle as control. We identified hundreds of genes with statistically significant (q-value<0.05) differential expression as the parasites became stressed by the effect of each drug. Interestingly, the expression of dozens of genes encoding histone reader proteins was affected by TSA, including a reader from an HMT complex with reduced expression. Analysis of known gene targets of this HMT complex using Ingenuity Pathway Analysis software suggested that the enzyme component of the complex had a reduced activity, because 67% of the known targets exhibited a consistent change in expression. Gene Ontology (GO) analyses of TSA-affected genes showed biological process categories significantly enriched with differentially expressed genes related to DNA replication, protein synthesis and chromatin regulation. Overall, large-scale gene expression analyses suggest a number of possible mechanisms of action of HME inhibitors involved in promoting parasite death.

Key words: *Schistosoma mansoni*, expression microarrays, RNA-Seq